CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761069Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

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

NDA/BLA #	761069
Product Name:	Durvalumab
PMR # Description: 3205-1	Submit the final report with datasets and labeling for the clinical trial entitled "A Phase II, Randomized, Open-label, Controlled, Multi-center, Global Study of First-line MEDI4736 Monotherapy and MEDI4735 in Combination with Tremelimumab Versus Standard of Care Chemotherapy in Patients with Unresectable Stage IV Urothelial Cancer."

PMR/PMC Schedule Milestones:

Study/Trial Completion:	09/2019
Final Report Submission:	03/2020

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

This is a confirmatory trial following the anticipated accelerated approval of durvalumab in patients with metastatic or locally advanced urothelial cancer (b) (4). Accelerated approval will be granted on the basis of response rate.

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."

This study will be done to confirm the clinical benefit of durvalumab.

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.

Required

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

Continuation of Question 4

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

_____

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

_____

Agreed upon:

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

_____

☒ Other
Confirmatory trial

_____

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

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

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

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

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

PMR/PMC Development Coordinator:

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

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(signature line for BLAs)

PMR/PMC Development Template

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

BLA #	761069
Product Name:	Durvalumab
PMC Description: 3205-2	Conduct updated analyses of the duration of response for the patients with urothelial cancer who had received prior platinum-based therapy (N = 182) in the clinical trial entitled "A Phase 1-2 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI4736 in Subjects with Advanced Solid Tumors." Present the median and updated information on the range of the duration of response for all patients, patients whose tumor have high PD-L1 staining, and patients whose tumors have low PD-L1 staining. Submit the final report with datasets and labeling.

PMC Schedule Milestones:

Study/Trial Completion:	12/2017
Final Report Submission:	06/2018

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

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

We anticipate granting accelerated approval, based on response rate, for durvalumab. The median duration of response has not been reached. We would like to update the package insert with information on the median duration and range.

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."

Patients and practitioners would like to have information on the duration of response that they can expect with durvalumab.

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.

Required

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

Continuation of Question 4

☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
This is an ongoing trial. The PMC is to provide updated information on the median duration of response and the range of duration.

☐ 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
Updated results from clinical trial used for accelerated approval.

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

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

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

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

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

PMR/PMC Development Coordinator:

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

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(signature line for BLAs)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review 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

BLA #	BLA 761069/0
Product Name:	durvalumab

PMC Description: 3205-3	Confirm that there is no significant growth of organisms at 2 - 8°C in the drug product diluted with 0.9% sodium chloride and 5% dextrose by performing microbiological challenge studies with diverse microorganisms to support the 24 hour storage time. Your study should include Gram-negative microorganisms (such as *E. coli* and/or *E. cloacae*) which are known to proliferate in these solutions. The challenge studies should include at a minimum time points at twice the label claim storage time. These studies can be completed as a post-marketing commitment.

PMC Schedule Milestones:

Study Completion:		07/2017
Final Report Submission:		01/2018
Other:	Study results will be submitted as a CBE-0.	01/2018

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

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

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

The proposed label for durvalumab drug product claims that the drug product diluted in 0.9% sodium chloride or 5% dextrose may be stored refrigerated at 2 – 8°C for up to 24 hours. Generally, the growth rates of organisms at these temperatures are slow. The sponsor has not reported any sterility or container closure integrity failures to date, and sterility testing is performed as part of lot release and the stability program. Due to these factors, the risk for microbial proliferation is deemed low. Finally, the drug product is administered through an infusion line containing a 0.22 micron in-line filter.

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

Microbial control data has not been provided to support the 24 hour storage time at 2 – 8°C. These growth promotion studies are necessary to ensure that potential contamination can be observed when the unpreserved drug product is diluted in 0.9% sodium chloride or 5% dextrose. While the growth rates of organisms are slow at 2 - 8°C generally, dextrose can be a growth-promoting medium, especially for certain Gram-negative bacteria. Thus, the goal of the study is to confirm that there is no significant growth of organisms at 2 - 8°C in the drug product diluted with 0.9% sodium chloride and 5% dextrose.

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 sponsor committed to performing microbiological challenge studies using diverse microorganisms to support the 24 hour storage time at 2 - 8°C in the drug product diluted with 0.9% sodium chloride and 5% dextrose to confirm that there is no significant growth of organisms to support the 24 hour storage time. The study will also include Gram negative microorganisms (such as *E. coli* and/or *E. cloacae*) which are known to proliferate in these solutions. The challenge studies should include at a minimum time points at twice the label claim storage time.

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

BLA # BLA 761069 Imfinzi (durvalumab)
Product Name:

PMC Description: Reevaluate the ADA confirmatory and triple mutation assay cut points using a 1.0% false positive rate.
3205-4

PMC Schedule Milestones:

Study Completion:	10/2017
Final Report Submission:	04/2018

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

   This is a priority review of a new therapeutic monoclonal antibody and the ADA method analysis used to confirm anti-drug antibody needs to be repeated to more accurately determine ADA rate for product labeling.

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

   FDA guidance recommends that a 1% false positive rate be used to determine the cut points for the confirmatory and triple mutation assay. The cut points provided in the BLA uses a 0.1% false positive rate. This may underestimate ADA rates. Thus, the Sponsor needs to reanalyze the immunogenicity data.

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:

We will contact the sponsor in the near future to coordinate this PMC. An information request has already been sent to the sponsor during the review informing the sponsor that the cut points were not set correctly.

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

BLA #	BLA 61069
Product Name:	Imfinzi (durvalumab)
PMC Description: 3205-5	Conduct drug tolerance studies for the screening, confirmatory, titering, and triple mutation assays that are in the range of the Ctrough of 182 ug/ml to better demonstrate that the assay can detect ADA in the presence of drug.

PMC Schedule Milestones:

Study Completion:	12/2017
Final Report Submission:	06/2018

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

   This is a priority review for a new therapeutic monoclonal antibody and the method is used to determine if the anti-drug antibody (ADA) assays are sensitive to interference with drug in patient serum.

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

   3. FDA guidance recommends that ADAs methods be developed that can detect ADA in the presence of drug. The results in the ADA method validation are suboptimal because additional concentrations of drug (between 100 ug/ml and 1 mg/ml) need to be evaluated to determine if the ADA methods are inhibited by drug in patient serum (Ctrough-182 ug/ml).

4. [OMIT – for PMRs only]

5. 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:

6. 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

BLA #	BLA 761069/0
Product Name:	durvalumab
PMC Description: 3205-6	Conduct a third media fill simulating worst case conditions for the durvalumab aseptic fill process. Include product contact parts and perform growth promotion studies (b) (4) of the media fill.

PMC Schedule Milestones:

Final Report Submission:	09/2017
Other: Study results will be submitted as a DMF update.	09/2017

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

Currently, the durvalumab fill process is supported by only two media fills (b) (4). The durvalumab fill process may occur over a period (b) (4). The firm has provided data from other media fills that cover the maximum filling duration (b) (4). However, these media fills do not use durvalumab product contact parts. Thus, the request for a third media fill will simulate worst case conditions and fill duration for the durvalumab fill process is appropriate as a PMC.

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

The durvalumab fill process may occur over a period (b) (4). Only two media fills were performed utilizing durvalumab product contact parts. However, the total fill processing times for these media fills lots are (b) (4). Therefore, a media fill simulating worst case durvalumab fill conditions and duration will be performed using product contact parts.

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 holder of DMF (b) (4) committed to perform a third media fill simulating worst case conditions for the durvalumab aseptic fill process that includes durvalumab product contact parts. The growth promotion studies and results of this lot will be provided.

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)

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

/s/

CHRISTINA D MARSHALL
05/04/2017

KATHERINE M FEDENKO
05/04/2017

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	In vitro diagnostic immunohistochemistry (IHC) for detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) human tissue sections
Device Trade Name:	VENTANA PD-L1 (SP263) Assay
Device Procode:	PLS
Applicant's Name and Address:	Ventana Medical Systems, Inc. 1910 E Innovation Park Drive Tucson, AZ 85755
Date(s) of Panel Recommendation:	None

Premarket Approval Application (PMA) Number: P160046

Date of FDA Notice of Approval: TBD

II. INDICATIONS FOR USE

VENTANA PD-L1 (SP263) Assay is a qualitative immunohistochemical assay using rabbit monoclonal anti-PD-L1 clone SP263 intended for use in the assessment of the PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) urothelial carcinoma tissue stained with OptiView DAB IHC Detection Kit on a VENTANA BenchMark ULTRA instrument.

PD-L1 status is determined by the percentage of tumor cells with any membrane staining above background or by the percentage of tumor-associated immune cells with staining (IC+) at any intensity above background. The percent of tumor area occupied by any tumor-associated immune cells (Immune Cells Present, ICP) is used to determine IC+, which is the percent area of ICP exhibiting PD-L1 positive immune cell staining. PD-L1 status is considered High if any of the following are met:

- $\geq$ 25% of tumor cells exhibit membrane staining; or,
- ICP > 1% and IC+ $\geq$ 25%; or,
- ICP = 1% and IC+ = 100%.

PD-L1 High status as determined by VENTANA PD-L1 (SP263) Assay was associated with increased objective response rate (ORR) in a single arm study of IMFINZI™ (durvalumab).

This product is intended for *in vitro* diagnostic (IVD) use.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the VENTANA PD-L1 (SP263) Assay product labeling.

V. DEVICE DESCRIPTION

VENTANA PD-L1 (SP263) Assay contains optimized reagents required to complete an immunohistochemical staining procedure for FFPE specimens on the BenchMark ULTRA automated staining instrument visualized using the OptiView DAB IHC Detection Kit. VENTANA PD-L1 (SP263) Assay includes a recombinant rabbit monoclonal antibody produced as purified cell culture supernatant and contains sufficient reagent for 50 tests. The antibody and detection reagents are provided as ready-to-use dispensers, as seen below in

Table 1.

Table 1. Overview of the VENTANA PD-L1 (SP142) Assay Components

Device Components	Packaged form	Description
VENTANA anti-PD-L1 (SP263) Rabbit Monoclonal Primary Antibody	Dispenser: 50 test	One 5 mL dispenser of VENTANA PD-L1 (SP263) contains approx. 8.05 µg of a rabbit monoclonal antibody. The antibody is diluted in 0.05 M Tris-HCI with 1% carrier protein, and 0.10% ProClin 300, a preservative. Total protein concentration of the reagent is approx. 10 mg/mL. Specific antibody concentration is approx. 1.61 µg/mL.
OptiView DAB IHC Detection Kit	Set of 6 dispensers packaged in a kit: 250 tests	**OptiView Peroxidase Inhibitor** contains 3.0% hydrogen peroxide solution.
		OptiView HQ Universal Linker contains a cocktail of HQ-labeled (HQ is a proprietary hapten covalently attached to the goat antibodies) antibodies (goat anti-mouse IgG, goat anti-mouse IgM, and goat anti-rabbit) (<50 µg/mL) in a buffer containing protein with ProClin 300, a preservative.
		OptiView HRP Multimer contains a mouse monoclonal anti-HQ-labeled HRP tertiary antibody (<40 µg/mL) in a buffer containing protein with ProClin 300, a preservative.
		OptiView H2O2 contains 0.04% hydrogen peroxide in a phosphate buffer solution.

Table 1. Overview of the VENTANA PD-L1 (SP142) Assay Components		
Device Components	**Packaged form**	**Description**
		OptiView DAB contains 0.2% 3, 3'-diaminobenzidine tetrahydrochloride (DAB) in a proprietary stabilizer solution with a proprietary preservative.
		OptiView Copper contains copper sulfate (5.0 g/L) in an acetate buffer with a proprietary preservative.
BenchMark ULTRA (IHC/ISH) automated staining instrument and VSS system software	Instrument installed with the VSS host system software	A PC that runs on Microsoft Windows controls and monitors the BenchMark ULTRA instrument via the host operating software.
		The BenchMark ULTRA software has been developed per FDA's guidance on the development of Medical Device Software.
Rabbit Monoclonal Negative Control Ig	1 dispenser packaged as 250 test kit	Intended for laboratory use as a control for nonspecific binding of rabbit immunoglobulin (Ig) in sections of FFPE tissue. One 25 mL dispenser contains approximately 250 µg of a rabbit monoclonal antibody. The antibody is diluted in 0.08 M PBS with 3% carrier protein and 0.05% ProClin 300, a preservative.

Device Instrumentation and Software

The VENTANA PD-L1 (SP263) Assay is performed on the BenchMark ULTRA automated staining instrument using the VSS Software. The VENTANA PD-L1 (SP263) Assay protocol is assay specific. The software has been designed to recognize and group VENTANA PD-L1 (SP263) Assay, requiring that all system reagents are used together.

Specimen Preparation

Routinely processed, FFPE tissues are suitable for use with this VENTANA PD-L1 (SP263) Assay. The recommended tissue fixation protocol is 10% neutral buffered formalin (NBF) for a period of at least 6 hours and for a maximum of 72 hours. Acceptable fixatives for use with VENTANA PD-L1 (SP263) are Zinc Formalin and Z-5 fixatives when used with at least 6 hours of fixation time. The amount used should be 15 to 20 times the volume of tissue. Fixation can be performed at room temperature (15°C - 25°C). Other fixatives, including 95% alcohol, AFA and PREFER, are not acceptable for use with the VENTANA PD-L1 (SP263) Assay.

Sections approximately 4-5 μm thick should be cut and mounted on positively-charged slides. Slides should be stained promptly, as antigenicity of cut tissue sections may diminish over time and is compromised within 6 months after cutting from the paraffin block for urothelial carcinoma specimens (UC) and 9 months for placenta specimens. See the Package Insert for additional details.

Quality Control Procedures

Run controls are included in each staining run to establish the validity of the test results. Ventana, in the device labeling, instructs that the following controls to be run with the assay.

A. **Placenta Tissue Control**

A tissue control must be included with each staining run. Qualified normal human term placental tissue is to be used as the control. Control tissue should be fixed as soon as possible and processed in a manner identical to patient tissues. Such tissue may monitor all steps of the analysis, from tissue preparation through staining. Placental tissue contains positive and negative staining elements for the PD-L1 protein and is therefore suitable for use as a tissue control. The positive and negative staining tissue components are used to confirm that the assay functioned properly.

Placental tissue shows moderate to strong uniform staining of the membrane and weak to strong uniform staining of the cytoplasm of trophoblast-lineage cells. Placental stromal tissue and vasculature can be used for assessment of any background staining.

B. **Rabbit Monoclonal Negative Control Ig**

A matched negative reagent control slide must be run for every specimen to aid in the interpretation of results. Rabbit Monoclonal Negative Control Ig, a negative reagent control antibody, is specifically matched for this assay and is used in place of the primary antibody to evaluate nonspecific staining. The staining procedure for the negative reagent control should equal the primary antibody incubation period. Use of a different negative control reagent, or failure to use the recommended negative control reagent, may cause false results.

Principles of Operation

Use of the VENTANA PD-L1 (SP263) Assay is fully automated on the BenchMark ULTRA automated slide stainer, from deparaffinization through counterstaining. Patient FFPE tissue specimens are cut to approximately 4-5 μm thick and mounted on positively charged glass slides. These slides are loaded into the Benchmark ULTRA instrument. This system first removes the paraffin wax from the tissue, and then subjects the tissue to heated antigen retrieval (cell conditioning). Antigen retrieval is the process by which the ability of antibodies to bind to the epitopes is restored to formalin-fixed tissues. Endogenous peroxidases that could potentially react with the horseradish peroxidase conjugates (HRP)

are blocked with OptiView Inhibitor (3% H2O2). After the endogenous peroxidase block, the VENTANA PD-L1 (SP263) Rabbit Monoclonal Primary Antibody is dispensed during the antibody incubation step and allowed to bind to its antigen. The slides are then incubated with the reagents in the OptiView DAB IHC Detection Kit, which is an indirect, biotin-free system for detecting mouse IgG, mouse IgM, and rabbit primary antibodies which produces a visible dark brown precipitate (3,3'-Diaminobenzidine) via a horseradish peroxidase (HRP) enzymatic reaction at the antigen site. Tissues are then counterstained blue using Hematoxylin II and Bluing Reagent to create brown/blue contrast to aid the pathologist when reviewing the slides using bright field microscopy.

Interpretation of PD-L1 Staining

The VENTANA automated immunostaining procedure causes a brown colored DAB reaction product to precipitate at the antigen sites localized by the VENTANA PD-L1 (SP263) Assay. The stained slide(s) are interpreted by a qualified pathologist using light microscopy. A qualified pathologist experienced in IHC procedures must evaluate tissue controls and qualify the stained product before interpreting results.

A. **Placenta Tissue Control**

A tissue control must be included with each staining run. Qualified normal human term placental tissue is to be used as the control. Control tissue should be fixed as soon as possible and processed in a manner identical to patient tissues. Such tissue may monitor all steps of the analysis, from tissue preparation through staining. Placental tissue contains positive and negative staining elements for the PD-L1 protein and is therefore suitable for use as a tissue control. The positive and negative staining tissue components are used to confirm that the assay functioned properly.

Placental tissue shows moderate to strong uniform staining of the membrane and weak to strong uniform staining of the cytoplasm of trophoblast-lineage cells. Placental stromal tissue and vasculature can be used for assessment of any background staining.

B. **Negative Reagent Control**

Non-specific staining, if present, will have a diffuse appearance and can be evaluated using the negative reagent control slide stained with Rabbit Monoclonal Negative Control Ig. Intact cells should be used for interpretation of staining results, as necrotic or degenerated cells often stain nonspecifically. If background staining is excessive, results from the test specimen should be considered invalid. Please refer to the VENTANA PD-L1 (SP263) Assay Interpretation Guide (P/N 1014738US) for Urothelial Cancer for additional details.

C. **Patient Tissue**

Patient tissue must be evaluated according to the VENTANA PD-L1 (SP263) Assay scoring algorithm provided in Table 2. Refer to the VENTANA PD-L1 (SP263) Assay Package Insert and VENTANA PD-L1 (SP263) Assay Interpretation Guide for Urothelial Cancer for additional details. Background staining is also evaluated and is deemed acceptable if Acceptable the background does not interfere with interpretation of PD-L1 status.

Table 2. VENTANA PD-L1 (SP263) Assay Scoring Algorithm for Urothelial Carcinoma

PD-L1 Interpretation	**Staining Description**
PD-L1 status is determined by the percentage of tumor cells with any membrane staining above background or by the percentage of tumor-associated immune cells with staining (IC+) at any intensity above background. The percent of tumor area occupied by any tumor-associated immune cells (Immune Cells Present, ICP) is used to determine IC+, which is the percent area of ICP exhibiting PD-L1 positive immune cell staining is also evaluated.	
High	PD-L1 Status is considered High if any of the following are met: • ≥ 25% of tumor cells exhibit membrane staining; or, • ICP > 1% and IC+ ≥ 25%; or, • ICP = 1% and IC+ = 100%.
Low/negative	PD-L1 Status is considered Low/negative if: • none of the criteria for PD-L1 High Status are met.

The VENTANA PD-L1 (SP263) Assay stained urothelial carcinoma tissue will be evaluated for tumor cell (TC) and immune cell (IC) staining. The cellular staining pattern for VENTANA PD-L1 (SP263) is membranous and/or cytoplasmic staining of tumor cells. Immune cells demonstrate linear membrane, diffuse cytoplasmic, and/or punctate staining.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There is currently no alternative FDA-cleared or approved immunohistochemistry assay available for detection of PD-L1 in FFPE urothelial cancer tissues to estimate the likelihood of response for patients treated with IMFINZI™ (durvalumab).

