CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203415Orig1s000

OTHER REVIEW(S)

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

PATIENT LABELING REVIEW

Date:	August 30, 2012
To:	Robert Justice, 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:	Latonia M. Ford, RN, BSN, MBA Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	XTANDI (enzalutamide)
Dosage Form and Route:	capsules for oral use
Application Type/Number:	NDA 203415
Applicant:	Medivation Inc.

1 INTRODUCTION

On May 17, 2012, Medivation Inc. submitted an Original New Drug Application (NDA) 203415 under Section 505(b)(1) of the Food, Drug, and Cosmetic Act for XTANDI **(**enzalutamide) capsules. The Applicant's proposed indication for XTANDI (enzalutamide) capsules is for the treatment of patients with castration-resistant prostate cancer who have received docetaxel.

On July 16, 2012 the Division of Oncology Products 1 (DOP1) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for XTANDI **(**enzalutamide) capsules.

This review is written in response to a request by DOP1 for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for XTANDI **(**enzalutamide) capsules.

2 MATERIAL REVIEWED

- Draft XTANDI **(**enzalutamide) capsules Patient Package Insert (PPI) received on May 17, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on August 28, 2012.
- Draft XTANDI **(**enzalutamide) capsules Prescribing Information (PI) received on May 17, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on August 28, 2012.
- Approved Zytiga (abiraterone acetate) Tablets comparator labeling dated July 3, 2012.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

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

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

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

7 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/

LATONIA M FORD
08/30/2012

BARBARA A FULLER
08/30/2012

LASHAWN M GRIFFITHS
08/30/2012

PMR 1
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 # Enzalutamide (Xtandi®)
Product Name:

PMR Description: **1918-1:**
Perform an in vitro screen to determine if N-desmethyl enzalutamide is metabolized by the major human CYP450 isozymes. Based on results from the in vitro screen, clinical drug-drug interaction trials may be needed.

PMR Schedule Milestones:		
	Final Protocol Submission:	12/2012
	Study Completion:	06/2013
	Final Report Submission:	12/2013
	Other:	MM/DD/YYYY

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

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

N-desmethyl enzalutamide is a major active metabolite of enzalutamide, however, the metabolism of N-desmethyl enzalutamide by major human CYP450 isozymes was not reported in the NDA submission. An *in vitro* screen to determine if N-desmethyl enzalutamide is metabolized by major CYP450 izozymes will help determine the likelihood of drug-drug interactions in which CYP450 inducers and inhibitors may alter concentrations of N-desmethyl enzalutamide *in vivo*.

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

The metabolism of N-desmethyl enzalutamide *in vitro* was not reported in the NDA submission. An *in vitro* screen to determine if N-desmethyl enzalutamide is metabolized by major human CYP450 isozymes will help determine the likelihood of drug-drug interactions in which CYP450 inducers and inhibitors may alter concentrations of N-desmethyl enzalutamide *in vivo*.

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

- **Which regulation?**

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

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

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

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

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

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

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

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

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

The required study will be an *in vitro* screen to assess if N-desmethyl enzalutamide is metabolized by major human CYP450 isozymes.

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

☐ Other

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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 #	203415
Product Name:	enzalutamide (Xtandi®)
PMR Description:	**PMR-1918-2:** Convene a panel of experts in oncology and neurology to obtain recommendations regarding which patients, if any, who were excluded from the randomized clinical trial because of increased risk of seizure should be evaluated in a postmarketing safety trial. Following the panel's recommendations, conduct a single-arm safety trial to assess the risk of seizure with enzalutamide 160 mg/day in at least 350 patients with metastatic castration-resistant prostate cancer who are at increased risk for seizure, e.g., patients with a history of seizure (taking/not taking anticonvulsants), loss of consciousness, transient ischemic attack or cerebrovascular accident, arteriovenous malformation in the brain, head trauma with loss of consciousness, treated brain metastases, use of medications which may decrease the seizure threshold, or other risk factors for the development of seizures. The primary endpoint should be the incidence of seizure. Patients should remain on study until disease progression, development of a seizure, or the development of an unacceptable adverse event. The protocol should contain clear stopping rules for an excessive incidence of seizures.