VII. MARKETING HISTORY

The VENTANA PD-L1 (SP263) Assay has not been marketed in the United States or any foreign country for use as an *in vitro* diagnostic kit.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect PD-L1 test results, and an inaccurate estimate of a patient's benefit from durvalumab and subsequently improper interpretation of the benefit/risks for patients with urothelial carcinoma who are considering treatment with durvalumab.

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

Preclinical studies were performed using the VENTANA PD-L1 (SP263) Assay to establish analytical performance of device. This assay was run using a VENTANA BenchMark ULTRA instrument using the VSS software version 12.2. These studies were conducted to characterize the assay, demonstrate the impact of pre-analytical variables on assay performance, verify precision and robustness of the assay, and establish assay stability. The study results detailed below establish sensitivity, specificity, precision and reproducibility of the device.

A. Laboratory Studies

1. Analytical Specificity

The antibody used in the VENTANA PD-L1 (SP263) Assay is Rabbit Anti-Human PD- L1/CD274 Monoclonal Antibody (Clone SP263). The molecular weight of the antibody's target (PD-L1) is 32 kDa, and the SP263 clone specifically targets a 19 amino acid sequence at the cytoplasmic tail of PD-L1. The following studies were conducted with PD-L1 (SP263) antibody to establish antibody specificity.

a. Western Blot Studies

Western blot analysis was performed on whole cell lysates from 4 cell lines with varying expression levels of PD-L1. The 4 cell lines were H820 (Lung), MDA-231 (Breast), H1975 (Lung) and Calu-3 (Lung). The cell lines were chosen for this study based on IHC staining for PD-L1 (SP263). Independent confirmation of the relative expression levels was based on assessment of mRNA expression levels for PD-L1. No unexpected staining or background was observed in any of the whole cell lysates. A second Western Blot analysis was performed to demonstrate that the PD-L1(SP263) antibody detected recombinant PD-L1 and did not detect recombinant PD-L2.

b. *Blast Results For SP263 Epitope*

PD-L1 is a member of the B7 family of ligands. PD-L1 (SP263) targets 7 amino acids in the cytoplasmic tail of PD-L1. NCBI BLASTp was used to search for sequence similarity using the SP263 epitope and no significant similarity was found to any other B7 family members.

c. *Peptide Inhibition Studies*

The specificity of primary antibody binding to PD-L1 was assessed by pre-incubating the antibody with four different concentrations of the specific peptide containing the antibody binding epitope, or a non-specific peptide. The antibody was diluted 1:1 with either the peptide solution under investigation or buffer with no peptide. One lot of antibody was used for this study. In the presence of high molar concentrations of this peptide, the PD-L1 SP263 antibody was completely inhibited from binding to tissue expressing PD-L1 protein as determined by the absence of IHC staining. The non- specific peptide had no effect on PD-L1 staining.

d. *Immunoreactivity in Human Tissues:*

One lot of VENTANA PD-L1 (SP263) Assay and Rabbit Monoclonal Negative Control Ig were used to stain slides of a commercially available multi-tissue array of normal and neoplastic tissue and evaluated by a PD-L1 (SP263) trained qualified reader for presence of positive staining, staining intensity, and background in tumor cells, tumor infiltrating immune cell, and normal cells.

A total of 93 normal tissues and 54 neoplastic tissues were analyzed in this study. The normal formalin-fixed, paraffin-embedded (FFPE) tissues included 25 common types of normal human organs which represent three cases per organ type from three unique individuals. Results for normal tissues are shown in Table 3 and results for neoplastic tissues are shown in Table 4.

Table 3. VENTANA PD-L1 (SP263) Assay staining of FFPE normal tissues.

Tissue	# positive/ total cases	Tissue	# positive/ total cases
Adrenal gland	0/3*	Mesothelium	0/3†
Bladder	0/3	Myeloid (bone marrow)	0/4*,†
Breast	0/3	Nerve (sparse)	0/3

Tissue	# positive/ total cases	Tissue	# positive/ total cases
Cerebellum	0/3	Ovary	0/3
Cerebrum	0/3	Pancreas	0/3*
Cervix	0/3	Parathyroid gland	0/4
Colon	0/3†	Prostate	0/3
Endometrium	0/3	Salivary gland	0/3†
Esophagus	1/3*,†	Skeletal muscle	0/3
Heart	0/3	Skin	0/4§
Hypophysis	0/3*,†	Spleen	0/3†
Intestine, small	0/3†	Stomach	0/3*,†
Kidney	0/3†	Testis	0/3
Larynx	0/3†	Thymus gland	0/3†
Liver	0/3	Thyroid	0/3*,†
Lung	0/3†	Tonsil	3/3†
Lymph node	0/3†		
Additional staining observed: * Cytoplasmic staining, † Immune cell staining, § Melanocyte staining. Percent of IC present above background cannot be evaluated in this study because there is no tumor area for which to score tumor infiltrating immune cells.			

Table 4. VENTANA PD-L1 (SP263) Assay staining of FFPE neoplastic tissues for any tumor cell or immune cell staining.

Origin	Pathology	# positive/total cases	
		Immune cells	Tumor cells
Cerebrum	Glioblastoma	0/1	1/1
Cerebrum	Atypical meningioma	0/1	0/1
Cerebrum	Malignant ependymoma	0/1	1/1
Cerebrum	Oligodendroglioma	0/1	0/1
Ovary	Serous adenocarcinoma	0/1	1/1
Ovary	Adenocarcinoma	0/1	0/1

Origin	Pathology	# positive/total cases	
		Immune cells	Tumor cells
Pancreas	Islet cell carcinoma	1/1	0/1
Pancreas	Adenocarcinoma	0/1	1/1
Testis	Seminoma	0/1	0/1
Testis	Embryonal carcinoma	0/1	0/1
Thyroid	Medullary carcinoma	0/1	0/1
Thyroid	Papillary carcinoma	1/1	0/1
Breast	Intraductal carcinoma	0/1	1/1
Breast	Invasive ductal carcinoma	0/2	0/2
Spleen	Diffuse B-cell lymphoma	0/1	1/1
Lung	Small cell undifferentiated carcinoma	1/1	1/1
Lung	Squamous cell carcinoma	1/1	1/1
Lung	Adenocarcinoma	0/1	0/1
Esophagus	Neuroendocrine carcinoma	0/1	0/1
Esophagus	Adenocarcinoma	0/1	0/1
Stomach	Signet-ring cell carcinoma	0/1	0/1
Intestine	Adenocarcinoma	0/1	0/1
Intestine	Stromal sarcoma	0/1	0/1
Colon	Adenocarcinoma	0/1	1/1
Colon	Interstitialoma	0/1	0/1
Rectum	Adenocarcinoma	0/1	0/1
Rectum	Moderate malignant interstitialoma	0/1	0/1
Liver	Hepatocellular carcinoma	0/1	0/1

Origin	Pathology	# positive/total cases	
		Immune cells	Tumor cells
Liver	Hepatoblastoma	0/1	0/1
Kidney	Clear cell carcinoma	0/1	0/1
Prostate	Adenocarcinoma	0/2	0/2
Uterus	Leiomyoma	0/1	0/1
Uterus	Adenocarcinoma	0/1	0/1
Uterus	Clear cell carcinoma of endometrium	0/1	0/1
Uterine cervix	Squamous cell carcinoma	0/2	2/2
Striated muscle	Embryonal rhabdomyosarcoma	0/1	0/1
Rectum	Malignant melanoma	0/1	0/1
Skin	Basal cell carcinoma	0/1	0/1
Skin	Squamous cell carcinoma	0/1	0/1
Back	Neurofibroma	0/1	1/1
Retroperitoneal	Neuroblastoma	0/1	0/1
Abdominal cavity	Malignant mesothelioma	0/1	0/1
Mediastinum	Diffuse B-cell lymphoma	1/1	1/1
Lymph node	Hodgkin's lymphoma	1/1	1/1
Lymph node	Diffuse B-cell lymphoma	1/1	1/1
Pelvic cavity	Anaplastic large cell lymphoma	1/1	1/1
Bladder	Low grade malignant leiomyosarcoma	0/1	0/1
Bone	Osteosarcoma	0/1	1/1
Retroperitoneum	Spindle cell rhabdomyosarcoma	0/1	0/1
Smooth muscle	Moderate malignant	0/1	0/1

Origin	Pathology	# positive/total cases	
		Immune cells	Tumor cells
	leiomyosarcoma		
Bladder	Transitional cell carcinoma (bladder)	1/1	1/1

2. Analytical Sensitivity

Analytical sensitivity was tested on total of 211 commercially sourced unique cases of urothelial carcinoma FFPE specimens that were tested with a single lot of antibody. A total of 169 of the 211 tissues were classified as PD-L1 high using the PD-L1(SP263) scoring criteria for urothelial carcinoma.

3. Repeatability

Repeatability studies for VENTANA PD-L1 (SP142) Assay staining of urothelial carcinoma specimens were completed to demonstrate:

a. Intra-day Repeatability – Five replicate slides each from the 13 unique urothelial carcinoma specimens were stained with VENTANA PD-L1 (SP263) Assay on a single BenchMark ULTRA instrument within one day.

b. Inter-day Precision – Two replicate slides each from the 13 unique urothelial carcinoma specimens were stained with VENTANA PD-L1 (SP263) Assay on a single Benchmark ULTRA instrument across 5 non-consecutive days spanning at least a 20 day period.

c. Inter-instrument and Inter-lot Precision – 27 replicate slides each from the 22 unique urothelial carcinoma specimens were stained with VENTANA PD-L1 (SP263) Assay using three lots of VENTANA PD-L1 (SP263) antibody and three lots of OptiView DAB IHC Detection Kit, on three BenchMark ULTRA instruments.

The 13 unique cases used for the Intra-day Repeatability and Inter-day Precision Studies had a case distribution of 9 PD-L1 High and 4 PD-L1 Low with 6 borderline cases for either the tumor cell or immune cell component of the scoring criteria. For intra-day repeatability, each case had 5 antibody slides, the mode of which determined the PD-L1 status for that case. For inter-day precision, each case had 10 antibody slides, the mode of which determined the PD-L1 status for that case.

The 22 unique cases used for the Inter-instrument and Inter-lot Precision Study had an overlapping case distribution of 13 PD-L1 High and 9 PD-L1 Low. Each case contributed one observation for each of the 9 combinations of antibody lot

and detection kit lot per instrument (27 observations in total per case). A reference PD-L1 status was established as the mode of all slides for each case and stratification level.

All slides were blinded and randomized, and then evaluated using the VENTANA PD-L1 (SP263) Assay scoring algorithm. Results are summarized in Table 5.

Table 5. Repeatability and Intermediate Precision of VENTANA PD-L1 (SP263) Assay staining of urothelial carcinoma specimens.

Repeatability/Intermediate precision parameter	Positive Agreement %* (95% CI)	Negative Agreement %* (95% CI)	Overall agreement % (95% CI)
Intra-day Repeatability (within a single day) N=65	100.0% (45/45) (92.1 – 100%)	95.0% (19/20) (76.4 – 99.1.0%)	98.5% (64/65) (91.8 – 99.7%)
Inter-day Precision (5 non-consecutive days) N = 130	100.0% (90/90) (95.9 – 100%)	100.0% (40/40) (91.2 – 100%)	100.0% (130/130) (97.1 – 100%)
Inter-instrument and Inter-lot Precision (3 instruments, 3 antibody lots, and 3 detection and amplification kit lots) N=594	98.3% (345/351) (96.3 – 99.2%)	99.6% (242/243) (97.7 – 99.9%)	98.8% (587/594) (97.6 – 99.4%)

*Confidence intervals were calculated using the Wilson Score method.

4. External Reproducibility

An Inter-laboratory Reproducibility Study for VENTANA PD-L1 (SP263) Assay was conducted to demonstrate reproducibility of the assay in determining PD-L1 expression in urothelial carcinoma tissue specimens. Twenty-six urothelial carcinoma specimens (18 PD-L1 High and 8 PD-L1 Low, with 4 borderline specimens for either the tumor or immune cell component of the scoring criteria) were stained at 3 external laboratories on each of 5 non-consecutive days over 20-days. At each site, the stained slides were independently evaluated by 2 pathologists (readers). The final staining acceptability rate for the VENTANA PD-L1 (S263) Assay was 99.7% in this study.

Results are summarized in Table 6.

Table 6. Inter-laboratory Reproducibility of VENTANA PD-L1 (SP263) Assay staining of urothelial carcinoma specimens.

Inter-laboratory Reproducibility	Positive agreement % (95% CI)	Negative agreement % (95% CI)	Overall agreement % (95% CI)
Overall agreement (across sites, days and readers) n =778 observations	95.2% (512/538) (93.0-96.7%)*	85.8% (206/240) (80.9-89.7%)*	92.3% (718/778) (90.2-94.0%)*
Inter-site agreement (average of site-to-site pairwise comparisons) n =7760 pairs	91.1% (84.2-95.8%)**	79.1% (61.9-89.1%)**	87.5% (86.8-88.2%)**
Inter-reader agreement (average of reader-to-reader pairwise comparisons within each site) n =389	90.1% (492/546) (82.3-95.7%)**	76.7% (178/232) (58.2-88.4%)**	86.1% (335/389) (82.3-89.2%)**
* Confidence intervals were calculated using the Wilson Score method. ** Percentile Bootstrap confidence intervals were constructed from the 2.5th and 97.5th percentiles using 2,000 replicates when sampling at the case level.			

The point estimate and lower bounds of the 95% confidence interval for NPA were below 80% for the Inter-site agreement and Inter-reader agreement analyses. The lower than expected estimates may be in part due to the few (n=8) PD-L1 Low/negative samples that were included in this study which can result in a less robust estimate of NPA. As a result, Ventana will be performing an a Inter-laboratory reproducibility study which with sufficient PD-L1 Low/negative samples to provide a robust estimate of NPA. Ventana will update the VENTANA PD-L1(SP263) Assay package insert when those results become available. Refer to the current package insert for any updates to these analytical studies.

5. Reader Precision

To assess Inter- and Intra-reader Precision, three pathologists evaluated fifty unique urothelial carcinoma specimens (22 PD-L1 high and 28 PD-L1 low) that were stained with VENTANA PD-L1 (SP263) Assay. Specimens were blinded and randomized prior to evaluation for PD-L1 status. Readers scored all specimens twice, with a minimum of two weeks between reads. Intra-reader agreement rate between the first and second read was calculated for each reader

separately and then averaged across three readers. Inter-reader agreement rates were based the weighted average across all reader permutations for the first set of reads (i.e., Reader 1 vs. Reader 2, Reader 1 vs. Reader 3 and Reader 2 vs. Reader 3). Agreement rates are measured as positive percent agreement, negative percent agreement, and overall percent agreement and are summarized in Table 7.

Table 7. Inter- and Intra-reader Precision of VENTANA PD-L1 (SP263) Assay staining of urothelial carcinoma specimens.

Reader Precision	Positive agreement % (95% CI)	Negative agreement % (95% CI)	Overall agreement % (95% CI)
Inter-reader Precision (average of all three readers'comparisons) N=143 pairs	92.8% (128/138) (85.5-98.3%)	93.2% (138/148) (86.5-98.5%)	93.0% (133/143) (87.1-98.6%)
Intra-reader Precision (average of all three readers' agreement rates between first and second reads) N=145 pairs	92.1% (128/139) (85.4-96.7%)	92.7% (140/151) (87.1-96.8%)	92.4% (134/145) (87.2-96.6%)

6. Impact of Tissue Specimen Preparation and Treatment Studies

a. Ischemia Study (Time to Fixation)

The objective of this study was to evaluate the effects of ischemic time on PD-L1 antigenicity as detected by staining with VENTANA PD-L1 (SP263) Assay. This study examined the effects of delay to fixation (Ischemia) for mouse xenografts at zero hour, 0.5 hours, 1 hour, 2 hours, 6 hours and 24 hours post excision, under refrigeration at 2-8°C. All samples were fixed in 10% NBF for 24 hours after being delayed for fixation at their various ischemia time points. The Assay demonstrated no significant change in staining intensity from hour zero to up to 24 hours using a xenograft tissue model.

b. Fixation Study

The objective of this study was to evaluate the effects of fixative type and fixation time on PD-L1 antigenicity as detected by staining with VENTANA PD-L1 (SP263) Assay. Two tonsil tissue cases were fixed for 1, 6, 12, 24, and 72 hours in six fixatives: 10% NBF, Zinc formalin, 95%

alcohol, AFA, Z-5 and PREFER for a total of 12 tissues. The data was then compared to the reference standard of 10%NBF for 24 hours.

Tissues fixed for one hour in 10% NBF, Zinc formalin and Z-5 were unacceptable when stained with PD-L1 (SP263). All other time points (6, 12, 24 and 72 hour) in 10% NBF, Zinc formalin and Z-5 were acceptable with the VENTANA PD-L1 (SP263) Assay. The VENTANA PD-L1 (SP263) Assay demonstrated poor performance on the following fixatives at all time points: PREFER, AFA, and 95% alcohol. PREFER, AFA, and 95% alcohol should not be used as a fixative for anti-PD-L1.

7. Impact of Tissue Thickness Studies

The objective of this study was to evaluate the staining performance of the VENTANA anti-PD-L1 (SP263) Assay on seven urothelial carcinoma tissues sectioned at various thicknesses (2 to 7 microns). At each thickness, two slides from each case were stained with VENTANA PD-L1 (SP263) CDx Assay and one slide was stained with Rabbit Monoclonal Negative Control lg to serve as a negative reagent control slide. This study demonstrated 100% concordance with PD-L1 status for all seven cases at all thickness of 3-7 microns. Ventana recommends that specimens be cut at 4-5 microns for the assay.

8. Impact of Cut Slide Stability

The objective of this study is to determine a time point at which the degradation of PD-L1 antigenicity occurs in formalin-fixed, paraffin-embedded (FFPE) urothelial carcinoma tissue sectioned on positively charged microscope slides after storage in two temperature conditions, 4°C and 30°C.

Four tissues were used for this study. Slides sectioned and stained at the day 0 time point served as the baseline comparator for the remainder of the time points tested. Tissue was sectioned from each of four cases onto glass slides and separated into two different storage conditions for the duration of the study. One box was stored at refrigerated temperature condition (4°C) and one at the incubator temperature condition (30°C) to simulate room temperature. Slides were stained at each pre-defined designated time point (monthly intervals) and staining results for each time point were compared to the Day Zero baseline slides.

PD-L1 antigen stability was determined to be 6 months for slides stored at 30°C and five months for slides stored at 4°C.

9. PD-L1 (SP263) Status in Matched Primary vs. Metastatic Urothelial Cancers.

Patients were enrolled into the clinical trial on the basis of PD-L1 status testing either primary or metastatic tumor tissue. This study was executed to compare the concordance of PD-L1 status between primary urothelial carcinoma and matched metastatic tumors in tissues. The concordance of PD-L1 status between 49 commercially sourced patient matched Primary and Metastatic Tumor urothelial carcinoma samples demonstrated an overall concordance of 63.3% (31 /49) for PD-L1 status with 60.0% (9/15) positive percent agreement and 64.7% (22/34) negative percent agreement. Results are shown in Table 8.

Table 8. Comparison of Primary Vs Metastatic tumor urothelial carcinoma specimens staining with VENTANA PD-L1 (SP263) Assay

	Primary Tumor		
Metastatic Tumor	**Positive**	**Negative**	**Total**
Positive	9	12	21
Negative	6	22	28
Total	15	34	49
Positive Percent Agreement (PPA) n/N (%) (95% CI)	9 / 15 (60.0%) (35.7 – 80.2)		
Negative Percent Agreement (NPA) n/N (%) (95% CI)	22 / 34 (64.7%) (47.9 – 78.5)		
Overall Percent Agreement (OPA) n/N (%) (95% CI)	31 /49 (63.3) (49.3 – 75.3%)		

10. Impact of Tissue Block and Intra-Case Heterogeneity

a) Intra-Block Heterogeneity

The intent of this study was to characterize the intra-block heterogeneity in urothelial carcinoma tissue blocks by evaluating the PD-L1 status for tumor cells and tumor-associated immune cells of multiple slide cuts from the same tissue block when stained with VENTANA PD-L1 (SP263) Assay. Five unique formalin-fixed, paraffin-embedded (FFPE) urothelial carcinoma tissues, which included three transurethral resections of the bladder (TURB) and two resection specimens, were sectioned to exhaustion. Duplicate slides from approximately every 5th section for the first 30 sections and approximately every 10th section thereafter were stained with VENTANA PD-L1 (SP263) Assay. Three out of the five cases tested maintained the same PD-L1 status throughout the block. Both cases with inconsistent PD-

L1 status were TURB specimens that were borderline positive based on either immune cell staining or tumor cell staining.

b) Intra-case heterogeneity

The intent of this study was to characterize UC case heterogeneity when multiple blocks from the same patient case were stained with the VENTANA PD-L1 (SP263) Assay. Forty three cases with two blocks per case were evaluated in this study. A total of thirty-four of the forty-three (79%) cases maintained the same PD-L1 status between blocks.

11. Stability Testing

The objective of this study is to assess the stability (shelf-life and in-use) and shipping category on 3 lots of the VENTANA PD=L1 (SP263) Assay. Dispensers from each of the 3 antibody lots were subjected to different stress conditions and then placed at intended storage (2-8°C) for the duration of the study. The stress conditions were as follows:

a. Intended storage (2-8°C) for the duration of the study.
b. Product held at 30±5°C for 192±5 hours, and then places at 2-8°C for the duration of the study.
c. Product held at 15±5°C for 192±5 hours, and then places at 2-8°C for the duration of the study.
d. Product held at -20±5°C for 192±5 hours, and then places at 2-8°C for the duration of the study.

Four urothelial carcinoma, 4 squamous carcinoma head and neck and 4 non-small cell lung carcinoma tissues were used for this study. Tissues are tested in triplicate at each time point. All lots passed for all conditions and support an 11 month stability claim.

B. Animal Studies

None

C. Additional Studies

None

X. SUMMARY OF PRIMARY CLINICAL STUDY

A. Study Design

The clinical performance of VENTANA PD-L1(SP263) Assay was evaluated in a single arm, multi-center, open label study of IMFINZI™ (durvalumab) on patients with locally advanced or metastatic urothelial carcinoma. Patients had progressed while on or after a platinum-based therapy, including those who progressed within 12 months of receiving therapy in a neo-adjuvant or adjuvant setting. All patients received IMFINZI at 10mg/kg every 2 weeks for up to 12 months until unacceptable toxicity or confirmed disease progression.

Tumor specimens were evaluated prospectively using VENTANA PD-L1 (SP263) Assay at a central laboratory and the results were used to define subgroups based on PD-L1 expression. The first 20 patients were enrolled regardless of PD-L1 expression. The next 43 patients that were enrolled required tumor expression of PD-L1 $\geq$ 5% positive staining. The remaining patients were enrolled regardless of PD-L1 status.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment was limited to patients who met the following inclusion criteria:
   - Adult (>18 years)
   - Patients must have histologically or cytologically confirmed inoperable or metastatic transitional cell carcinoma of the urothelium (including transitional cell and mixed transitional cell/nontransitional cell histologies) carcinoma of the urothelium (including the urinary bladder, ureter, urethra, and renal pelvis).
   - Subjects must have received and have progressed or are refractory to at least 1 but not more than 2 prior lines of systemic therapy for inoperable or metastatic disease, including a standard platinum-based regimen. Interval progression between 2 lines of therapy defines separate lines of therapy. Prior definitive chemoradiation for locally advanced disease, adjuvant treatment, or neoadjuvant treatment will be considered a prior line of therapy, provided that progression has occurred < 12 months from therapy [for chemoradiation and adjuvant treatment] or < 12 months from surgery [for neoadjuvant treatment]
   - Subjects must have consented to provide an archived tumor specimen from within 6 months prior to study entry or provide a pretreatment fresh biopsy.
   - Eastern Cooperative Oncology Group (ECOG) status of 0 or 1

   Patients were not permitted to enroll if they met any of the following exclusion criteria:

   - History of primary immunodeficiency
   - Receipt of any immunotherapy, or investigational anticancer therapy within 4 weeks prior to the first dose of IMFINZI and no mAb therapy (for investigational use or immunotherapy) within 6 weeks prior to the first dose of durvalumab.

   Prior treatment with immunotherapy agents including, but not limited to, tumor necrosis factor receptor superfamily agonists or checkpoint inhibitors or natural killer

(NK) cell inhibitors including agents targeting KIR, PD-1, PD-L1, CTLA-4, OX40, CD27, CD137 (4-1BB), CD357 (GITR), and CD40. Prior treatment with Bacillus Calmette-Guerin therapy was permitted.

2. Follow-up Schedule

   Follow up for Efficacy:
   Tumor assessments were performed at Weeks 6, 12 and 16, then every 8 weeks for the first year and every 12 weeks thereafter.

   Follow up for Safety:
   Patients were closely monitored for safety and tolerability throughout the study at each patient contact. Safety assessments consisted of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest, measurement of protocol-specified safety laboratory assessments, measurement of protocol-specified vital signs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study. An adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. Patients were followed for safety for 30 days following their last dose of study treatment (in both the initial treatment period and the re-treatment period) or until they receive another anti-cancer therapy, whichever comes first.

3. Clinical Endpoints

   The primary efficacy outcome measures were confirmed Objective Response Rate (ORR) according to RECIST v1.1 as assessed by Blinded Independent Central Review (BICR) and duration of response (DoR).

B. Accountability of PMA Cohort

A total of 451 subjects were screened for enrollment in study 1. Eighty seven (of 451) subjects were excluded prior to submitting a tissue sample for testing with the VENTANA PD-L1 (SP263) Assay because they either did not meet inclusion/exclusion criteria (n=68), consent was withdrawn (n=12), no tissue was available for testing (n=5) or subject enrolled in another study (n=2). This resulted in 364 patients with sufficient tissue available to be considered in the intent to diagnose population.

Three hundred sixty three (363) of 364 subjects were tested with VENTANA (SP263) assay and 173 subjects were excluded from the clinical trial because they did not meet inclusion criteria based on PD-L1 testing (n=89), they did not meet other inclusion/exclusion criteria (n=74) or withdrawal of consent (n=10).

One hundred and ninety one patients were treated with IMFINZI. Nine patients were excluded from efficacy analysis of IMFINZI because they were not 2nd-line post-platinum patients. The remaining 182 subjects were included in the primary efficacy

analysis for IMFINZI. Of the 182 enrolled patients who met the inclusion criteria, 128 were enrolled without regard to PD-L1 status and after the PD-L1 scoring algorithm were finalized. The analyses with respect to drug efficacy by PD-L1 status are limited to these 128 patients.

C. Study Population Demographics and Baseline Parameters

The median age of the patients was 66 years, 72% were male, 64% patients were Caucasian. Thirty-four percent had non-bladder urothelial carcinoma and 66% of patients had visceral metastases, including 34% with metastases to the liver, which portends a worse prognosis. Nineteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Thirty-five percent of patients had received ≥ 2 prior systemic regimens in the metastatic setting. Seventy (70) percent of patients received prior cisplatin and 30% had prior carboplatin. One patient was previously treated with oxaliplatin.

D. Safety and Effectiveness Results

1. Safety Results

   As an in vitro diagnostic test, the VENTANA PD-L1 (SP263) Assay involves testing on FFPE urothelial carcinoma specimens. These tissues are routinely removed as part of the practice of medicine for the diagnosis of urothelial carcinoma by pathologists. Removal of these tissues, therefore, presents no additional safety hazard to the patient being tested.

2. Effectiveness Results

   Tissues from 363 patients were submitted for testing with VENTANA PD-L1(SP263) Assay. PD-L1 status was obtained for 332 (91.5%) and 31 (8.5%) were not evaluable. PD-L1 status was not evaluable for 31 patients due to insufficient tumor cells present in sample (n=25), inappropriate tissue being submitted (n=3), tissue folding (n=1), dye trapping (n=1) or tissue washing off the slide (n=1). There were no instances where a sample was non-evaluable for PD-L1 status due to assay failure.

   The analysis of effectiveness of VENTANA PD-L1(SP263) Assay was based on the 128 patients that were enrolled into study 1 without regard to PD-L1 status and after the PD-L1 scoring algorithm was finalized. The primary efficacy outcome measures were confirmed Objective Response Rate (ORR) according to RECIST v1.1 as assessed by Blinded Independent Central Review (BICR) and duration of response (DoR). Table 9 summarizes the results in Study 1. The median follow-up time was 5.6 months.

Table 9. Efficacy Results for Study 1

	Final PD-L1 Assay[1] N = 128		
	PD-L1 High N = 58	**PD-L1 Low/Negative N = 56**	**PD-L1 NE N = 14**
Objective Response Rate by BICR n (%) (95% CI)	11 (19.0%) (9.9, 31.4)	2 (3.6%) (0.4, 12.3)	3 (21.4%) (4.7, 50.8)
Complete Response	2	0	1
Partial Response	9	2	2
Median Duration of Response months (range)	NE (0.9+, 4.2)	NR (1.9+, 4.2+)	NR (2.3+, 2.6+)

[1]Enrolled regardless of PD-L1 status; BICR = Blinded Independent Central Review; NE = Not Evaluable; NR = Not Reached, + denotes a censored value

The VENTANA PD-L1 (SP263) Assay is intended to be used on either primary tumor tissue or metastases. Concordance of the VENTANA PD-L1 (SP263) Assay PD-L1 comparing matched primary and metastatic urothelial cancers found 18/49 pairs (36.6%) pairs gave discordant results. As an exploratory analysis, efficacy data from Study 1 was stratified by source of biopsy (tumor vs. metastatic). Similar associations were observed between PD-L1 status and drug efficacy in patients whose PD-L1 status was determined by primary tissue compared to those patients whose status was determined by metastatic tissue.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Hematology and Pathology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The clinical performance of VENTANA PD-L1 (SP263) Assay was investigated in Study 1, was evaluated in a non-randomized, multi-center, open label study of IMFINZI (durvalumab) on patients with locally advanced or metastatic urothelial carcinoma. Patients had progressed while on or after a platinum-based therapy, including those who progressed within 12 months of receiving therapy in a neo-adjuvant or adjuvant setting. All patients received IMFINZI (durvalumab) at 10mg/kg every 2 weeks for up to 12 months until unacceptable toxicity or confirmed disease progression. High PD-L1 status as determined by VENTANA PD-L1 (SP263) Assay was associated with increased objective response rate (ORR) in this trial.

The performance of the VENTANA PD-L1 (SP263) Assay was also supported by the analytical validation studies.

B. Safety Conclusions

The VENTANA PD-L1 (SP263) Assay is an in vitro diagnostic device, which tests tumor FFPE specimens collected from patients with urothelial carcinoma. The risks of the device are based on data collected in the clinical study. Failure of the device to perform as expected may lead to a failure to correctly interpret test results. The process of testing on FFPE tumor specimens does not present additional significant safety concerns, as these samples are routinely removed for diagnosis.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. High PD-L1 status, as determined by VENTANA PD-L1(SP263) Assay, is associated with increased ORR for patients with locally advanced or metastatic urothelial carcinoma that have progressed while on or after a platinum-based therapy who are treated with IMFINZI (durvalumab). This assay may help physicians determine the best treatment regimen and tailor therapies accordingly. The main risk of the VENTANA PD-L1 (SP263) Assay is in getting a false result and the potential to adversely affect patient management. However, since this test result does not dictate the choice of therapy

and patients that are classified as either PD-L1 High or PD-L1 Low/Negative may receive a benefit from IMFINZI, the risks caused by a false result is relatively low.

1. Patient Perspectives

   This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for

VENTANA PD-L1 (SP263) Assay is a qualitative immunohistochemical assay using rabbit monoclonal anti-PD-L1 clone SP263 intended for use in the assessment of the PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) urothelial carcinoma tissue stained with OptiView DAB IHC Detection Kit on a VENTANA BenchMark ULTRA instrument.

PD-L1 status is determined by the percentage of tumor cells with any membrane staining above background or by the percentage of tumor-associated immune cells with staining (IC+) at any intensity above background. The percent of tumor area occupied by any tumor-associated immune cells (Immune Cells Present, ICP) is used to determine IC+, which is the percent area of ICP exhibiting PD-L1 positive immune cell staining. PD-L1 status is considered High if any of the following are met:

- ≥ 25% of tumor cells exhibit membrane staining; or,
- ICP > 1% and IC+ ≥ 25%; or,
- ICP = 1% and IC+ = 100%.

PD-L1 High status as determined by VENTANA PD-L1 (SP263) Assay was associated with increased objective response rate (ORR) in a single arm study of IMFINZI™ (durvalumab).

This product is intended for *in vitro* diagnostic (IVD) use.

the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIII. CDRH DECISION

CDRH issued an approval order on TBD.

The final conditions of approval cited in the approval order are described below.

1. The clinical study that was used to support the VENTANA PD-L1(SP263) Assay was a single cohort study in which a portion of the cohort was used to train the device. Therefore additional data is needed to provide assurance the results are generalizable to the post-approval target population. Submit the results from the ongoing, confirmatory studies of durvalumab in urothelial bladder cancer to provide an estimate of the association between your PD-L1 status and the clinical response to durvalumab. Submit updated labeling to include the results of this study.

2. Abbreviated study design and limited numbers of samples from the intended use specimen type were used in repeatability and precision studies for the PD-L1 (SP263) Assay in urothelial carcinoma. Additional testing of samples and analyses with appropriate study design is required for a more robust characterization of these analytical validation studies of your device. Include the results from these studies in the updated labeling.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

Aaron J. Schetter -S
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/s/

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04/26/2017
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LABEL AND LABELING REVIEW AMENDMENT

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:	March 14, 2017
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	BLA 761069
Product Name and Strength:	Imfinzi (Durvalumab) Injection, 50 mg/mL
Total Product Strength:	500 mg/10 mL and 120 mg/2.4 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	AstraZeneca Pharmaceuticals LP
Submission Date:	October 17, 2016 and December 22, 2016
OSE RCM #:	2016-2536
DMEPA Primary Reviewer:	Tingting Gao, PharmD
OMEPRM Acting Deputy Director:	Lubna Merchant, MS, PharmD

REASON FOR AMENDMENT:

FDA recently issued a final guidance entitled *Nonproprietary Naming of Biological Products* on January 13, 2017 stating the Agency's intention to designate proper names for certain biological products that include four-digit distinguishing suffixes. This 351(a) application is within the scope of this guidance. However, the issuing of the guidance occurred at a point in our review of the application that did not allow for sufficient time for FDA to designate a proper name with a suffix, as described in the guidance. Therefore, in order to avoid delaying the approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix [and intend to work with the applicant post-approval to implement a proper name consistent with the principles outlined in the guidance].

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:	December 28, 2016
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	BLA 761069
Product Name and Strength:	Imfinzi (Durvalumab) Injection, 500 mg/10 mL and 120 mg/2.4 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	AstraZeneca Pharmaceuticals LP
Submission Date:	October 17, 2016 December 22, 2016
OSE RCM #:	2016-2536
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

AstraZeneca submitted the container labels, carton labeling, and prescribing information (PI) for Imfinzi (Durvalumab) Injection for BLA 761069. This is a New Molecular Entity (NME) product with a proposed indication for the treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4) (b) (4).

The Division of Oncology Products 1 (DOP1) requested that we review the submitted Imfinzi container labels, carton labeling, and PI 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
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the proposed Imfinzi container label and noticed that this is a small label since the height of the vial is only 4.5 cm, and the surface area of the vial for container label is 3.1 cm in height. Therefore, although the container label does not contain the NDC number and the usual dose statement, the container label does contain the minimum amount of information required per 21 CFR 201.10(i). However, we recommend that the statement "IMFINZI is a trademark of the AstraZeneca group of companies © AstraZeneca XXXX" be replaced with the statement "Must dilute before use. See prescribing information." on the side panel to minimize the risk of the product administered without dilution. We also plan to clarify what the (b) (4) box is with the Applicant. The proposed carton labeling is acceptable from a medication error perspective.

We reviewed the proposed Imfinzi PI and recommend adding unit of measurement at the end of each numerical doses for clarity. We also recommend specifying the appropriate volume for the intravenous bag, and providing minor editorial edits for the preparation instructions for clarity.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container label, carton labeling and PI labeling for Imfinzi may be improved to promote the safe use of the product as described in Section 4.1 and Section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
    a. Dosage and Administration section, Full PI
        i. Consider adding a unit of measurement after each numerical dose in Table 1 for clarity. For example, “1 mg/kg/day to 2 mg/kg/day”.
        ii. In section 2.3, consider specifying the appropriate volume of the intravenous bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP for clarity.
        iii. In section 2.3, relocate the sentence “Do not shake the solution.” after the sentence “Mix diluted solution by gentle inversion.” for clarity.

4.2 RECOMMENDATIONS FOR ASTRAZENECA

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

A. Container label
    a. Replace the statement “IMFINZI is a trademark of the AstraZeneca group of companies © AstraZeneca XXXX” with “Must dilute before use. See prescribing information.” on the side panel to minimize the risk of the product administered without dilution.
    b. Clarify what the (b) (4) square box is on the side panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Imfinzi that AstraZeneca submitted on October 13, 2016.

Table 2. Relevant Product Information for Imfinzi	
Initial Approval Date	N/A
Active Ingredient	durvalumab
Indication	Treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4) (b) (4)
Route of Administration	Intravenous
Dosage Form	Solution for injection
Strength	50 mg/mL
Dose and Frequency	10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks. Dose escalation or reduction is not recommended. Dosing withholding or discontinuation may be required based on individual safety and tolerability.
How Supplied	Supplied in a carton containing one single-dose vial: • 500 mg/10 mL • 120 mg/2.4 mL
Storage	Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in original carton to protect from light
Container Closure	**Vial:** (b) (4) USP/Ph. Eur./JP Type I (b) (4) **Stopper:** (b) (4) (b) (4) USP/Ph. Eur./JP **Seal:** (b) (4), (b) (4)

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Clinical Inspection Summary

Date	March 8, 2017
From	Lauren Iacono-Connors, Reviewer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H, Branch Chief Division of Clinical Compliance Evaluation (DCCE)
To	Janice Kim, Regulatory Project Manager Daniel Suzman, Clinical Reviewer Division of Oncology Products 1
BLA #	761069
Applicant	AstraZeneca UK Limited
Drug	Durvalumab (MEDI4736)
NME	Yes
Therapeutic Classification	Priority
Proposed Indication	Treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) (b) (4)
Consultation Request Date	November 3, 2016
Summary Goal Date	Updated: March 8, 2017 (Original: February 24, 2017)
Action Goal Date	March 13, 2017
PDUFA Date	June 13, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study CD-ON-MEDI4736-1108 were submitted to the Agency in support of BLA 761069. Three clinical sites, Dr. Collin Blakely (Site 2001024), Dr. Peter O'Donnell (Site 2000112), Dr. Alexander Spira (Site 2001023), and the study sponsor, MedImmune LLC, were selected for audit.

The primary efficacy endpoint, objective response rate (ORR) as determined by the clinical investigators, was verified with the source records generated at the inspected clinical sites. There were no significant inspectional findings for clinical investigators Dr. Collin Blakely, Dr. Alexander Spira, and study sponsor MedImmune LLC.