PMR Schedule Milestones:	Final Protocol Submission:	06/2013
	Trial Completion:	06/2018
	Final Report Submission:	03/2019
	Other: Expert Panel Recommendations	12/2012

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

The Phase 3 trial excluded patients at high-risk for seizure and no clinical trial information is available concerning the safety of enzalutamide in this subpopulation.

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."

Enzalutamide is associated with a 0.9% risk of seizure in a population at low-risk for seizure. The goal of the trial is to evaluate whether the risk of seizure is increased in patients who were excluded from the Phase 3 trial. The Phase 3 trial excluded patients with a history of seizure, loss of consciousness, TIA or CVA, AVM in the CNS, or head trauma with loss of consciousness. It also excluded patients treated brain metastases (brain metastases are uncommon in prostate cancer) and patients taking medications which may lower the seizure threshold.

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

- **Which regulation?**

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

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

X 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

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

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

The applicant has agreed to convene an expert panel and, based on their recommendations, to conduct a single-arm safety trial of 350 patients with metastatic castration-resistant prostate cancer who are at increased risk for seizure.

Required

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

Continuation of Question 4

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

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

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)

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

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

PMR/PMC Development Coordinator:

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

PMR3
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 #	NDA 203415, Enzalutamide (Xtandi®)
Product Name:	
PMR Description:	**1918-3:** Conduct a clinical trial in patients with normal hepatic function and patients with pre-existing severe hepatic impairment to assess the effect of severe hepatic impairment on the pharmacokinetics of enzalutamide and N-desmethyl enzalutamide. The proposed protocol must be submitted for review prior to trial initiation.

PMR Schedule Milestones:	Final Protocol Submission:	03/2013
	Trial Completion:	05/2014
	Final Report Submission:	11/2014
	Other:	MM/DD/YYYY

6. 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

Insufficient clinical and pharmacokinetic data are available to determine if a starting dose adjustment is needed for patients with pre-existing severe hepatic impairment. Therefore, a clinical trial in patients with normal hepatic function and patients with pre-existing severe hepatic impairment is required to identify the appropriate dose for patients with severe hepatic impairment.

7. 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."

A change in enzalutamide exposure is expected in individuals with pre-existing severe hepatic impairment, compared to patients with normal hepatic function. Therefore, a clinical trial in patients with normal hepatic function and patients with pre-existing severe hepatic impairment is required to identify the appropriate dose for patients with severe hepatic impairment.

8. 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?

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

The required clinical trial will be a trial designed to assess the pharmacokinetics of enzalutamide and N-desmethyl enzalutamide in patients with pre-existing severe hepatic impairment compared to those with normal hepatic function.

Required

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

Continuation of Question 4

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

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☐ 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

_____

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

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

PMR/PMC Development Coordinator:

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

_____

(signature line for BLAs)

PMR4
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 #	NDA 203415, Enzalutamide (Xtandi®)
Product Name:	
PMR Description:	**1918-4:** Conduct a drug interaction trial to evaluate the effect of rifampin (a strong CYP3A inducer and a moderate CYP2C8 inducer) on the pharmacokinetics of enzalutamide and N-desmethyl enzalutamide. The proposed trial protocol must be submitted for review prior to trial initiation.

PMR Schedule Milestones:	Final Protocol Submission:	04/2013
	Trial Completion:	07/2014
	Final Report Submission:	4/2015
	Other:	MM/DD/YYYY

11. 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

In vitro screens showed that CYP2C8 and CYP3A4 are responsible for the metabolism of enzalutamide. Thus, co-administration of Xtandi with CYP3A4 or CYP2C8 inducers can lead to a change in enzalutamide and N-desmethyl enzalutamide concentrations. However, no clinical drug-drug interaction trial has been conducted to address this issue. Therefore, a drug interaction trial with a strong rifampin (a strong CYP3A4 inducer and a moderate CYP2C8 inducer) is required.

12. 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."