Significant regulatory violations were identified at Dr. Peter O'Donnell's site. Regulatory violations included substantial under reporting of AEs in the datasets submitted to support the application. Based on these findings, we recommend that the review division conduct sensitivity analyses for efficacy and safety with and without the data from Dr. Peter O'Donnell's site.

The data from all inspected sites associated with Study CD-ON-MEDI4736-1108 appear reliable.

II. BACKGROUND

AstraZeneca seeks approval of durvalumab (MEDI4736) for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) (b) (4) (b) (4).

The following overview of the Study CD-ON-MEDI4736-1108 is intended as background context for interpreting the inspectional findings.

Study CD-ON-MEDI4736-1108 is a Phase 1/2, multicenter, open-label, first-time-in-human (FTIH), dose-escalation, dose-exploration, and dose-expansion study to evaluate the safety, tolerability, PK, immunogenicity, and antitumor activity of durvalumab in adult subjects with advanced solid tumors. Subjects enrolled into the urothelial carcinoma (UC) Cohort were the focus of these inspections. Subjects in the UC cohort must have had histologically- or Cytologically-confirmed inoperable or metastatic transitional cell (including transitional cell and mixed transitional cell/non-transitional cell histologies) carcinoma of the urothelium (including the urinary bladder, ureter, urethra, and renal pelvis). The study enrolled 191 subjects (UC) at 79 clinical centers in nine countries.

Study Period: Study initiation date (first subject enrolled): August 28, 2012
Data cut-off date for primary analysis (UC): July 24, 2016
Primary efficacy endpoint: Objective Response (OR), defined as a best overall response of confirmed response (CR) or partial response (PR) according to RECIST v1.1 as determined by a Blinded Independent Review Center (BIRC).
Objectives of Inspections:

a. Assess primary efficacy endpoint source documentation; including dates of imaging timepoints, investigator assessed tumor response and evidence of imaging transfer to the BIRC. Verify that this information corroborates the best confirmed response of CR or PR as assessed by the BIRC using RECIST Version 1.1.
b. Identification, documentation, and reporting of adverse events (AEs) for a sample of enrolled subjects.
c. General compliance with the investigational plan.

III. RESULTS (by site):

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI#1: Collin Blakely (Site 2001024) University of California San Francisco Medical Center, 1600 Divisadero St 4th Floor San Francisco, CA 94115	Protocol: CD-ON-MEDI4736-1108 Subjects: 6	January 4-13, 2017	Preliminary Classification NAI
CI #2: Peter O'Donnell (Site 2000112) University of Chicago Comprehensive Cancer Center, 5841 South Maryland Avenue MC 2115 Chicago, IL 60637	Protocol: CD-ON-MEDI4736-1108 Subjects: 8	December 13, 2016 – January 19, 2017	Preliminary Classification OAI
CI #3: Spira, Alexander (Site 2001023) Virginia Cancer Specialists, PC, 8503 Arlington Boulevard Suite 400 Fairfax, VA 22031	Protocol: CD-ON-MEDI4736-1108 Subjects: 5	January 3-6, 2017	Preliminary Classification NAI
Sponsor: MedImmune LLC (a wholly owned subsidiary of AstraZeneca) One MedImmune Way Gaithersburg, MD 20878	Protocol: CD-ON-MEDI4736-1108 Site Numbers: 2000112, 2001023, and 2001024	December 6-9, 2016	Preliminary Classification NAI

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

1. Dr. Collin Blakely, M.D. (Site 2001024)

The site screened 11 subjects and enrolled six subjects into the UC cohort. At the time of this inspection, four subjects had discontinued from the study. A complete record review was done for all subjects. Signed informed consent documents were reviewed and confirmed for subjects. Study subject source documents were compared to the eCRF and data listings submitted to BLA 761069, focusing on AE/SAEs, tumor assessments, protocol deviations, and general protocol and GCP compliance.

The inspection revealed no significant deficiencies. The primary endpoint is the confirmed Best Overall Response for each subject, per RECIST 1.1, as determined by the BIRC. Source documents at the site corroborated primary efficacy endpoint data reported by the BIRC. The secondary efficacy endpoint, OR per the investigator, was verifiable. There was no evidence of under-reporting of AEs.

2. Dr. Peter O'Donnell, M.D. (Site 2000112)

Dr. O'Donnell was the third Principal Investigator for Site 2000112. Dr. Hedy Kindler was the Principal Investigator from 11/11/2013 – 3/9/2015; Dr. Jason Luke from 3/10/2015 – 2/9/2016; and Dr. O'Donnell from 2/10/2016 until this inspection. Twenty-nine subjects were screened and 10 subjects were enrolled at Site 2000112, including 8 subjects with urothelial carcinoma (UC). At the time of this inspection all eight UC subjects had discontinued due to progressive disease or death. A complete record review was done for the eight enrolled subjects with UC. Protocol compliance, data verification, informed consent process/documentation, Serious Adverse Event (SAE) and Adverse Event (AE) reporting, study endpoints, institutional review board (IRB) approvals and communications, monitoring, subject screening and eligibility, study drug accountability and storage, facilities, study staff financial disclosure, delegation of tasks, and training were reviewed.

Source documents at the site corroborated primary efficacy endpoint data reported by the BIRC. Efficacy endpoints as determined by the clinical investigator(s) were also verified. A Form FDA 483 was issued at the conclusion of the inspection citing four inspectional observations. Noteworthy deficiencies are summarized below.

Seven UC Subjects;1553, 1221, 2360, 1747, 1662, 2506 and 2442, had one SAE that was not reported to the sponsor within the protocol-specified 24 hours of the site becoming aware of the SAE. Of the seven late reported SAEs, three occurred and were reported to the sponsor, albeit late, prior to the data cut-off date for analysis (July 24, 2016). Briefly, the site became aware on June 16, 2015 that Subject 1553 died on (b) (6), but did not report the SAE for until July 16, 2015. The site became aware on March 6, 2015, that Subject 1221 had grade 3 acute kidney injury that began on February 17, 2015, but the site did not report the SAE until March 12, 2015. The site became aware on April 4, 2016 that Subject 2360 had a grade 2 pleural effusion event that began on March 29, 2016, but the site did not report the SAE until May 5, 2016. These three SAEs were included in the data listings submitted to the application.

Four SAEs were not included in the data listings submitted to the application because, with one exception, the site did not become aware of these SAEs until after the data cut-off date for analysis. Briefly, the site became aware on December 8, 2016 that Subject 1747 died on (b) (6), but did not report the SAE until January 3, 2017. The site became aware on December 9, 2016 that Subject 1662 had died on (b) (6) (b) (6), but did not report the SAE until January 3, 2017. The site became aware on July 19, 2016 that Subject 2506 had died on (b) (6), but the site did not report

the SAE until July 28, 2016. This SAE could have been included in the datalistings had the site reported the SAE within 24 hours of awareness of the event. Finally, the site became aware on August 9, 2016 that Subject 2442 died on (b) (6), but did not report the SAE until October 11, 2016. The protocol deviations noted here should not importantly impact study outcomes.

The protocol specifies follow-up visits to include the following; End of Treatment (EOT); Day 14; Day 30; Month 2; Month 3; Month 4; Month 6; Month 8; Month 10; Month 12, and then every 6 months thereafter. The protocol specifies that AE/SAE assessment must occur at each visit up to and including the Month 3 visit and survival status assessment will begin at every visit starting with the Month 2 visit and allows for phone contact with subjects who refuse to return for evaluations. Follow-up visits were not performed for three UC Subjects; 1221, 1747, and 1662. These subjects were improperly identified as having withdrawn consent. However, each of these subjects stopped study treatment and entered hospice care. Therefore, the subjects were in follow-up status and the site was still responsible for the study subjects' follow-up per the protocol. These protocol violations resulted in limited follow-up of late AEs.

Study records show that Subject 1221 was discontinued from treatment due to toxicity in the absence of progressive disease. Subject 1221 received their last dose of MEDI4736 on February 17, 2015. Subject 1221 was seen on March 17, 2015 for their EOT visit and one last time on April 14, 2015 for their 30 day follow-up visit. The site did not schedule any additional follow-up visits and there was no attempt to contact Subject 1221 by phone to follow-up on AEs/SAEs after April 14, 2015. The status of this subject is unknown. The protocol violation data listing for Subject 1221 includes the following missing protocol-specified follow-up visits; 14-Day post visit, 4 month post visit, 6 month post visit, and 8 month post visit. Protocol violations also included missing blood laboratory assessment from the 3-month post visit. This listing of missed protocol-specified follow-up visits is an incomplete accounting of missed study visits for Subject 1221 while in follow-up status.

Subject 1747 received their first dose of study treatment on June 9, 2015 and discontinued study treatment on June 30, 2015 due to disease progression. Subject 1747 died (b) (6). Subject 1662 discontinued from treatment due to progressive disease. Subject 1662 received their first dose of study treatment on June 16, 2015, and their last dose of MEDI4736 on July 28, 2015. There was no EOT visit or any follow-up visits for this subject. There was no attempt to contact Subject 1662 by phone to follow-up on AEs/SAEs. The subject entered hospice on September 18, 2015 and died (b) (6) The missed study visits, EOT, and all subsequent follow-up visits, for Subject 1662 were not included as protocol deviations in the data listings submitted to the application.

These protocol violations resulted in limited follow-up of AEs for these subjects. Dr. O'Donnell concurred with the inspectional findings in a written response, dated February 2, 2017.

He committed to updating subject records and eCRFs and provided a corrective action plan to minimize these inspectional findings moving forward.

It was noteworthy that the inspection revealed that for four subjects, (1221, 1747, 2306, and 2442) there were numerous incidences where AEs were not reported to the sponsor according to protocol specifications. As such, these AEs were not included in the data listings submitted to the application. These unreported AEs, in many cases, were not assessed for grade, study drug relationship, and whether these were serious events. During the inspection the site staff reviewed all source documents for all study subjects and identified all AEs in subject records and whether they had been reported to the sponsor. Based upon a preliminary review of the Establishment Inspection Report, Subject 1221 had 17 unreported AEs, Subject 1747 had 12 unreported AEs, Subject 2306 had 17 unreported AEs, and Subject 2442 had 3 unreported AEs prior to the current inspection. For the four subjects listed above, a total of 42 AEs were reported to the sponsor prior to this inspection and a total of 49 additional AEs had not been reported to the sponsor. Examples of all AEs found in source documents and those reported prior to the inspection are provided below for Subject 1221 and Subject 2442 as examples.

Reported and Unreported AEs – Subject 1221
AE Description and Date of Occurrence
Reported Prior to the Inspection (N=5)
bilateral lower extremity edema (12/2/2014 – 12/16/2014)
insomnia (11/20/2014 – 11/21/2014)
neuropathy bilateral feet (1/20/2015 – 2/3/2015)
acute kidney injury - Grade 3 (2/25/2015 - 3/17/2015) *related
acute kidney injury - Grade 1 (3/17/2015 – ongoing) *related
Not evaluated or Reported until the Inspection (N=17)
tremor (3/17/2015 – unknown)
blurry vision (3/17/2015 – unknown)
labile mood (3/17/2015 – unknown)
skin changes (3/17/2015 – unknown)
leg edema (2/2015 – unknown)
chest discomfort (3/17/2015 – unknown)
anemia – Grade 2 (1/6/2015 - 3/17/2015)
acute kidney injury – Grade 2 (1/20/2015 – 2/25/2015) *related
acute kidney injury – Grade 1 (12/16/2014 – 1/20/2015) *related
dyspnea on exertion (2/3/2015 – 2/17/2015)
hematuria (5/2015 – unknown)
nausea (3/6/2015 – 3/17/2015)
elevated BUN (2/17/2015 - unknown) *related
anorexia (12/16/2014 - 1/20/2015)
face rash (2/25/2015 – 3/6/2015) *related
face rash (5/15/2015 – ongoing) *related
anemia – Grade 1 (3/17/2015 – ongoing)

Reported and Unreported AEs – Subject 2442
AE Description and Date of Occurrence
Reported Prior to the Inspection (N=10)
diarrhea – Grade 1 (4/21/2016 – 5/3/2016)
diarrhea – Grade 2 (5/3/2016 – 5/17/2016) *related
leukocyturia (5/3/2016 - ongoing)
diarrhea – Grade 1 (5/17/2016 – 6/2/2016)
AST increase – Grade 3 (6/2/2016 – 7/14/2016) *related
hyperkalemia (6/2/2016 – 6/2/2016)
difficulty sleeping (6/9/2016 – 7/14/2016)
ALT increase – Grade 3 (6/2/2016 - 7/14/2016) *related
elevated ALT – Grade 3 (8/9/2016 - 9/6/2016) *related
elevated AST – Grade 3 (8/9/2016 - 9/6/2016) *related
Not Evaluated or Reported Until the Inspection (N=3)
elevated ALT – Grade 1 (9/6/2016 - ongoing) *related
elevated ALT – Grade 2 (7/26/2016 – 8/9/2016) *related
elevated AST – Grade 1 (7/26/2016 – 8/9/2016) *related

OSI Review Notes: Dr. O'Donnell indicated in a written response, dated February 2, 2017, to the Form FDA 483, inspectional observations, that he concurred with the inspectional observations of protocol deviations and unreported AEs, discovered during the inspection. According to the FDA field investigator, and Dr. O'Donnell's written response, the clinical site study staff updated records as appropriate to capture the unreported AEs as well as other noted protocol deviations identified during the inspection. The protocol deviations and unreported AEs discovered during the inspection were transcribed into each subject's eCRF. Therefore, the study clinical data base should now be updated to reflect all AEs documented for all subjects enrolled at this site. The AE data listings submitted to the original application were verified; however, the data listings under-represented AEs documented in source records at this site.

The inspectional observations were communicated to Dr. Ellen Maher, DOP1 CDTL for the application. Dr. Maher reviewed the preliminary findings and confirmed that a subset of these AEs were key events that could impact overall study outcomes for safety. A sensitivity analysis excluding the UC cohort subjects from Site 2000112 was conducted to assess the impact, if any, on AE incidence rates for the UC cohort in Study CD-ON-MEDI4736-1108. The results of the sensitivity analysis were that if the eight UC study subjects enrolled at this site are excluded from the analysis of AEs, the incidence of grade 1-4 AEs becomes 172/174 (99%) and grade 3-4 AEs becomes 92/174 (53%). These rates are identical to the incidence of grade 1-4 AEs and grade 3-4 AEs in all 182 evaluable subjects. Therefore, the safety data from this site does not importantly impact overall study outcomes for safety.

The preliminary classification for this inspection is OAI (official action indicated). OSI conducted a thorough review of the inspectional findings, the actions taken by Dr. O'Donnell and study site staff during the inspection, and the corrective action plan included in the written response, dated February 2, 2017, to the Form FDA 483,

inspectional observations. OSI concluded that a classification of OAI is not warranted because, while regulatory violations exist, the regulatory violations should not have a significant impact on data integrity or the rights, safety, or welfare of subjects. The inspection classification has been downgraded to VAI.

3. Dr. Alexander Spira, M.D. (Site 2001023)

The site screened 10 subjects and enrolled five subjects into the UC cohort. At the time of this inspection, four subjects had completed the study and one subject withdrew consent. A complete record review was done for all enrolled subjects. Signed informed consent documents were reviewed and confirmed for all subjects. Study subject source documents were compared to the eCRF and data listings submitted to BLA 761069, focusing on AE/SAEs, tumor assessments, protocol deviations, and general protocol and GCP compliance.

The inspection revealed no significant deficiencies. Source documents at the site corroborated primary efficacy endpoint data reported by the BIRC. Efficacy endpoints as determined by the clinical investigator were also verified. There were several incidences where AEs were reported in the eCRFs after the data cut-off date for analysis. This affected two study subjects' AE listings.

Briefly, the source documents and notes-to-file for Subject 1897 revealed that the subject consistently reported that they felt great and did not have any issues [AEs] at each study visit. Subject 1897 was hospitalized, (b) (6), for a grade 3 UTI and did inform the site of the hospitalization. When the site staff accessed the hospital EMR for Subject 1897 to obtain the details of the SAE event, they found additional visits with the subject's primary care physician documenting numerous unreported AEs. According to the FDA field investigator, the additional AEs were listed in the subject's AE Log and were entered into the eCRF system, but after the data cut-off date. Subject 2140 had additional AEs added to the eCRF in December 2016 at the request of the clinical monitor. The AEs and concomitant medications were related to the subject's hospitalization (b) (6). AEs associated with the hospitalization that were included in the data listings submitted to the application includes grade 3 subcutaneous abscess (b) (6), grade 3 small intestinal obstruction (b) (6)), and grade 4 sepsis (b) (6). Subject 2140 withdrew consent on October 26, 2015.

OSI Reviewer Note: Subject 1897 was the only subject who completed the study with 12 months of study treatment. In addition, according to the BIRC, Subject 1897 achieved a CR at study Day 64 and maintained a CR through the final tumor assessment on study day 333, with a duration response of a minimum of 291 days. A review of the 90 Day-AE data listing update submitted to the application on January 9, 2017 found no additional AE entries for Subject 1897. Therefore, for Subject 1897 the AEs that are included in the data listings are valid but the AEs for this subject may be under-represented. It is unlikely that the missing AEs would alter overall study outcomes because of the isolated nature of the event.

4. Sponsor: MedImmune LLC

The inspection focused on the sponsor's control, oversight, and management of Study CD-ON-MEDI4736-1108. Records reviewed included monitoring reports, study site investigator agreements, financial disclosure forms, test article accountability records, test article storage and shipping conditions, study site monitoring reports, correspondence, SAEs and data line listings submitted to the application. Other records reviewed included the firm's procedures, contracts and agreements, and training records.

The inspection revealed no significant deficiencies. There was no evidence of under-reporting of AEs. Documents at the site corroborated primary efficacy endpoint data, BOR for each subject, per RECIST 1.1, as determined by the BIRC. The study records were complete and in compliance with FDA regulations. The sponsor provided protocols, investigator brochures, and Site Initiation Visit (SIV) training to each site. Data from CRFs and external vendors, such as ECGs or imaging data, was received in Medidata Rave. Monitoring was provided by CRO (b) (4). Review of the clinical management plan and all SOPs pertaining to monitoring found no deficiencies. No sites were terminated due to serious non-compliance; however, two sites were placed on hold temporarily for noncompliance. A review of the firm's correspondence related to these sites being placed on hold demonstrated resolution of compliance issues before reactivation. The monitoring for this study by MedImmune LLC appears to have been adequate to ensure investigator compliance and to verify study data.

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

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

cc:
Central Doc. Rm. BLA #761069
DOP1/Division Director/Geoffrey Kim
DOP1/Clinical Team Leader/V. Ellen Maher
DOP1/Project Manager/Janice Kim
DOP1/Medical Officer/Daniel Suzman
OSI/Office Director (Acting)/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Susan D. Thompson
OSI/DCCE/GCP Reviewer/Lauren Iacono-Connors
OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

LAUREN C IACONO-CONNORS
03/08/2017

SUSAN D THOMPSON
03/08/2017

KASSA AYALEW
03/08/2017

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

PATIENT LABELING REVIEW

Date:	March 3, 2017
To:	Geoffrey Kim, MD Director **Division of Oncology Products 1 (DOP1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Linda Park, PharmD, MS, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TRADENAME (durvalumab)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761069
Applicant:	AstraZeneca

1 INTRODUCTION

On October 12, 2016, AstraZeneca submitted for the Agency's review a Biologics License Application (BLA) 761069 for TRADENAME (durvalumab) injection. The proposed indication for TRADENAME (durvalumab) is for the treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4) (b) (4).

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 1 (DOP1) on November 21, 2016, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRADENAME (durvalumab) injection.

2 MATERIAL REVIEWED

- Draft TRADENAME (durvalumab) injection MG received on October 12, 2016, and received by DMPP and OPDP on February 17, 2017.
- Draft TRADENAME (durvalumab) injection Prescribing Information (PI) received on October 12, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 17, 2017.
- Approved TECENTRIQ (atezolizumab) comparator labeling dated May 18, 2016.

3 REVIEW METHODS

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

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

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- 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/

MORGAN A WALKER
03/03/2017

LINDA M PARK
03/03/2017

BARBARA A FULLER
03/03/2017

LASHAWN M GRIFFITHS
03/05/2017

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

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

Memorandum

Date: March 2, 3017

To: Janice Kim, Regulatory Project Manager
Division of Oncology Products (DOP1)

From: Linda Park, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Susannah O'Donnell, Team Leader, OPDP

Subject: BLA 761069
Imfinzi (durvalumab) injection, for intravenous infusion
OPDP Comments on proposed labeling

OPDP has reviewed the proposed Package Insert (PI), Medication Guide (MG), and the Carton/Container Labeling as requested in your consult dated November 4, 2016.

OPDP's comments are based on the substantially complete version of the proposed PI titled, "durvalumab package-insert-complementary-diagnostic(2).VEM-1.docx" accessed via the DOP1 SharePoint website on February 21, 2017. OPDP's comments are provided directly in the attached document.

Combined Division of Medical Policy Programs (DMPP) and OPDP comments on the proposed Medication Guide will be provided to DOP1 under separate cover.

Carton and Container Label

OPDP has reviewed the proposed carton/container labeling, obtained from the EDR link (Application 761069 – Sequence 0042 – 1.14 Labeling) on February 8, 2017, and has the following comment:

OPDP notes that the graphic logo presented in conjunction with the tradename on the carton labeling may make a misleading representation about the benefit or mechanism of action of the drug. Specifically, the graphic logo may represent an arrow pointing to a

target and may imply that this drug targets only tumor cells, when this is not the case. OPDP recommends deleting the logo.

Thank you for your consult. If you have any questions regarding this consult review, please contact Linda Park at (240) 402-7942 or Linda.Park@fda.hhs.gov.

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/s/

LINDA M PARK
03/02/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	February 28, 2017
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	BLA 761069
Product Name and Strength:	Imfinzi (Durvalumab) Injection, 500 mg/10 mL and 120 mg/2.4 mL
Submission Date:	February 8, 2017
Applicant/Sponsor Name:	AstraZeneca Pharmaceuticals LP
OSE RCM #:	2016-2536-2
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

The Division of Oncology Products (DOP1) requested that we review the revised container labels and carton labeling for Imfinzi (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] Additionally, AstraZeneca provided additional clarification (b) (4)

We reviewed AstraZeneca's response with the understanding (b) (4) he serialization requirements of the Drug Supply Chain Security Act and the linear bar code rule at 21 CFR 201.25. Therefore, the revised Imfinzi container labels and carton labeling are acceptable from a medication error perspective.

[a] Gao T. Label and Labeling Review for Imfinzi (BLA 761069). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 FEB 2. 8 p. OSE RCM No.: 2016-2536-1.
[b] AstraZeneca Pharmaceuticals LP. BLA 761069 Imfinzi (durvalumab): Response to FDA Information Request – Carton/Container Labels. Gaithersburg (MD): AstraZeneca Pharmaceuticals LP. 2017 Feb 8.

2 CONCLUSION

The revised Imfinzi container labels and carton labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDIX A. LABEL AND LABELING SUBMITTED ON FEBRUARY 8, 2017

Container labels

(b) (4)

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/s/

TINGTING N GAO
02/28/2017

CHI-MING TU
02/28/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 2, 2017
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	BLA 761069
Product Name and Strength:	Imfinzi (Durvalumab) Injection, 500 mg/10 mL and 120 mg/2.4 mL
Submission Date:	January 10, 2017
Applicant/Sponsor Name:	AstraZeneca Pharmaceuticals LP
OSE RCM #:	2016-2536-1
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

The Division of Oncology Products (DOP1) requested that we review the revised container labels and carton labeling for Imfinzi (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] Additionally, AstraZeneca clarified that the (b) (4) box on the side panel of the carton near LOT and EXP is being reserved for US serialization barcode. (b) (4)

2 DISCUSSION

The revised Imfinzi container labels and carton labeling are unacceptable from a medication error perspective. As currently present, the strength per milliliter ("50 mg/mL") competes for prominence with the strength per total volume (120 mg mg/2.4 mL and 500 mg/10 mL)

[a] Gao T. Label and Labeling Review for Imfinzi (BLA 761069). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 DEC 28. 11 p. OSE RCM No.: 2016-2536.

[b] AstraZeneca Pharmaceuticals LP. BLA 761069 Imfinzi (durvalumab): Response to FDA Information Request – Clinical/CMC/Labeling. Gaithersburg (MD): AstraZeneca Pharmaceuticals LP. 2017 JAN 10.

because they are presented in the same font size and both statements are bolded. We recommend reducing the prominence of the strength per mL (50 mg/mL) either by reducing the font size or de-bolding the "50 mg/mL" statement to minimize the risk of confusion where users fail to determine the total amount of the drug in the container.

Additionally, although AstraZeneca clarified the [redacted] (b) (4) on the container label, we are unfamiliar with the terminology and how it is different from the "US serialization barcode" on the carton labeling.

3 CONCLUSION

The revised Imfinzi container labels and carton labeling are unacceptable from a medication error perspective. We provide specific recommendations for AstraZeneca in Section 4 below.

4 RECOMMENDATIONS FOR ASTRAZENECA

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

A. Container label and carton labeling

1. The strength per total volume should be the primary and prominent expression on the principal display panel.[c] Reduce the prominence of the strength per mL (50 mg/mL) either by reducing the font size or de-bolding the "(50 mg/mL)" statement to minimize the risk of confusion where users fail to determine the total amount of the drug in the container.
2. [redacted] (b) (4)

[c] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

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TINGTING N GAO
02/02/2017

CHI-MING TU
02/02/2017

Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

IND or NDA	BLA 761069
Brand Name	-
Generic Name	Durvalumab (MEDI4736)
Sponsor	AstraZeneca
Indication	Locally advanced or metastatic urothelial carcinoma (b) (4)
Dosage Form	Injection solution 50 mg/mL
Drug Class	Human monoclonal antibody (mAb) of the immunoglobulin G1 kappa (IgG1κ) subclass
Therapeutic Dosing Regimen	10 mg/kg Q2W
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	No MTD was identified in patients treated within the dose range of 0.1 to 10 mg/kg Q2W, 15 mg/kg Q3W, or 20 mg/kg Q4W
Submission Number and Date	Sequence 0018, 12/05/2016
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

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

The clinical data evaluated is from Study ATLANTIC (D4191C00003) with a data cut-off date of 25 September 2015 (per the dataset submitted by the sponsor). There will be some differences in the results reported in this review versus those in the final clinical study report (CSR) for this study because the CSR has reported results with data cut-off date of 3 June 2016. This study is a Phase 2, non-comparative, open label, multi-center, international study of durvalumab (MEDI4736), in patients with locally advanced or metastatic non-small cell lung cancer (Stage IIIB-IV) who have received at least two prior systemic treatment regimens including one platinum-based chemotherapy regimen. In the QTc substudy of ATLANTIC, a total of 256 out of 265 patients who enrolled and received durvalumab monotherapy at 10 mg/kg Q2W IV (proposed therapeutic dose) had baseline ECG recorded. By-time central tendency analysis of the data at Day 1 (first

dose) and Week 16 (steady state) visits, where there was adequate sample size and ECG evaluation near T_{max}, suggest a lack of large mean increases (>20 ms) in the QTcF interval at the therapeutic exposures with 10 mg/kg Q2W dosing (Table 1).

Table 1: Analysis Results of QTcF and ΔQTcF for Durvalumab 10 mg/kg Q2W IV (FDA Analysis)

	QTcF (ms)		ΔQTcF (ms)			
Time	**N**	**Mean (SD)**	**N**	**Mean**	**SD**	**90% CI**
Baseline	256	406.2 (20.8)				
Day 1 /0.5 hour Post	247	409.0 (20.5)	247	2.7	10.6	(1.6, 3.8)
Day 1 /3 hours Post	245	406.9 (20.3)	245	0.5	11.2	(-0.7, 1.7)
Week 16/1 hour prior	104	408.6 (20.4)	103	1.6	12.8	(-0.5, 3.7)
Week 16/0.5 hour post	94	412.5 (20.1)	93	5.4	13.4	(3.1, 7.7)
Week 16/3 hours post	90	411.8 (19.6)	89	4.2	12.3	(2.1, 6.4)

There was no exposure-response relationship between durvalumab plasma concentrations and ΔQTcF.

The studied dose of durvalumab of 10 mg/kg Q2W is the proposed therapeutic dose and it is not the MTD. The accumulation ratio for C_{max} with multiple dosing is 1.83. Based on population PK analysis, there was no clinically significant effect of age, body weight, gender, positive ADA status, race, creatinine levels, mild to moderate renal impairment, mild hepatic impairment on the PK of durvalumab (change in exposure metrics < 30%). There is no data available for exposure changes in patients with moderate or severe hepatic impairment. Given that the clearance pathway for monoclonal antibodies is through proteolytic degradation, it is less likely that hepatic impairment and drug-drug interaction would lead to considerable increases in drug exposure.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS TO THE DIVISION

Query from the Division: The medical officer wanted to confirm whether the QT-IRT is looking at Phase I Study CD-ON-MEDI4736-1108 as well in addition to Study ATLANTIC (D4191C00003), because as per the medical officer even though in both studies ECGs were performed Q8W, the prior study likely had the greatest number of ECGs available and included the bladder cancer cohort on which approval would be based.

QT-IRT's response: Study CD-ON-MEDI4736-1108, a multicenter, open-label, first-time-in-human (FTIH) study, studied doses ranging from 0.3 mg/kg Q2W (n=4) to 20 mg/kg Q4W (n=21) during dose-escalation/-exploration phase and eventual therapeutic dosing regimen of 10 mg/kg Q2W (n=964) in dose-expansion phase (all studied dose levels are noted in clinical cardiac safety section in Appendix 6.1). ECGs for this study were collected as part of routine safety monitoring of subjects receiving study therapy. ECG collection was limited and was not performed with the specific intent of a formal

ECG interval, rhythm, rate, or morphology analysis. Local ECG reads were performed in the majority of subjects; while central ECG reads were performed in a small subset of subjects. In the dose-escalation/-exploration cohorts, ECGs for the large majority of subjects were monitored locally. Central ECG data were available for only 3 of 48 subjects in dose-escalation/-exploration cohort, all in the 20 mg/kg Q4W dose-exploration cohort. ECG findings in all these 3 subjects were unremarkable (e.g. none of them had QTcF>450 ms or ΔQTcF >30 ms at 0.5 h and 3 h post end-of-infusion after first dose). Since the RR interval from local reads was not captured in the eCRFs, no QTcB or QTcF values for ECGs examined locally were derived. Thus, even though this study had studied a higher dose level (in terms of C_{max}) of 20 mg/kg Q4W in some subjects compared to therapeutic dose level of 10 mg/kg Q2W, because of absence of appropriately corrected QT values (QTc) for higher doses and adequacy of Study ATLANTIC (D4191C00003) for QTc characterization at therapeutic dose level (10 mg/kg Q2W), data from the Study CD-ON-MEDI4736-1108 have not been considered for evaluation in this review.

2 PROPOSED LABEL

The sponsor did not include any QT-related language in their current proposed label. This seems reasonable given that the labels of 7 approved monoclonal antibodies in 2016 do not include a description of the QTc evaluation and results.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that blocks the interaction of programmed cell death ligand-1 (PD-L1) with PD-1 and CD80 (B7.1) molecules while leaving PD-1/PD-L2 interaction intact. Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination without inducing antibody dependent cell-mediated cytotoxicity (ADCC). Durvalumab has a molecular weight of ~150 kDa.

3.2 MARKET APPROVAL STATUS

Durvalumab is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Refer to preclinical cardiac safety section in Appendix 6.1. Briefly, in the GLP 4- and 13-week repeat-dose toxicity studies in cynomolgus monkeys, no durvalumab-related effects on any of the cardiovascular parameters (heart rate, wave form morphology, ST segment and PR and QT/QTc interval [QTcM or QTcB]) were noted.

3.4 PREVIOUS CLINICAL EXPERIENCE

Refer to clinical cardiac safety section in Appendix 6.1.

3.5 CLINICAL PHARMACOLOGY

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

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The sponsor submitted their QT findings in their Phase 2 study report D4191C00003 (ATLANTIC) for durvalumab, including electronic datasets and waveforms to the ECG warehouse. The protocol for this study was not reviewed by the QT-IRT. The clinical data evaluated as a part of this review is from this study, with a data cut-off date of 25 September 2015 (per the dataset submitted by the sponsor). There will be some differences in the results reported in this review versus those in the final clinical study report (CSR) for this study because the CSR has reported results with data cut-off date of 3 June 2016.

4.2 QT STUDY

4.2.1 Title

A Phase 2, Non-comparative, Open label, Multi-centre, International Study of MEDI4736, in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (Stage IIIB-IV) Who Have Received at Least Two Prior Systemic Treatment Regimens Including One Platinum-based Chemotherapy Regimen (ATLANTIC).

4.2.2 Protocol Number

D4191C00003

4.2.3 Study Dates

First patient enrolled: 25 February 2014. Last patient enrolled: 28 December 2015

4.2.4 Objectives

The primary objective of this study is to evaluate the overall objective response rate after exposure of durvalumab. One of the secondary objectives is to evaluate ECG changes after exposure to durvalumab.

4.2.5 Study Description

4.2.5.1 Design

This was a prospective, phase 2, non-comparative, open-label, multi-center, international study.

4.2.5.2 Controls

Neither a placebo nor a positive control (moxifloxacin) was used.

4.2.5.3 Blinding

The study was open-label.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There was only one treatment arm: Durvalumab 10 mg/kg administered every two weeks (Q2W).

4.2.6.2 Sponsor's Justification for Doses

Based on an analysis of the dose-escalation data from the ongoing First Time in Human study (Study CD-ON-MEDI4736-1108 [Study 1108]), a dose of 10 mg/kg Q2W administered for up to a maximum of 12 months was recommended for further development [Study D4191C00003]. This dosing regimen was based on multiple lines of evidence including in vitro data, nonclinical activity, clinical PK-pharmacodynamics, clinical biomarkers, and clinical activity data collected from Study 1108.

Reviewer's comment: The studied dose of durvalumab of 10 mg/kg Q2W is the proposed therapeutic dose and it is not the MTD. The accumulation ratio for C_{max} with multiple dosing is 1.83. Based on population PK analysis, there was no clinically significant effect of age, body weight, gender, positive ADA status, albumin levels, LDH levels, creatinine levels, soluble PD-L1 (sPD-L1) levels, tumor type, race, mild to moderate renal impairment, mild hepatic impairment, or ECOG status on the PK of durvalumab. None of the above covariates were found to be clinically relevant since the change in PK parameters or exposure metrics (steady state Cmax, Cmin, and AUC) were < 30%. The studied dose is adequate for the oncology indication.

4.2.6.3 Instructions with Regard to Meals

Reviewer's comment: Not relevant because durvalumab is administered by IV injection.

4.2.6.4 ECG and PK Assessments

Refer to schedule of assessments in Appendix 6.2. Briefly,

ECG: On screening day (Day -28 to 1); Day 1 and Week 16 (predose within an hour prior to start of infusion, within 0.5 h post end-of-infusion and at 3 h post end-of-infusion after 1 h infusion duration); Week 8, 24, 32, 40, and 48 (timing is not specified; likely predose values)

PK: Durvalumab serum concentration was measured on Day 1 (end of infusion) and on Week 4, 16, 28, 40, 52 (predose trough values).

Reviewer's comment: It appears that the time-matched ECG/PK samples are available only on Day 1 (end of infusion), Week 16 (predose trough values) and Week 40 (predose trough values). There is significant attrition in sample size by Week 40 (only 13% subjects had ECG/PK sampling compared to baseline measurement). Time-matched ECG/PK data near T_{max} just on Day 1 is not optimal for exposure-response analysis since it does not cover the steady state C_{max} (C_{max} accumulation ratio is ~1.8 with multiple dosing).

4.2.6.5 Baseline

The average of predose QT/QTc values was used as baseline.

4.2.7 ECG Collection

Triplicate resting 12-Lead digital ECGs were collected. Standard 12-Lead ECGs were obtained while subjects were recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 265 patients were enrolled and received durvalumab monotherapy at 10 mg/kg Q2W in Cohort 2 of the ATLANTIC study as of the 24-week data cut-off on 25Sep2015. ECG data from the 265 patients were evaluated. All of the 265 patients were in safety population, and 239 patients were in PK population. At the baseline visit, ECGs were recorded from 256 patients out of the 265 patients enrolled in the study. Triplicate ECG readings were centrally and digitally collected/ collated per visit, including 30 days following the last dose of study therapy, and compared against baseline ECG results.

The average age (SD) of the 265 patients (162 males, 103 females) was 61.8 (9.4) years, ranging from 30 to 85 years. The majority of the patients were White (212/265, 80%), and the rest of the patients were either Asian (51/265, 19.2%) or Black or African American (2/265, 0.8%). Most of the patients were of ethnic Not Hispanic or Latino (246/256, 92.8%).

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

Exposure-response analysis was used for primary analysis. The findings of the study are discussed in Section 4.2.8.2.4 and Section 4.2.8.4.2.

4.2.8.2.2 Assay Sensitivity

Not Applicable.

4.2.8.2.3 Categorical Analysis

There were no patients who had a QTcF prolongation of >480 msec during therapy. During therapy, 7 patients who had normal QTcF at baseline had a single transient QTcF interval measure of >450 msec. Five individuals with normal QTcF intervals at baseline had multiple QTcF measures of >450 msec during the study. These individuals either had a cardiac medical history or were receiving potentially cardioactive concomitant medications at the time of abnormality.

There were no patients who had a QTcF change from baseline of >60 msec during the study. Eleven patients (all with normal QTcF interval at baseline) had a single transient prolongation of >30 msec during this study and 4 patients with normal baseline had multiple prolongations of >30 msec during the study. These patients were further evaluated. These individuals either had a cardiac medical history or were receiving potentially cardioactive concomitant medications at the time of abnormality. Notably, the same number of patients (15 [5.7%]) had a QTcF interval decrease from baseline of between 30 and 60 msec.

There were 2 patients who had a QTcF duration of >450 msec plus a change from baseline of >30 msec during the study. These individuals both had a cardiac medical history and were receiving potentially cardioactive concomitant medications at the time of abnormality.