CYP3A4 and CYP2C8 are responsible for the metabolism of enzalutamide. A clinical trial with a strong CYP3A inducer and a moderate CYP2C8 inducer, such as rifampin, is needed to accurately determine the magnitude of enzalutamide and N-desmethyl enzalutamide exposure changes when a strong CYP3A4 inducer or a moderate CYP2C8 inducer is co-administered with Xtandi. Depending on the results, a safe dose of Xtandi will be identified when co-administered with CYP3A4 and CYP2C8 inducers.

13. 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?

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

The required drug-drug interaction trial may be a crossover or parallel trial to evaluate the effect of a strong CYP3A4 inducer and a moderate CYP2C8 inducer, rifampin, on the pharmacokinetics of enzalutamide and N-desmethyl enzalutamide.

Required

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

Continuation of Question 4

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

_____

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

_____

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

_____

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

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

PMR/PMC Development Coordinator:

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

_____

(signature line for BLAs)

PMR5
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 #	NDA 203415, Enzalutamide (Xtandi®)
Product Name:	
PMR Description:	**1918-5:** Conduct a drug interaction trial to evaluate the effect of enzalutamide at steady state on the pharmacokinetics of CYP2D6 substrates. The proposed trial protocol must be submitted for review prior to initiation of the trial.

PMR Schedule Milestones:	Final Protocol Submission:	07/2013
	Trial Completion:	12/2014
	Final Report Submission:	06/2015
	Other:	MM/DD/YYYY

16. 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

In vitro screens showed that enzalutamide is an inhibitor of CYP2D6. Thus, co-administration of Xtandi with sensitive CYP2D6 substrates can lead to an increase in CYP2D6 substrate concentrations and risk of toxicity. However, no clinical drug-drug interaction trial has been conducted to address this issue. Therefore, a drug interaction trial with a sensitive CYP2D6 subtrate is required.

17. 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."

Enzalutamide inhibits CYP2D6. A clinical trial with a sensitive CYP2D6 substrate is needed to accurately determine the magnitude of CYP2D6 substrate exposure changes when a sensitive CYP2D6 substrate is co-administered with Xtandi.

18. 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?

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

The required drug-drug interaction trial can use a crossover or parallel trial design to evaluate the effect of enzalutamide at steady state on the pharmacokinetics of a sensitive CYP2D6 substrate.

Required

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

Continuation of Question 4

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

_____

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

_____

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

_____

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

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

PMR/PMC Development Coordinator:

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

_____

(signature line for BLAs)

PMR6
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 #	NDA 203415, Enzalutamide (Xtandi®)
Product Name:	
PMR Description:	**1918-6:** Conduct a drug interaction trial to evaluate the effect of enzalutamide at steady state on the pharmacokinetics of CYP1A2 substrates. The proposed trial protocol must be submitted for review prior to initiation of the trial.

PMR Schedule Milestones:	Final Protocol Submission:	07/2013
	Trial Completion:	12/2014
	Final Report Submission:	06/2015
	Other:	MM/DD/YYYY

21. 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

In vitro screens showed that enzalutamide is an inhibitor of CYP1A2. Thus, co-administration of Xtandi with sensitive CYP1A2 substrates can lead to an increase in CYP1A2 substrate concentrations and risk of toxicity. However, no clinical drug-drug interaction trial has been conducted to address this issue. Therefore, a drug interaction trial with a sensitive CYP1A2 subtrate is required.

22. 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."

Enzalutamide inhibits CYP1A2. A clinical trial with a sensitive CYP1A2 substrate is needed to accurately determine the magnitude of CYP1A2 substrate exposure changes when a sensitive CYP1A2 substrate is co-administered with Xtandi.

23. 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?

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

The required drug-drug interaction trial can use a crossover or parallel trial design to evaluate the effect of enzalutamide at steady state on the pharmacokinetics of a sensitive CYP1A2 substrate.