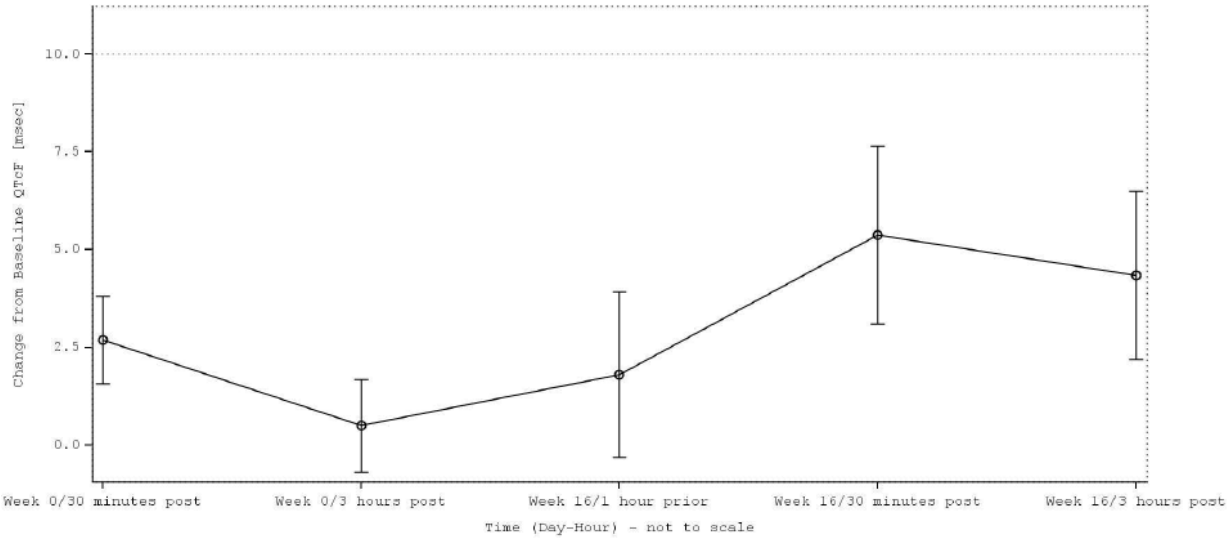
4.2.8.2.4 Additional Analyses

The mean changes from baseline in QTcF at Day 1 and Week 16 time points were analyzed by the sponsor and the results are shown in the following Figure 1.

On Day 1, the mean changes from baseline for QTcF at 30 minutes and 3 hours post infusion were 2.69 msec (SD 10.585; range: -46.3 to 34.7 msec) and 0.50 msec (SD 11.246; range: -55.3 to 41.3 msec), respectively.

At Week 16, the mean change from baseline for QTcF was 1.80 msec (SD 12.896; range: -33.3 to 45.3 msec), 5.37 msec (SD 13.362; range: -26.7 to 37.0 msec) 30 mins post infusion, and 4.34 msec (SD 12.264; range: -22.3 to 36.0 msec) 3 hrs post infusion.

Figure 1: Mean Change in QTcF from Baseline (Day 1 and Week 16; Safety Analysis Set)



Source: The sponsor's EXPERT ECG report, Figure 2, page 39

Reviewer's Comments: The reviewer's independent assessment is presented in Section 5.2.

4.2.8.3 Safety Analysis

Nineteen patients (7.2%) in Cohort 2 in the ATLANTIC study (up to the 25 Sep. 2015 data cut-off) had an AE in the Cardiac disorders System Organ Class (SOC) of the Medical Dictionary for Regulatory Activities. The most common cardiac AEs reported were atrial fibrillation (in 9 patients [3.4%]), tachycardia (in 5 patients [1.9%]) and sinus tachycardia (in 2 patients [0.8%]). The rest of the cardiac events occurred in 1 patient (0.4%) each. The majority of the patients (16 out of 19) only had AEs that were Grade 1 or Grade 2 in severity. None of the events led to therapy discontinuation. In 7 of the 19

patients with a cardiac event in the study, the event was classified as not resolved at the time of data cut-off (25 Sep. 2015) or study withdrawal.

In addition, 1 patient had a Grade 2 event of ECG QT prolonged within the Investigations SOC.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

As of the 03 June 2016 DCO, PK data were available for a total of 398 patients (PK analysis set) following treatment with 10 mg/kg Q2W of durvalumab administered as an iv infusion over 60 minutes. The summaries of durvalumab serum concentrations are presented in Table 2. No formal non-compartmental analysis was conducted due to the sparse PK sampling scheme in this study. Following 10 mg/kg Q2W durvalumab geometric mean (n, %CV) of $C_{trough,w16}$, $C_{trough,w28}$, $C_{trough,w40}$, and $C_{trough,w52}$ were 149 (n=193, 59.9%), 175 (n=128, 51.6%), 201 (n=90, 43.3%) and 200 (n=57, 69.7%) µg/mL, respectively. The exposures were similar among the 3 cohorts (Table 3).

Table 2: Summary of Durvalumab serum concentration-time profile (PK analysis set)

		Result (ng/mL)							
Nominal time (days)	n	Mean	SD	Min	Median	Max	CV%	Geometric Mean	CV% of Geometric Mean
Week 0 (Day 1) Pre-Dose	17	16420.9	42508.50	55	133.8	151840	258.9	395.4	3343.7
Week 0 (Day 1) Post-Dose	398	207452.6	54179.70	28200	204800.0	489500	26.1	200291.1	28.1
Week 4 (Day 29)	354	87823.5	39128.93	70	86985.0	404900	44.6	77597.9	70.1
Week 16 (Day 112)	193	168192.2	76879.28	3915	164700.0	418080	45.7	148837.4	59.9
Week 28 (Day 196)	128	194734.6	85958.12	31650	187315.0	478620	44.1	175174.7	51.6
Week 40 (Day 280)	90	216569.4	78434.46	31140	210765.0	384810	36.2	200927.8	43.3
Week 52 (Day 364)	57	224423.0	84300.50	5420	225120.0	404700	37.6	199526.6	69.7
Month 3 Follow-up	73	25861.0	23371.87	1111	20410.0	101020	90.4	15100.7	179.7

n = number of subjects with data, SD = standard deviation, Min = Minimum, Max = Maximum, CV% = percent coefficient of variance.

Source: The sponsor's CSR for Study D4191C00003, Table 11.2.11.1.A, page 646

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Table 3: Summary of durvalumab steady state serum concentrations (µg/mL) (geometric mean [n, geometric %CV])

	Trough Concentrations (µg/mL) $C_{trough,w16}$	Trough Concentrations (µg/mL) $C_{trough,w28}$	Trough Concentrations (µg/mL) $C_{trough,w40}$	Trough Concentrations (µg/mL) $C_{trough,w52}$
Cohort 1 (EGFR/ALK +ve)	177 (n=41, 45.5%)	209 (n=26, 42.5%)	232 (n=17, 29.7%)	233 (n=5, 11.2%)
Cohort 2 (EGFR/ALK WT)	142 (n=112, 48.6%)	155 (n=77, 52.3%)	183 (n=60, 45.9%)	195 (n=48, 76.7%)
Cohort 3 (EGFR/ALK WT)	141 (n=40, 97.8%)	214 (n=25, 45.4%)	258 (n=13, 29.0%)	217 (n=4, 27.3%)
All Cohorts	149 (n=193, 59.9%)	175 (n=128, 51.6%)	201 (n=90, 43.3%)	200 (n=57, 69.7%)

$C_{trough,w16}$, $C_{trough,w28}$, $C_{trough,w40}$, and $C_{trough,w52}$ are the pre-dose concentrations of Weeks 16, 28, 40, and 52, respectively.
n = number of subjects, %CV = coefficient of variation
NA = Data not available

Source: The sponsor's CSR for Study D4191C00003, Table 33, page 148

4.2.8.4.2 Exposure-Response Analysis

The concentration-QTcF analysis dataset included protocol-specified post-therapy time points where there was both an ECG measurement and a corresponding durvalumab serum concentration sample, which included 1) Week 0 end of infusion, 2) Week 16 pre-infusion, and 3) Week 40 pre-infusion.

A total of 256 out of 265 patients who enrolled and received durvalumab monotherapy at 10 mg/kg Q2W in Cohort 2 of the ATLANTIC study had baseline ECG recorded. Among the 256 patients, 239 who had ≥1 post-therapy time-matched observation of QTcF and detectable durvalumab concentration (per protocol specified post-therapy collection times) were included in the concentration-ΔQTcF analysis population. Durvalumab concentration values reported as below the limit of quantitation (BLQ; <50.00 ng/mL) were omitted from the analysis, as inter-occasional variability of the QTcF could not be investigated and samples with BLQ values could potentially bias the concentration-ΔQTcF relationship. A total of 345 time-matched post-therapy concentration-ΔQTcF records from those 239 patients at Week 0 end of infusion, Week 16 pre-infusion, and Week 40 pre-infusion were utilized to perform the concentration-ΔQTcF analysis.

Triplicate QTcF values for each patient at each time point were averaged, and baseline QTcF was defined as the mean of QTcF at Screening and Day 1 pre-dose.

A linear mixed-effects modelling approach was used to quantify the relationship between durvalumab serum concentration and QTcF interval change from baseline using a PROC NLMIXED procedure of SAS. Observed serum concentrations for each patient at each visit were used as the independent variable and intercept was included in the model as

subject-specific random effects (Garnett CE et al 2008), according to the following equation:

$$\Delta QTcF_{it} = (\alpha + \eta_i) + \beta * conc(t)_i + \varepsilon_{it}$$
$$\eta_i \sim N(0, \omega^2); \varepsilon_{it} \sim N(0, \sigma^2);$$

Linear mixed-effects modeling of QTcF as a function of durvalumab concentrations estimated a non-significant relationship between durvalumab concentration and change in QTcF. The slope for the relationship of the change in QTcF to durvalumab concentration was -0.00114 msec per µg/mL (90% CI: -0.0165, 0.0142), with a p-value of 0.902, indicating that the slope is not significantly different from 0 or no effect, and the mean intercept was 2.16 msec (p-value: 0.253; 90% CI: -0.956, 5.28 ms).

As seen in Table 4, the mean predicted ΔQTcF at end of infusion following first dose at week 0 (the only PK C_{max} sample that is collected in the study) is less than 5 msec and the upper bound on the 90% CI of predicted mean ΔQTcF is less than 10 msec, lower than expressed QTc interval prolongation levels of concern for assessment of ECG in a thorough-QT study to regulatory bodies comprising the ICH (ICH E14 Guidance 2005). Also the predicted mean change in QTcF and upper 90% CI at each of the post-therapy visits are below the threshold of clinical concern.

Figure 2 presents the observed change in QTcF plotted against time-matched observed concentration and the regression line for the concentration-change in QTcF relationship. The graph shows a lack of concentration effect relationship between durvalumab serum concentrations and the change in QTcF.

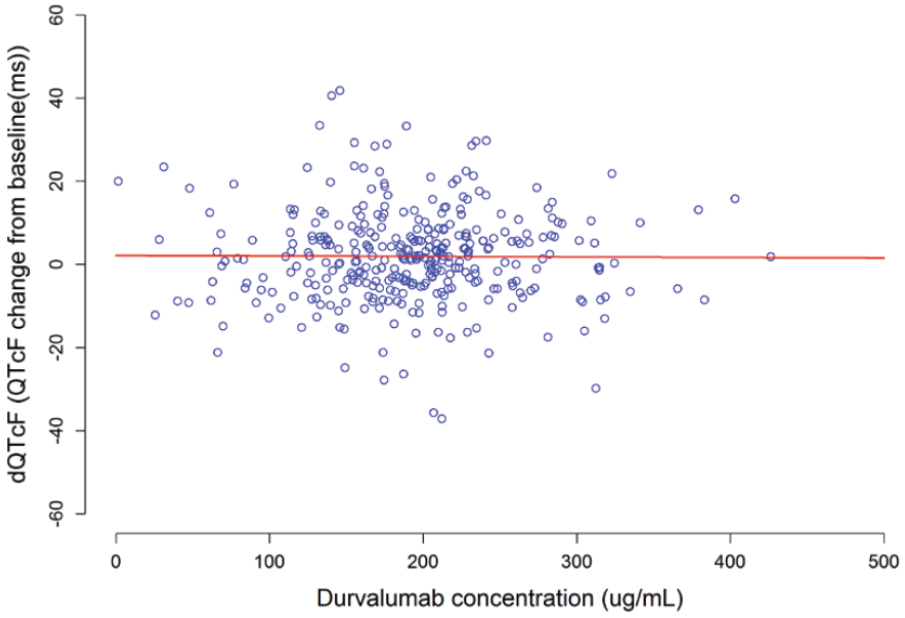
Table 4: Summary of observed mean durvalumab serum concentration and predicted mean ΔQTcF by time points

Study week	Visit	Number of Patients	Geometric mean durvalumab concentration (µg/mL)	Predicted mean ΔQTcF (ms)	90% CI of predicted mean ΔQTcF (ms)
0	End of infusion	227	196	1.93	(1.82, 2.03)
16	Pre-infusion	96	142	1.98	(1.85, 2.12)
40	Pre-infusion	22	170	1.95	(1.80, 2.10)

ΔQTcF = change from baseline value of QTcF; CI = confidence interval; QTcF = Fridericia's heart rate correction formula.

Source: The sponsor's EXPERT ECG report, Table 11, page 48

Figure 2: QTcF change from baseline versus durvalumab serum concentration



Source: The sponsor's CSR for Study D4191C00003, Figure 24, page 222

Reviewer's Analysis: A plot of ΔQTcF vs. drug concentrations from reviewer's assessment is presented in Figure 5.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The relationship between different correction methods and RR is presented in Figure 3. QTcF was used in the statistical and exposure-response analyses.

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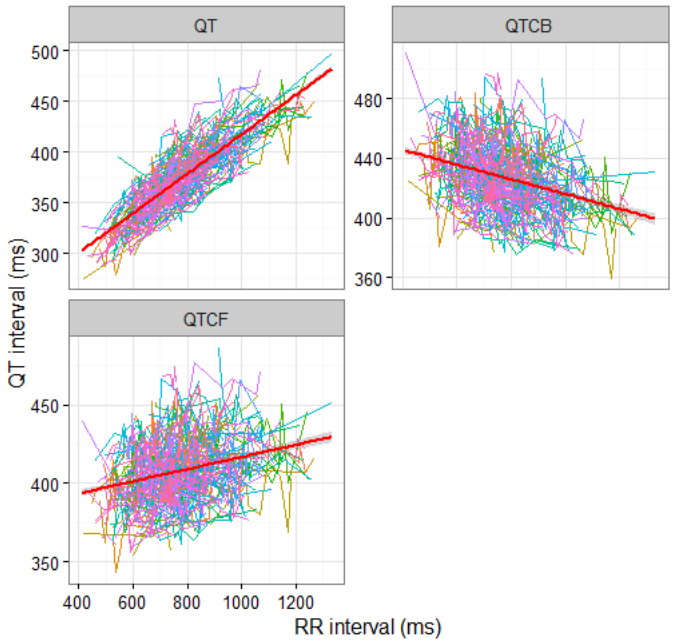
Figure 3: QT, QTcB and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Durvalumab (MEDI4736)

The primary end point is mean change from baseline in QTcF (ΔQTcF). The statistical reviewer used descriptive analysis to show the ΔQTcF effect. The analysis results are listed in the following table.

Table 5: Analysis Results of QTcF and ΔQTcF for Durvalumab 10 mg/kg Q2W IV

	QTcF (ms)		ΔQTcF (ms)			
Time	**N**	**Mean (SD)**	**N**	**Mean**	**SD**	**90% CI**
Baseline	256	406.2 (20.8)				
Day 1 /0.5 hour Post	247	409.0 (20.5)	247	2.7	10.6	(1.6, 3.8)
Day 1 /3 hours Post	245	406.9 (20.3)	245	0.5	11.2	(-0.7, 1.7)
Week 8	156	406.4 (19.9)	155	0.9	14.1	(-1.0, 2.8)
Week 16/1 hour prior	104	408.6 (20.4)	103	1.6	12.8	(-0.5, 3.7)
Week 16/0.5 hour post	94	412.5 (20.1)	93	5.4	13.4	(3.1, 7.7)
Week 16/3 hours post	90	411.8 (19.6)	89	4.2	12.3	(2.1, 6.4)
Week 24	74	409.3 (18.3)	73	1.7	15.8	(-1.4, 4.7)
Week 32	54	410.8 (18.6)	54	1.6	15.1	(-1.8, 5.0)
Week 40	34	408.4 (20.1)	34	3.6	13.9	(-0.4, 7.7)
Week 48	12	416.8 (22.9)	12	3.7	16.1	(-4.6, 12.1)

The largest mean change from baseline in QTcF (ΔQTcF) was 5.4 ms with a 90% CI of 3.1 ms to 7.7 ms.

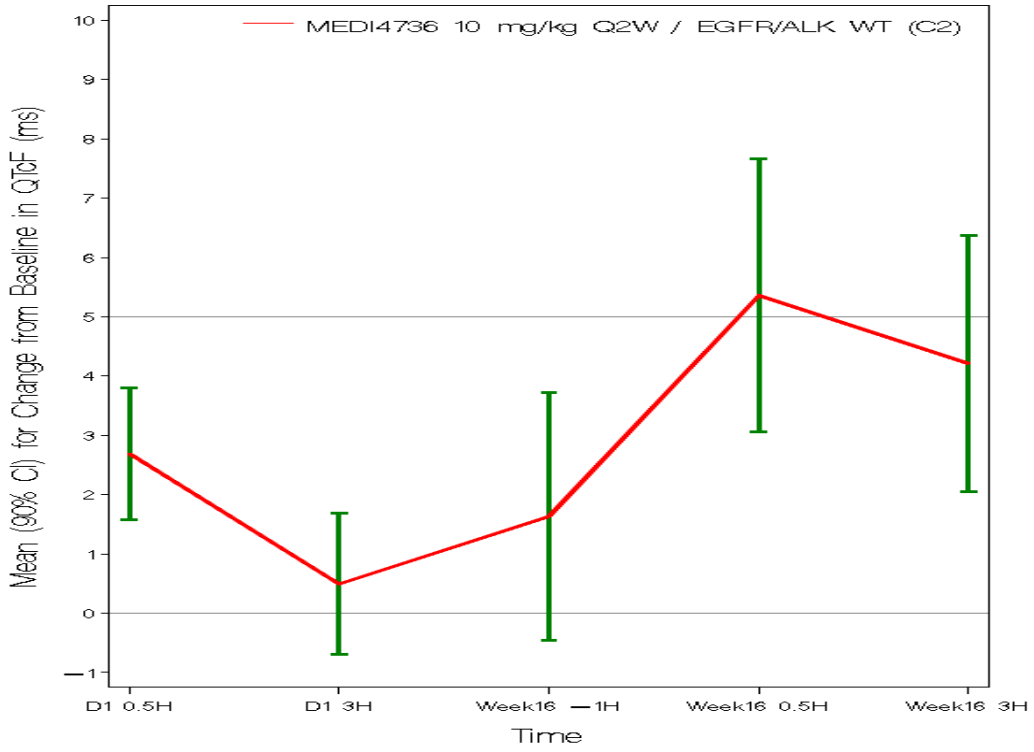
5.2.1.2 Assay Sensitivity Analysis

Not Applicable.

5.2.1.3 Graph of ΔQTcF Over Time

The following figure displays the time profile of ΔQTcF for Durvalumab (MEDI4736) 10 mg/kg Q2W IV.

Figure 4: Mean and 90% CI ΔQTcF Timecourse



5.2.1.4 Categorical Analysis

Table 6 lists the number of subjects as well as the number of observations whose QTcF values were ≤ 450 ms, between 450 ms and 480 ms, and between 480 ms and 500 ms.

Table 6: Categorical Analysis for QTcF

	Total N		QTcF<=450 ms		450<QTcF<= 480 ms		480<QTcF<= 500 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Baseline	256	256	250 (97.7%)	250 (97.7%)	5 (2.0%)	5 (2.0%)	1 (0.4%)	1 (0.4%)
Day 1 post-infusion	252	492	242 (96.0%)	477 (97.0%)	10 (4.0%)	15 (3.0%)	0 (0.0%)	0 (0.0%)
Week 8	156	156	152 (97.4%)	152 (97.4%)	4 (2.6%)	4 (2.6%)	0 (0.0%)	0 (0.0%)
Week 16	104	288	99 (95.2%)	281 (97.6%)	5 (4.8%)	7 (2.4%)	0 (0.0%)	0 (0.0%)
> Week 16	89	175	87 (97.8%)	172 (98.3%)	2 (2.2%)	3 (1.7%)	0 (0.0%)	0 (0.0%)

* Categorical analysis tables were up to week 48; follow-up visit was not included.

Table 7 lists the categorical analysis results for ΔQTcF. No subject's change from baseline in QTcF was above 60 ms.

Table 7: Categorical Analysis of ΔQTcF

	Total N		ΔQTcF<=30 ms		30<ΔQTcF<=60 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Day 1 post-infusion	252	492	249 (98.8%)	489 (99.4%)	3 (1.2%)	3 (0.6%)
Week 8	155	155	152 (98.1%)	152 (98.1%)	3 (1.9%)	3 (1.9%)
Week 16	103	285	96 (93.2%)	276 (96.8%)	7 (6.8%)	9 (3.2%)
> Week 16	88	174	82 (93.2%)	166 (95.4%)	6 (6.8%)	8 (4.6%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 8. A small HR decreasing effect was observed for durvalumab.

The outlier analysis results for HR are presented in Table 9.

Table 8: Analysis Results of HR and ΔHR for Durvalumab 10 mg/kg Q2W IV

	HR (bpm)		ΔHR (bpm)			
Time	**N**	**Mean (SD)**	**N**	**Mean**	**SD**	**90% CI**
Baseline	256	82.4 (14.9)				
Day 1 /0.5 hour Post	247	80.0 (15.2)	247	-1.9	8.1	(-2.8, -1.1)
Day 1 /3 hours Post	245	82.1 (14.7)	245	0.1	8.0	(-0.7, 1.0)
Week 8	156	82.1 (16.1)	155	0.4	13.0	(-1.3, 2.1)
Week 16/1 hour prior	104	76.8 (13.3)	103	-1.7	13.2	(-3.9, 0.5)
Week 16/0.5 hour post	94	73.7 (12.6)	93	-4.9	14.5	(-7.4, -2.4)
Week 16/3 hours post	90	75.2 (14.2)	89	-3.2	14.5	(-5.8, -0.7)
Week 24	74	74.3 (13.8)	73	-5.0	14.0	(-7.7, -2.2)
Week 32	54	74.1 (13.0)	54	-3.1	12.6	(-6.0, -0.2)
Week 40	34	75.9 (12.3)	34	-2.6	10.6	(-5.6, 0.5)
Week 48	12	69.9 (10.4)	12	-5.1	10.4	(-10.5, 0.3)

Table 9: Categorical Analysis for HR

	Total N	HR<=100 bpm	HR>100 bpm	HR>45 bpm	HR<=45 bpm
Treatment Group	**Subj. #**	**Subj. #**	**Subj. #**	**Subj. #**	**Subj. #**
Baseline	256	224 (87.5%)	32 (12.5%)	256 (100%)	0 (0.0%)
Day 1 post-infusion	252	219 (86.9%)	33 (13.1%)	252 (100%)	0 (0.0%)
Week 8	156	135 (86.5%)	21 (13.5%)	156 (100%)	0 (0.0%)
Week 16	104	96 (92.3%)	8 (7.7%)	104 (100%)	0 (0.0%)
> Week 16	89	84 (94.4%)	5 (5.6%)	89 (100%)	0 (0.0%)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR. The point estimates and the 90% confidence intervals are presented in Table 10. The largest mean change from baseline in PR (ΔPR) was 4.9 ms with a 90% CI of 2.4 ms to 7.4 ms.

The outlier analysis results for PR are presented in Table 11.

Table 10: Analysis Results of PR and ΔPR for Durvalumab 10 mg/kg Q2W IV

	PR (ms)		ΔPR (ms)			
Time	**N**	**Mean (SD)**	**N**	**Mean**	**SD**	**90% CI**
Baseline	252	159.8 (23.1)				
Day 1 /0.5 hour Post	242	162.7 (25.0)	242	2.5	7.4	(1.8, 3.3)
Day 1 /3 hours Post	240	161.5 (24.0)	240	1.4	7.4	(0.6, 2.1)
Week 8	151	160.0 (23.4)	151	-0.8	11.1	(-2.3, 0.7)
Week 16/1 hour prior	103	163.4 (24.1)	102	2.0	14.6	(-0.4, 4.4)
Week 16/0.5 hour post	93	164.5 (24.0)	92	4.1	15.1	(1.5, 6.7)
Week 16/3 hours post	89	166.2 (24.7)	88	4.9	14.2	(2.4, 7.4)
Week 24	73	166.6 (22.5)	72	3.9	11.0	(1.7, 6.1)
Week 32	52	165.8 (21.2)	52	3.5	11.3	(0.8, 6.1)
Week 40	33	163.8 (19.5)	33	1.9	12.0	(-1.7, 5.4)
Week 48	12	179.5 (24.4)	12	4.6	13.6	(-2.4, 11.7)

Table 11: Categorical Analysis for PR

	Total N		PR<=200 ms		PR>200 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Baseline	252	252	235 (93.3%)	235 (93.3%)	17 (6.7%)	17 (6.7%)
Day 1 post-infusion	247	482	222 (89.9%)	439 (91.1%)	25 (10.1%)	43 (8.9%)
Week 8	151	151	144 (95.4%)	144 (95.4%)	7 (4.6%)	7 (4.6%)
Week 16	103	285	92 (89.3%)	260 (91.2%)	11 (10.7%)	25 (8.8%)
> Week 16	88	171	80 (90.9%)	157 (91.8%)	8 (9.1%)	14 (8.2%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS. The point estimates and the 90% confidence intervals are presented in Table 12. The magnitude of mean change in QRS (ΔQRS) was small and there was no trend for ΔQRS.

The outlier analysis results for QRS are presented in Table 13.

Table 12: Analysis Results of QRS and ΔQRS for Durvalumab 10 mg/kg Q2W IV

	QRS (ms)		ΔQRS (ms)			
Time	**N**	**Mean (SD)**	**N**	**Mean**	**SD**	**90% CI**
Baseline	256	92.8 (13.2)				
Day 1 /0.5 hour Post	247	93.2 (12.9)	247	0.2	6.1	(-0.4, 0.9)
Day 1 /3 hours Post	245	93.4 (13.0)	245	0.5	5.6	(-0.1, 1.1)
Week 8	156	92.7 (13.4)	155	0.4	5.3	(-0.3, 1.1)
Week 16/1 hour prior	104	93.3 (12.0)	103	0.9	6.0	(-0.0, 1.9)
Week 16/0.5 hour post	94	94.0 (12.2)	93	1.0	5.9	(-0.0, 2.0)
Week 16/3 hours post	90	94.5 (11.1)	89	1.3	5.6	(0.3, 2.3)
Week 24	74	94.7 (12.9)	73	1.9	6.0	(0.7, 3.1)
Week 32	54	94.2 (13.8)	54	1.0	5.7	(-0.3, 2.3)
Week 40	34	96.9 (16.1)	34	1.7	4.9	(0.3, 3.2)
Week 48	12	108.8 (23.3)	12	4.4	12.3	(-2.0, 10.7)

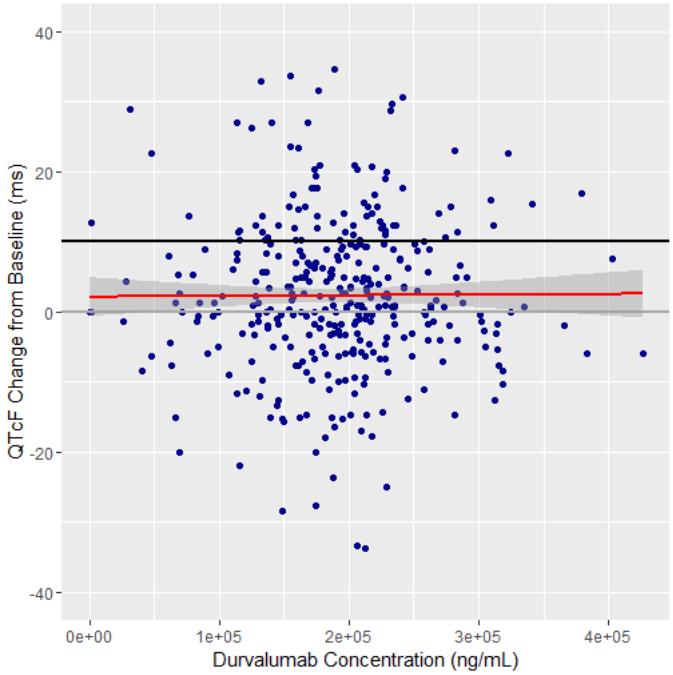
Table 13: Categorical Analysis for QRS

	Total N		QRS<=110 ms		QRS>110 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Baseline	256	256	236 (92.2%)	236 (92.2%)	20 (7.8%)	20 (7.8%)
Day 1 post-infusion	252	492	230 (91.3%)	455 (92.5%)	22 (8.7%)	37 (7.5%)
Week 8	156	156	145 (92.9%)	145 (92.9%)	11 (7.1%)	11 (7.1%)
Week 16	104	288	92 (88.5%)	264 (91.7%)	12 (11.5%)	24 (8.3%)
> Week 16	89	175	81 (91.0%)	160 (91.4%)	8 (9.0%)	15 (8.6%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between ΔQTcF and durvalumab plasma concentrations is visualized in Figure 5 with no evident exposure-response relationship.

Figure 5: ΔQTcF vs. Drug concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

In Study D4191C0003 (ATLANTIC) with a cut-off date of 3 June 2016, no patients had a QTcF value >500 ms, but 4 subjects had an increase QTcF from baseline >60 ms. No significant ventricular arrhythmias occurred. There was 1 case of sudden death (described below). Overall, the ECG analyses suggest no effect of durvalumab on QT interval.

Patient E7007008 died due to a TEAE of sudden death 230 days after the first dose of durvalumab. The patient's past medical history included asthma, anal fistula, hemorrhoids, and malignant neoplasm. Current medical conditions at baseline included rhinitis, insomnia, gastroesophageal reflux disease, hypertension, arthralgia, musculoskeletal pain, aortic dilatation, musculoskeletal chest pain, pleural fibrosis, paresthesia, pulmonary embolism, myositis ossificans, and catarrh. On the day of the patient's last dose, the patient had an abnormal ECG with sinus rhythm with first degree AV block, intraventricular conduction defect, moderate ST depression, and anterolateral and inferior infarct probably recent with posterior extension. Four days later, the patient was admitted to the emergency room due to costal right pain radiating to the rest of the scapular region and low grade fever. The patient was discharged the same day and died the following day. Around the same time, the patient also experienced nonserious AEs of rash, blood lactate dehydrogenase increased, hordeolum, skin lesion, eye pruritus, hypothyroidism, dry mouth, lymphadenitis, musculoskeletal chest pain, nausea, fatigue decreased appetite, and pyrexia. The sudden death was assessed as

potentially related to the patient's basal status and/or comorbidities. The Investigator considered the death not to be related to the underlying cancer.

5.4.2 ECG assessments

Digital ECG waveforms are not submitted.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure	Durvalumab 10 mg/kg every 2 weeks (Q2W) administered as an intravenous (IV) infusion over 60 minutes. Mean (%CV) Cmax and AUC0-14 days after the first administration of the maximum proposed clinical dose (10 mg/kg Q2W IV) are 220 µg/mL (28.3%) and 1370 µg·day/mL (27.8%), respectively, based on population pharmacokinetic (PK) simulations. Mean (%CV) Cmax and AUC at the steady state with the maximum proposed clinical dosing regimen (10 mg/kg Q2W IV) are 380 µg/mL (27.0%) and 3460 µg.day/mL (35.0%), respectively, based on population PK simulations.	
Maximum tolerated dose	NOAEL for durvalumab is 200 mg/kg IV loading dose followed by 4 or 13 weekly doses of 100 mg/kg IV in cynomolgus monkeys. No maximum tolerated dose (MTD) for durvalumab was identified in patients treated within the dose range of 0.1 to 20 mg/kg Q2W, 15 mg/kg every 3 weeks (Q3W), or 20 mg/kg every 4 weeks (Q4W).	
Principal adverse events	In the urothelial carcinoma (UC) cohort, the most common (any grade; ≥ 20% of patients) adverse events (AEs) were fatigue and constipation. The majority of patients had events of Grade 1 or 2 severity; Grade 3 or 4 AEs were reported in 45 (23.6%) patients. The most common (> 3% of patients) Grade 3 or 4 AEs were anemia, hyponatremia, acute kidney injury, urinary tract infection, fatigue, back pain, and asthenia. No dose-limiting toxicities (DLTs) were observed, therefore, a MTD of durvalumab was not defined.	
Maximum dose tested	Single Dose	No single ascending dose (SAD) studies were conducted for durvalumab.
	Multiple Dose	10 mg/kg Q2W IV for 12 months 15 mg/kg Q3W IV for 12 months 20 mg/kg Q4W IV for 12 months
Exposures Achieved at	Single Dose	No SAD studies were conducted for durvalumab.

	Multiple Dose	All data are depicted as geometric mean (n, geometric %CV) **First Dose:** <u>10 mg/kg Q2W</u> $Cmax_{Dose1}$ = 224 µg/mL (851, 35.7%) AUC_{Dose1} = 1780 µg·day/mL (5, 39.1%) <u>15 mg/kg Q3W</u> $Cmax_{Dose1}$ = 427 µg/mL (7, 25.5%) AUC_{Dose1} = 2940 µg·day/mL (7, 36.3%) <u>20 mg/kg Q4W</u> $Cmax_{Dose1}$ = 416 µg/mL (18, 23.9%) AUC_{Dose1} = 4500 µg·day/mL (18, 23.1%)
		Steady State Dose: <u>10 mg/kg Q2W</u> $Cmax_{Dose8}$ = 409 µg/mL (34, 35.7%) <u>15 mg/kg Q3W</u> $Cmax_{Dose6}$ = 582 µg/mL (3, 54.8%) <u>20 mg/kg Q4W</u> $Cmax_{Dose4}$ = 489 µg/mL (n=9, 32.7%)
Range of linear PK	≥ 3 mg/kg Q2W IV to 10 mg/kg Q2W IV or 15 mg/kg Q3W IV or 20 mg/kg Q4W IV	
Accumulation at steady state	**Accumulation Ratio of Cmin:** 10 mg/kg Q2W = 3.15 (n=27, CV=57.3%) 15 mg/kg Q3W = 2.05 (n=3, 67.5%) 20 mg/kg Q4W = 1.44 (n=10, 47.6%) **Accumulation Ratio of Cmax:** 10 mg/kg Q2W = 1.83 (n=34, CV=35.7%) 15 mg/kg Q3W = 1.43 (n=3, 28.5%) 20 mg/kg Q4W = 1.07 (n=9, 41.4%)	
Metabolites	Not applicable	
Absorption	Absolute/Relative Bioavailability	Durvalumab is administered as an IV infusion.
	Tmax	0 0780 day (n = 5, %CV = 222%)
Distribution	Vd/F or Vd	V_1 = 3.51 L (%CV = 21.2%); V2 = 3.51 L (%CV = 39.9%)
	% bound	Not applicable
Elimination	Route	IV
	Terminal t½	21.8 days (%CV = 51.6%)
	CL/F or CL	0 226 L/day (%CV = 29.3%)

Intrinsic Factors	Age	Not identified as a covariate influencing durvalumab PK based on population PK analysis
	Sex	Females had +18% higher Cmax,ss and +15% higher AUCss than males
	Race	Not identified as a covariate influencing durvalumab PK based on population PK analysis
	Hepatic & Renal Impairment	**Renal impairment:** Based on the population PK analysis, Cmax,ss and AUCss increased by +2% and +5% for a patient with CRCL estimate at the 10th percentile (56.9 ml/min) of the distribution of CRCL values observed (range from 26.6 to 271 mL/min) compared to the typical individual (median = 87.3 mL/min); no clinically relevant effect of renal function on durvalumab PK was noticeable for patients with mild renal impairment (n = 522) and for patients with moderate renal impairment (n = 179); data were not sufficient to draw a definite conclusion on severely renally impaired patients (n = 2).
		Hepatic impairment: Based on the population PK analysis, no effect of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin (BIL) on durvalumab PK was observed; no clinically relevant effect of hepatic function on durvalumab PK was noticeable for patients with mild hepatic impairment (n = 220); data were not sufficient to draw definite conclusion on patients with moderate hepatic impairment (n = 4) and patients with severe hepatic impairment (none have received durvalumab).
Extrinsic Factors	Drug interactions	Not tested
	Food Effects	Not tested
Expected High Clinical Exposure Scenario	Based on population PK analysis, there was no clinically significant effect of age, body weight, gender, positive ADA status, albumin levels, LDH levels, creatinine levels, soluble PD-L1 (sPD-L1) levels, tumor type, race, mild to moderate renal impairment, mild hepatic impairment, or ECOG status on the PK of durvalumab. None of the above covariates were found to be clinically relevant since the change in PK parameters or exposure metrics (steady state Cmax, Cmin, and AUC) were < 30%. In fact, the changes were < 20% for majority of these covariates.	

Preclinical Cardiac Safety	Whilst biotechnology-derived products are not specifically excluded from ICH S7B guidance, it is widely recognized that monoclonal antibodies are unlikely to interact with the hERG channel or other cardiac ion channels to impact on cardiac repolarization (Vargas et al, 2008). For durvalumab in particular, this is based on its mode of action (i.e. PD-L1 blockade), high binding specificity and selectivity, large molecular size and weight (~150 kDa), and inability to cross plasma membranes. Therefore, in accordance with ICH S6(R1), ICH S9 and ICH S7A, safety pharmacology endpoints –including potential impact of durvalumab on cardiovascular parameters- were evaluated in the GLP 4- and 13-week repeat-dose toxicity studies in cynomolgus monkeys. In the GLP 4-week study cardiovascular parameters were assessed pre-treatment (3 occasions) and on Day 8 and 29 (pre-dose and approximately 1 hour post dose), and in the GLP 13-week study assessments were carried out pre-treatment (2 occasions) and on Days 36 and 85 (pre-dose and approximately 1 hour post dose). Parameters evaluated by 6-lead ECG included heart rate, wave form morphology, ST segment and PR and QT interval (including corrected QT interval [QTcM or QTcB]), with blood pressure being assessed by a compression cuff attached to the base of the tail. In these studies, no durvalumab-related effects on any of the parameters assessed were noted.

Clinical Cardiac Safety	The safety data included in the BLA package were obtained from 2 monotherapy studies, Study 1108 and ATLANTIC. In-depth assessment of centrally-read ECG were done in 265 patients from ATLANTIC and summarized in the QTc report. The study showed no evidence of clinically meaningful cardiac effects associated with durvalumab. In addition, the durvalumab serum concentration versus ΔQTcF analysis did not indicate a risk for clinically significant QT prolongation. In Study 1108, the number of subjects at different drug exposure levels are 4 at 0.3 mg/kg Q2W, 3 at 1.0 mg/kg Q2W, 3 at 3.0 mg/kg Q2W, 6 at 10 mg/kg Q2W, 7 at 15 mg/kg Q3W, 21 at 20 mg/kg Q4W during dose-escalation/-exploration phase, and 970 at 10 mg/kg Q2W. In addition, 444 patients were treated at 10 mg/kg Q2W in ATLANTIC. In patients treated with durvalumab at 10 mg/kg Q2W (Study 1108 n=970, ATLANTIC n=444), there were 14 syncope cases (12 from Study 1108, 2 from ATLANTIC), 6 seizure cases (4 from Study 1108, 2 from ATLANTIC), 1 ventricular tachycardia from Study 1108, 3 QT prolonged reported (2 from ATLANTIC; 1 from Study 1108) under Investigations SOC; no other ventricular arrhythmia, ventricular fibrillation and flutter, or torsade de pointes were observed. There was 1 sudden death reported in ATLANTIC (Patient E7007008), which was assessed as potentially related to this patient's prior medical history and/or comorbidities. In patients treated with a higher dose of durvalumab at 15 mg/kg Q3W (n=7) and 20 mg/kg Q4W (n=21) in Study 1108, there was no QT prolongation, syncope, seizure, ventricular arrhythmia, ventricular fibrillation and flutter, torsade de pointes, or sudden death reported. In conclusion, the AEs of syncope, seizure, ventricular tachycardia and QT prolonged described above did not indicate durvalumab's effect on cardiac safety. Along with in-depth QTc assessment in QTc substudy of ATLANTIC and nonclinical data, it suggests that durvalumab is not associated with any clinically significant adverse impact on cardiac depolarization and repolarization, which is consistent with other PD-1/PD-L1 antibodies in the same class.