Required

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

Continuation of Question 4

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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

/s/

CHRISTY L COTTRELL
08/30/2012

KATHERINE M FEDENKO
08/30/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
Division of Prescription Drug Promotion (DPDP)
Division of Consumer Drug Promotion (DCDP)

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

Memorandum

Date: August 29, 2012

To: Christy Cottrell, Regulatory Project Manager
Division of Oncology Products 1 (DOP1)
Office of Hematology Oncology Products (OHOP)

From: Marybeth Toscano, PharmD, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
OPDP

Michelle Safarik, MSPAS, PA-C, Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
OPDP

Subject: OPDP comments on draft product labeling for Xtandi (enzalutamide) capsules
NDA 203415

In response to your consult request dated June 6, 2012, OPDP has reviewed the draft labeling (Package Insert [PI], Patient Package Insert [PPI], carton and container labels) for Xtandi capsules. OPDP's comments are based on the proposed, substantially complete version of the PI sent to OPDP via email on August 28, 2012, and on the carton and container labels submitted by the applicant, available in the EDR at \\CDSESUB1\EVSPROD\NDA203415\203415.enx

OPDP has no comments on the carton and container labels.

If you have any questions about OPDP's comments on the PI, please contact Marybeth Toscano at 6-2617 or at Marybeth.Toscano@fda.hhs.gov. If you have any questions about our comments on the PPI, please contact Michelle Safarik at 6-0620 or at Michelle.Safarik@fda.hhs.gov.

4 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/

MARYBETH TOSCANO
08/29/2012

MICHELLE L SAFARIK
08/29/2012

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: August 14, 2012

TO: Y. Max Ning, M.D., Ph.D.
V. Ellen Maher, M.D., Clinical Team Leader
Christy Cottrell, Regulatory Project Manager
Division of Oncology Products I
Office of Hematology and Oncology Products

FROM: Jean Mulinde, M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
(Acting for: Susan D. Thompson, M.D.
Acting Branch Chief, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations)

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 203415

APPLICANT: Astellas Pharma Global Development, Inc. (on behalf of Medivation, Inc.)

DRUG: Enzalutamide [Xtandi™ (proposed)]

NME: Yes

REVIEW PRIORITY: Priority Review

INDICATION: For the treatment of patients with castration-resistant prostate cancer who have received docetaxel (b) (4).

CONSULTATION REQUEST DATE: June 6, 2012
CLINICAL INSPECTION SUMMARY DATE: July 30, 2012
DIVISION ACTION GOAL DATE: August 31, 2012
PDUFA DATE: November 22, 2012

I. BACKGROUND:

Xtandi™ (Enzalutamide, MV3100) is an androgen receptor signaling inhibitor. It is provided as soft gelatin capsules for oral administration (40 mg enzalutamide per capsule). The mechanism of action of enzalutamide is proposed to occur via inhibition of (b) (4) steps in the androgen receptor signaling pathway, which is believed to result in decreased growth of prostate cancer cells and induction of cancer cell death and tumor regression. Based on the Applicant's summary of pivotal Phase 3 data, use of enzalutamide in subjects with castration-resistant prostate cancer who had received prior docetaxel therapy resulted in statistically significantly higher survival rates when compared to placebo (median survival (months): enzalutamide, 18.4 vs. placebo, 13.6).

According to the Applicant, the most common adverse events (≥5% and at least 2% greater than placebo) occurring in subjects enrolled in the enzalutamide Phase 3 development program were fatigue, diarrhea, hot flush, musculoskeletal pain, headache, insomnia, hematuria, paresthesia, anxiety, hypertension, and nasopharyngitis. Of note, increased risk of seizure was also observed in subjects treated with enzalutamide. Because enzalutamide is eliminated primarily by hepatic metabolism and has a long half life, caution is also warranted when administered with similarly metabolized drug products (e.g., paclitaxel, phenytoin, warfarin, colchicine, dabigatran etexilate, digoxin) as co-administration may result in altered pharmacokinetics and increased risk of drug related adverse events.

In support of the efficacy and safety of Xtandi™ (Enzalutamide, MV3100), for the treatment of patients with castration-resistant prostate cancer who have received docetaxel therapy, the Applicant has submitted data from one pivotal Phase 3 study (CRPC2). A brief description of this study follows.