6.2 SCHEDULE OF ASSESSMENTS

Visit (Assessments were to be performed at the times stipulated in the table and as clinically required in the management of the patient.)	Pre screening for PD-L1 status only	Screening	All assessments were to be performed preinfusion unless stated otherwise								
								Every 2 weeks	Every 4 weeks	Every 8 Weeks	Every 12 weeks
Day	-42 to -1	-28 to -1	1	15	29	43	57	Day 1 of the week			
Week	-6 to -1	-4 to -1	0	2	4	6	8	10, 12, 14, 16, etc	12, 16, 20, 24, 28, etc	16, 24, 32, 40, and 48	16, 28, 40, 52
				(±3 days)						(±7 days)	
Written informed consent/assignment of patient identification number	X										
Preliminary eligibility fulfilment (Investigator's opinion)	X										
Demography and history of tobacco and alcohol use[a]	X										
Previous treatments for NSCLC	X										
Archival FFPE tumor tissue sample for PD-L1 assay[a]	X										
Recent formalin-fixed tumor biopsy for PD-L1 assay[a]	X										
Formal verification of eligibility criteria		X	X								
Medical and surgical history		X									
Hepatitis B and C; HIV		X									
Urine hCG or serum βhCG		X	X	X	X	X	X	X			
Kit assignment and durvalumab administration			X	X	X	X	X	X			
Physical examination		X	X	X	X	X	X		X		
Vital signs (pre and post infusion vital signs assessments)		X	X	X	X	X	X	X			
Weight		X	X		X		X		X		
ECG		X	X[b]				X			X[b]	
Adverse event/serious adverse event assessment		X	X	X	X	X	X	X			
Concomitant medications		X	X	X	X	X	X	X			

Visit (Assessments were to be performed at the times stipulated in the table and as clinically required in the management of the patient.)	Pre screening for PD-L1 status only	Screening	All assessments were to be performed preinfusion unless stated otherwise								
								Every 2 weeks	Every 4 weeks	Every 8 Weeks	Every 12 weeks
Day	-42 to -1	-28 to -1	1	15	29	43	57	Day 1 of the week			
Week	-6 to -1	-4 to -1	0	2	4	6	8	10, 12, 14, 16, etc	12, 16, 20, 24, 28, etc	16, 24, 32, 40, and 48	16, 28, 40, 52
				(±3 days)						(±7 days)	
Palliative radiotherapy		As clinically indicated →									
WHO performance status		X	X	X	X	X	X	X			
Serum chemistry[c]		X	X	X	X	X	X	X			
Amylase, lipase (where available)		X	X		X		X		X		
Thyroid function tests (TSH and T3 and T4)		X	X		X		X		X		
Hematology[c]		X	X	X	X	X	X	X			
Urinalysis[d]		X	X		X		X		X		
Coagulation parameters[e]		X									
Pharmacokinetic assessment[a]			X (and EOI)		X						X[f]
Immunogenicity assessment (ADA sampling [including ADA neutralizing antibodies] to identify ADA responses in patient circulation)[a]			X		X						X[f]
sPD-L1 concentration (to assess target engagement)[a]			X								X[g]
Circulating soluble factors (to assess cytokines, chemokines, growth factors and antibodies against tumor and self-antigens in circulation)			X		X				X (Week 12 only)		
miRNA/mRNA (to examine immune cell gene expression profiles in circulation)			X				X			X (Week 48 only)	

Visit (Assessments were to be performed at the times stipulated in the table and as clinically required in the management of the patient.)	Pre screening for PD-L1 status only	Screening	All assessments were to be performed preinfusion unless stated otherwise								
								Every 2 weeks	Every 4 weeks	Every 8 Weeks	Every 12 weeks
Day	-42 to -1	-28 to -1	1	15	29	43	57	Day 1 of the week			
Week	-6 to -1	-4 to -1	0	2	4	6	8	10, 12, 14, 16, etc	12, 16, 20, 24, 28, etc	16, 24, 32, 40, and 48	16, 28, 40, 52
				(±3 days)						(±7 days)	
PGx sample (optional [DNA element])[a]		X									
Tumor assessment (CT or MRI)[h,i,j]		X					X			X	

a Assessment was not to be repeated if patient was re-treated.

b On Day 1 and Week 16, ECGs were to be taken within an hour prior to the start of the infusion, within 30 minutes post-infusion, and 3 hours (±15 minutes) post-infusion.

c If screening laboratory assessments were performed within 3 days prior to Day 1, they did not need to be repeated at Day 1. Results for urea and electrolytes, full blood count, and liver function tests were to be available before commencing an infusion. Gamma-glutamyltransferase was tested at Screening, Day 1, and as clinically indicated. Creatinine clearance, magnesium, amylase, lipase, and uric acid tested were at Screening and every 4 weeks thereafter.

d Urinalysis was performed at Screening, Day 1, every 4 weeks, and as clinically indicated.

e Coagulation tests: prothrombin time, APTT and INR – only performed at Screening and as clinically indicated.

f These assessments were performed every 12 weeks following the Week 4 assessment; thus at Week 16, Week 28, etc.

g sPD-L1 concentration were performed at Day 1 and Week 16 of the treatment period only.

h RECIST 1.1 assessments were performed using CT/MRI assessments of the chest and abdomen (including liver and adrenal glands). Additional anatomy was imaged based on signs and symptoms of individual patients. Baseline assessments were to be performed no more than 28 days before start of durvalumab, and ideally were to be performed as close as possible to the start of durvalumab. Follow-up assessments were performed every 8 weeks for the first 48 weeks (relative to the date of the first infusion of durvalumab) until confirmed objective disease progression per RECIST 1.1. The confirmatory scans were preferably to have been performed at the next scheduled visit (relative to the date of the first infusion) and no less than 4 weeks after the initial assessment of CR/PR and PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient had not progressed, every attempt was made to perform the subsequent assessments at their scheduled visits (relative to the date of the first infusion). All confirmatory scans were recorded on the database. For all patients who were treated through progression, the Investigator was to ensure that patients did not have any significant, unacceptable or irreversible toxicities that indicated that continuing treatment would not further benefit the patient, and that the patient still fulfilled eligibility criteria for this study including re-consenting to continue treatment. The patient must have still met those inclusion and exclusion criteria that were relevant to treatment through disease progression and retreatment as specified in Appendix 12.1.1, CSP Section 4.3. Patients with rapid tumor progression or with symptomatic progression that required urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) were not eligible to continue to receive durvalumab.

i Patients who achieved and maintained disease control (ie, CR, PR, or SD) through to the end of the 12-month durvalumab treatment period could restart treatment with durvalumab upon evidence of PD, with or without confirmation, during follow-up. Before restarting durvalumab, the Investigator was to ensure patients did not have any significant, unacceptable, or irreversible toxicities that indicated continuing treatment would not further benefit the patient, and that the patient still fulfilled eligibility criteria for this study including re-consenting to restart durvalumab. To restart treatment the patient must not have received an intervening systemic anticancer therapy

post-durvalumab discontinuation. Patients were to have a baseline tumor assessment within 28 days of restarting treatment with durvalumab, all further scans were to occur every 8 weeks (relative to the date of restarting treatment) until durvalumab was stopped (maximum of 12 months of further treatment).

j Patients with confirmed PD who continued to receive durvalumab at the discretion of the Investigator could receive treatment for a maximum of 12 months. Patients were to have scans every 8 weeks while on treatment (relative to the date of the first infusion) until durvalumab was stopped. Patients with rapid tumor progression or with symptomatic progression that required urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) were not eligible to continue to receive durvalumab. Durvalumab was discontinued if there was confirmed PD following a previous response (PR or CR) to durvalumab.

Note: If a patient had a delay to an infusion of durvalumab all assessments were to be conducted relative to the date of the first infusion.

Note: For 'retreatment' patients who went on to have a subsequent 12 months of treatment, the same assessments were to be done as in the screening and first 12 month treatment period with the exception of the PK, ADA, sPD-L1, PGx, and biopsy assessments, which did not need to be collected a second time.

ADA anti-drug antibody, APTT activated partial thromboplastin time, CR complete response, CT computed tomography, EOI end of infusion, FFPE formalin-fixed paraffin-embedded, hCG human chorionic gonadotropin, HIV human immunodeficiency virus, INR international normalized ratio, miRNA micro RNA, MRI magnetic resonance imaging, mRNA messenger RNA, NSCLC non-small cell lung cancer, PD progression of disease, PGx pharmacogenetic(s), PR partial response, RECIST Response Evaluation Criteria in Solid Tumors, RNA ribonucleic acid, sPD-L1 soluble programmed cell death ligand-1, T3 triiodothyronine, T4 thyroxine, TSH thyroid stimulating hormone.

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/s/

DHANANJAY D MARATHE
02/22/2017
Hongshan Li was the primary reviewer for this submission.

HONGSHAN LI
02/22/2017

JANELL E CHEN
02/22/2017

QIANYU DANG
02/22/2017

MICHAEL Y LI
02/22/2017

CHRISTINE E GARNETT
02/22/2017

LABEL AND LABELING REVIEW

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

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

Date of This Review:	December 28, 2016
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	BLA 761069
Product Name and Strength:	Imfinzi (Durvalumab) Injection, 500 mg/10 mL and 120 mg/2.4 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	AstraZeneca Pharmaceuticals LP
Submission Date:	October 17, 2016 December 22, 2016
OSE RCM #:	2016-2536
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

AstraZeneca submitted the container labels, carton labeling, and prescribing information (PI) for Imfinzi (Durvalumab) Injection for BLA 761069. This is a New Molecular Entity (NME) product with a proposed indication for the treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4) (b) (4).

The Division of Oncology Products 1 (DOP1) requested that we review the submitted Imfinzi container labels, carton labeling, and PI 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
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the proposed Imfinzi container label and noticed that this is a small label since the height of the vial is only 4.5 cm, and the surface area of the vial for container label is 3.1 cm in height. Therefore, although the container label does not contain the NDC number and the usual dose statement, the container label does contain the minimum amount of information required per 21 CFR 201.10(i). However, we recommend that the statement "IMFINZI is a trademark of the AstraZeneca group of companies © AstraZeneca XXXX" be replaced with the statement "Must dilute before use. See prescribing information." on the side panel to minimize the risk of the product administered without dilution. We also plan to clarify what the (b) (4) box is with the Applicant. The proposed carton labeling is acceptable from a medication error perspective.

We reviewed the proposed Imfinzi PI and recommend adding unit of measurement at the end of each numerical doses for clarity. We also recommend specifying the appropriate volume for the intravenous bag, and providing minor editorial edits for the preparation instructions for clarity.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container label, carton labeling and PI labeling for Imfinzi may be improved to promote the safe use of the product as described in Section 4.1 and Section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
    a. Dosage and Administration section, Full PI
        i. Consider adding a unit of measurement after each numerical dose in Table 1 for clarity. For example, “1 mg/kg/day to 2 mg/kg/day”.
        ii. In section 2.3, consider specifying the appropriate volume of the intravenous bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP for clarity.
        iii. In section 2.3, relocate the sentence “Do not shake the solution.” after the sentence “Mix diluted solution by gentle inversion.” for clarity.

4.2 RECOMMENDATIONS FOR ASTRAZENECA

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

A. Container label
    a. Replace the statement “IMFINZI is a trademark of the AstraZeneca group of companies © AstraZeneca XXXX” with “Must dilute before use. See prescribing information.” on the side panel to minimize the risk of the product administered without dilution.
    b. Clarify what the (b) (4) box is on the side panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Imfinzi that AstraZeneca submitted on October 13, 2016.

Table 2. Relevant Product Information for Imfinzi	
Initial Approval Date	N/A
Active Ingredient	durvalumab
Indication	Treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4) (b) (4)
Route of Administration	Intravenous
Dosage Form	Solution for injection
Strength	50 mg/mL
Dose and Frequency	10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks. Dose escalation or reduction is not recommended. Dosing withholding or discontinuation may be required based on individual safety and tolerability.
How Supplied	Supplied in a carton containing one single-dose vial: • 500 mg/10 mL • 120 mg/2.4 mL
Storage	Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in original carton to protect from light
Container Closure	**Vial:** (b) (4) (b) (4) USP/Ph. Eur./JP Type I **Stopper:** (b) (4) (b) (4) USP/Ph. Eur./JP **Seal:** (b) (4) (b) (4)

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

TINGTING N GAO
12/28/2016

CHI-MING TU
12/28/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

<table>
<tr><th colspan="3">Application Information</th></tr>
<tr><td>NDA #
BLA# 761069</td><td>NDA Supplement #: S-
BLA Supplement #: S-</td><td>Efficacy Supplement Category:
☐ New Indication (SE1)
☐ New Dosing Regimen (SE2)
☐ New Route Of Administration (SE3)
☐ Comparative Efficacy Claim (SE4)
☐ New Patient Population (SE5)
☐ Rx To OTC Switch (SE6)
☐ Accelerated Approval Confirmatory Study (SE7)
☐ Labeling Change With Clinical Data (SE8)
☐ Manufacturing Change With Clinical Data (SE9)
☐ Animal Rule Confirmatory Study (SE10)</td></tr>
<tr><td colspan="3">Proprietary Name: Imfinzi
Established/Proper Name: durvalumab
Dosage Form: Injection
Strengths: 500 mg/vial and 120 mg/vial</td></tr>
<tr><td colspan="3">Applicant: AstraZeneca UK Limited
Agent for Applicant (if applicable): Jamie Gillette</td></tr>
<tr><td colspan="3">Date of Application: October 13, 2016
Date of Receipt: October 13, 2016
Date clock started after Unacceptable for Filing (UN):</td></tr>
<tr><td colspan="2">PDUFA/BsUFA Goal Date: June 13, 2017</td><td>Action Goal Date (if different): March 13, 2017</td></tr>
<tr><td colspan="2">Filing Date: December 12, 2016</td><td>Date of Filing Meeting: December 6, 2016</td></tr>
<tr><td colspan="3">Chemical Classification (original NDAs only) :
☐ Type 1- New Molecular Entity (NME); NME and New Combination
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
☐ Type 3- New Dosage Form; New Dosage Form and New Combination
☐ Type 4- New Combination
☐ Type 5- New Formulation or New Manufacturer
☐ Type 7- Drug Already Marketed without Approved NDA
☐ Type 8- Partial Rx to OTC Switch
☐ Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval)
☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)</td></tr>
<tr><td colspan="3">Proposed indication(s)/Proposed change(s): urothelial cancer</td></tr>
<tr><td colspan="2">Type of Original NDA:
AND (if applicable)
Type of NDA Supplement:

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

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☒ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	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 (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): (b) (4) 112249	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into electronic archive.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

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

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	☐		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☐	☒	

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

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

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

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

Forms and Certifications
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

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

Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☐	☒	☐	Only US official included
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]***	☒	☐		

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

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

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

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

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

If no, request in 74-day letter.				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	CDRH
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** March 3, 2015 (pre phase 3 meeting)	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** September 13, 2016	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 6, 2016

BACKGROUND: AstraZeneca UK Limited has submitted a new BLA 761069 for Imfinzi (durvalumab) for the treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4) is requesting priority review. The associated IND (b) (4) received breakthrough therapy designation. This application was submitted on a rolling basis and the last piece that started the PDUFA clock arrived October 13, 2016.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Janice Kim	Y
	CPMS/TL:	Alice Kacuba	Y
Cross-Discipline Team Leader (CDTL)	V. Ellen Maher		Y
Division Director/Deputy	Geoffrey Kim/Amna Ibrahim		Y/N
Office Director/Deputy	Richard Pazdur/Amy McKee		N/N
Clinical	Reviewer:	Daniel Suzman	Y
	TL:	V. Ellen Maher	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Yuhong Chen	Y
	TL:	Stacy Shord	Y
• Genomics	Reviewer:	Sarah Dorff	Y

• Pharmacometrics	Reviewer:	Rosane Charlab Orbach	N
Biostatistics	Reviewer:	Laura Fernandes	Y
	TL:	Shenghui Tang	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Eias Zahalka	Y
	TL:	Todd Palmby	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC) Review Team:	ATL:	Howard Anderson	Y
	RBPM:	Kelly Ballard/Melinda Bauerlien	N/N
• Drug Substance	Reviewer:	(DMA) Maria Jose Lopez-Barragan, Monica Markovski	Y
• Drug Product	Reviewer:	Michael Di, Davinna Ligons	Y
• Process	Reviewer:		
• Microbiology	Reviewer:		
• Facility	Reviewer:	Zhong Li	Y
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:	Jibril Abdus-Samad	Y
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Rowe Medina	N
	TL:	Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Linda Park	Y
	TL:	N/A	
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Tingting Gao	N
	TL:	Chi-Ming Tu	N
OSE/DRISK (REMS)	Reviewer:	Mei-Yean Chen	N
	TL:	Naomi Redd	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connor	N
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers/disciplines: QT, Compliance			
• CDRH *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:	Aaron Schetter	N
	TL:	Bob Becker, Reena Philip, Donna Roscoe	N
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

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., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ 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 ☒ No comments

CLINICAL **Comments**:	☐ 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:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **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
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	☐ YES ☐ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **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?	
• 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, MD, OHOP Director **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): January 13, 2017 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): Target action date: March 13, 2017 **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

APPEARS THIS WAY ON ORIGINAL

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

/s/

JANICE H KIM
12/09/2016

ALICE KACUBA
12/09/2016

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

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

Application: BLA 761069

Application Type: New BLA

Drug Name(s)/Dosage Form(s): Imfinzi (durvalumab) Injection

Applicant: AstraZeneca UK Limited

Receipt Date: October 13, 2016

Goal Date: June 13, 2016, **target date: March 13, 2017**

1. Regulatory History and Applicant's Main Proposals

AstraZeneca UK Limited has submitted a new BLA 761069 for Imfinzi (durvalumab) for the treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4) is requesting priority review. The associated IND has breakthrough therapy designation. This application was submitted on a rolling basis and the last piece that started the PDUFA clock arrived October 13, 2016.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

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

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

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

Comment:

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

Comment:

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

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

Comment:

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

Comment:

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

Heading	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information

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

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

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

Comment:

Boxed Warning (BW) in Highlights

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

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term

"**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

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

Comment:

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

Comment:

Recent Major Changes (RMC) in Highlights

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

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

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

Comment:

Dosage Forms and Strengths in Highlights

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

Comment:

Contraindications in Highlights

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

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

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

Comment:

Revision Date in Highlights

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

Comment:

Contents: Table of Contents (TOC)

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

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

Comment:

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

Comment:

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

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

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

Comment:

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

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

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

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

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment:

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

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

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

Comment:

BOXED WARNING Section in the FPI

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

Comment:

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

Comment:

CONTRAINDICATIONS Section in the FPI

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

Comment:

ADVERSE REACTIONS Section in the FPI

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

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

Comment:

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

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

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

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

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

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

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

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

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

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

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

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

Limitations of Use: Text (1)

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

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

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

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

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

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

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

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

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

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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/s/

JANICE H KIM
12/08/2016