PROTOCOL CRPC2, ENTITLED "A MULTINATIONAL PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED EFFICACY AND SAFETY STUDY OF ORAL MDV3100 IN PATIENTS WITH PROGRESSIVE CASTRATION-RESISTANT PROSTATE CANCER PREVIOUSLY TREATED WITH DOCETAXEL-BASED CHEMOTHERAPY"

Study CRPC2 (AFFIRM) was a randomized, double-blind, placebo-controlled, multicenter, Phase 3 study evaluating the efficacy and safety of MDV3100 in patients with progressive castration-resistant prostate cancer previously treated with 1 or 2 prior chemotherapy regimens, at least 1 of which was docetaxel-based. Once determined to be eligible [key eligibility criterion required a histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features, ongoing androgen deprivation therapy (i.e. medical or surgical castration), and history of disease progression on prior

docetaxel-based chemotherapy] subjects were randomized to receive either MDV3100 (160 mg daily) or placebo. Randomized subjects were to receive their assigned therapy until disease progression was documented and confirmed (i.e., confirmed radiographic progression or the occurrence of a skeletal-related event) AND the subject initiated another systemic antineoplastic therapy. The occurrence of an adverse event, where continued administration of study drug was deemed not in the subject's best interest by the investigator and/or the sponsor, also resulted in the removal of the subject from therapy.

The study was conducted at 154 clinical investigator sites in 15 countries: Argentina (4), Australia (16), Austria (2), Belgium (6), Canada (12), Chile (3), Germany (12), Spain (6), France (19), Italy (4), Netherlands (3), Poland (3), South Africa (3), United Kingdom (11), and USA (50). A total of 1199 subjects were randomized into the trial and 780 subjects were treated with MDV3100. The first subject was enrolled in the study September 22, 2009 and the last subject was enrolled November 15, 2010. Study CRPC2 is an ongoing study; however, the data cutoff date for the NDA submission was (b) (6) and the database was locked for NDA submission on December 16, 2011. According to the NDA submission this study was sponsored by Medivation, Inc. (San Francisco, CA). The study medical monitor was Mohammad Hirmand, MD. Three contract research organizations provided monitoring support: (b) (4) . The clinical database was built and clinical data management support provided by (b) (4) The safety database (for serious adverse events) was managed by (b) (4) recently renamed (b) (4) performed the randomization using an interactive voice response system/interactive web response system (IVRS/IWRS) and worked with (b) (4) who shipped drug to study sites with IVRS management of study drug inventories. Laboratory samples for chemistry, hematology, and prostate-specific antigen (PSA) were collected and sent to 1 of 3 (b) (4) central laboratory facilities: (b) (4) Pharmacokinetic (PK) samples were analyzed at (b) (4) Electronic copies of computed tomography (CT)/magnetic resonance imaging (MRI) and bone scans were sent to (b) (4) for storage. Electrocardiograms (ECGs) from all study patients were electronically transferred to (b) (4) for a blinded, independent analysis of ECGs, conducted with a limited number of skilled readers. (Note: A QTc study was embedded within this study and conducted at a subset of clinical sites.) Selected sites sent samples to the (b) (4) for measurement of circulating tumor cell counts.

An independent data monitoring committee (DMC) performed several functions during this study, according to a charter that defined its roles and responsibilities. The DMC was a multidisciplinary group consisting of clinicians and a biostatistician that was external to the Sponsor, any associated contract research organization, or participating Investigators. The DMC was responsible for providing an independent and ongoing general review of accumulated safety data, including survival, approximately every 4 months during the study by

masked treatment group (i.e., Treatment A and B). The data sets for these reviews were provided by an independent statistics unit at (b) (4). In addition, this study was also overseen by a Steering Committee consisting of experts in prostate cancer and members of the Sponsor's staff. The Steering Committee played a central role in the design of the study, oversaw the conduct of the study, and agreed on a plan for communication of the results. The Steering Committee was to have been blinded to patients' treatment assignment until the database was officially locked and unblinded.

The primary endpoint is overall survival. Survival is defined as time from randomization to death, due to any cause. Key secondary endpoints included disease progression endpoints:

- A comparison of radiographic progression-free survival between the MDV3100-treated and the placebo groups. Radiographic progression-free survival is defined as time from randomization to the earliest objective evidence of radiographic progression or death due to any cause. Patients were to be assessed for objective disease progression at regularly scheduled visits. Radiographic disease progression is defined by RECIST 1.1 for soft tissue disease, or the appearance of two or more new bone lesions on bone scan. Progression at the first scheduled reassessment at Week 13 required a confirmatory scan 6 or more weeks later. Please note, in this study endpoint assessment was made by the investigator, not by central radiograph readers.
- A comparison of time to first skeletal-related event between the MDV3100-treated and the placebo groups. The time to first skeletal-related event is defined as time from randomization to the occurrence of the first skeletal-related event. Patients were to be assessed for skeletal-related events at regularly scheduled visits. A skeletal-related event was defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. Please note, this study endpoint assessment was also made by the investigator.

Safety measurements included assessment of adverse events, the frequency of discontinuation of MDV3100 treatment due to adverse events, laboratory evaluations, and ECGs.

The clinical investigator sites were selected for inspection based on enrollment characteristics, patterns of protocol violations reported for the sites, and patterns of serious adverse event reporting. In addition, a sponsor inspection was conducted to evaluate the sponsor's overall conduct of the study.

II. RESULTS (By Site)

Name of CI	Protocol # Site# Subject#	Inspection Dates	Final Classification
Andrew Armstrong, M.D. Duke University Hospital Medical Center 10 Bryan Searle Dr. 471 Seeley G. Mudd Bldg Durham, NC 27710	Protocol: CRPC2 Site: #025 Subjects Enrolled: 15	June 13-15, 2012	NAI

Name of CI	Protocol # Site# Subject#	Inspection Dates	Final Classification
Oscar Goodman, M.D. Nevada Cancer Institute One Breakthrough Way Las Vegas, NV 89135	Protocol: CRPC2 Site: #017 Subjects Enrolled: 7	June 25 – July 3, 2012	Pending (Preliminary Classification NAI)
Karim Fizazi, M.D. Department of Medical Oncology Institut Gustave-Roussy 39 Rue Camille Desmoulins Villejuif 94805, France	Protocol: CRPC2 Site: #300 Subjects Enrolled: 90	July 30 – August 3, 2012	Pending (Preliminary Classification NAI)
Wolfgang Loidl, M.D. Krankenhaus der Barmherzigen Schwestern Linz Urologie Abteilung Seilerstätte 4 Linz 4010, Austria	Protocol: CRPC2 Site: #204 Subjects Enrolled: 14	August 6-9, 2012	Pending (Preliminary Classification NAI)
Medivation, Inc. 201 Spear Street, Third Floor San Francisco, CA 94105	Protocol: CRPC2	June 8-27, 2012	Pending (Preliminary Classification VAI)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
Pending = Preliminary classification based on information in 483, if issued, and preliminary communication with the field; the EIR has not been received from the field and complete review of EIR is pending.

1. **Andrew Armstrong, M.D.**
   Duke University Hospital Medical Center
   10 Bryan Searle Dr.
   471 Seeley G. Mudd Bldg
   Durham, NC 27710
   Site #025

   a) **What was inspected:**
   For Study CRPC2, at this site, 24 subjects were screened, 15 subjects were enrolled, and 14 subjects completed the study. Nine enrolled subjects' records were reviewed in depth during the inspection. In addition, 100% of the informed consents were reviewed. The record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to inclusion/exclusion criteria compliance, primary efficacy and key secondary endpoint data, concomitant medication usage, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also

evaluated test article accountability, monitoring and sponsor correspondence with the site, and IRB approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:
Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 203415 were compared. While minor record keeping errors were noted in the Establishment Inspection Report, the investigator's execution of the protocol was found to be generally adequate and a Form FDA 483, Inspectional Observations was not issued to the clinical investigator.

c) Assessment of data integrity:
The data provided by Armstrong's site for Study CRPC2 that were submitted to the Agency in support of NDA 203415 appear to be reliable and acceptable for use in support to the pending application.

2. Oscar Goodman, M.D.
Nevada Cancer Institute
One Breakthrough Way
Las Vegas, NV 89135
Site #017

a) What was inspected:
For Study CRPC2, at this site, 9 subjects were screened, 7 subjects were enrolled, and 7 subjects completed the study. All 9 subjects' records were reviewed during the inspection. The record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, primary efficacy and key secondary endpoint data, concomitant medication usage, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated test article accountability, monitoring and sponsor correspondence with the site, and IRB approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:
Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 203415 were compared. The investigator's execution of the protocol was found to be adequate and a Form FDA 483, Inspectional Observations was not issued to the clinical investigator.

c) Assessment of data integrity:
The data provided by Goodman's site for Study CRPC2 that were submitted to the Agency in support of NDA 203415 appear to be reliable and acceptable for use in support to the pending application.

Note: The EIR and associated exhibits for this inspection were not available at the time this CIS was written. The general observations described above are based on review of preliminary summary information provided by the ORA investigator. An inspection summary addendum will be generated if conclusions change upon review of the final EIR.

3. Karim Fizazi, M.D.
Department of Medical Oncology
Institut Gustave-Roussy
39 Rue Camille Desmoulins
Villejuif 94805, France
Site #300

a) What was inspected:
For Study CRPC2, at this site, 114 subjects were screened, 90 subjects were enrolled, and 16 subjects remained on study at the (b) (6) data cut off point. Currently 7 subjects are participating in the open label extension study. All enrolled subjects' records were reviewed to ensure appropriateness of consent procedures. Five enrolled subjects' records were reviewed in depth during the inspection. The record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to inclusion/exclusion criteria compliance, primary and key secondary efficacy endpoint data, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated protocol deviation reports, concomitant medication usage, monitoring and sponsor correspondence with the site, and IRB approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:
Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 203415 were compared. A Form FDA 483, Inspectional Observations, was not issued to the CI; however, several issues were discussed with the CI at inspection close-out. Discussion items included: 1) Two subjects that did not meet all eligibility criteria (Subject #002 was taking 20 mg of prednisone daily in violation of exclusion criterion #10, and Subject #005 with a history of stroke in violation of exclusion criterion #15), and 2) for four of the five subject records reviewed, source records did not include documentation of the relatedness of occurring adverse events to study medication.

<u>OSI Reviewer Comment:</u> Eligibility criteria violations for Subject #002 and Subject #005 were reported in the NDA. While the relatedness determinations for AEs reported were not supported by source documentation, the events themselves appear to have been accurately reported.

c) Assessment of data integrity:
Not withstanding the observations noted above, the data provided by Dr. Fizazi's site for Study CRPC2 that were submitted to the Agency in support of NDA 203415 appear to be adequately reliable and acceptable for use in support of the pending application.

Note: The EIR and associated exhibits for this inspection were not available at the time this CIS was written. The general observations described above are based on review of preliminary summary information provided by the ORA investigator. An inspection summary addendum will be generated if conclusions change upon review of the final EIR.

4. Wolfgang Loidl, M.D.
Krankenhaus der Barmherzigen Schwestern Linz Urologie Abteilung
Seilerstätte 4
Linz 4010, Austria
Site #204

a) What was inspected:
For Study CRPC2, at this site, 22 subjects were screened and 14 subjects were enrolled. Currently three subjects are participating in the open label extension study. All enrolled subjects' records were reviewed to ensure appropriateness of consent procedures. Five enrolled subjects' records were reviewed in depth during the inspection. The record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to inclusion/exclusion criteria compliance, primary and key secondary efficacy endpoint data, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated concomitant medication usage, monitoring and sponsor correspondence with the site, and IRB approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:
Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 203415 were compared. The investigator's execution of the protocol was found to be adequate and a Form FDA 483, Inspectional Observations was not issued to the clinical investigator.

c) Assessment of data integrity:
The data provided by Loidl's site for Study CRPC2 that were submitted to the Agency in support of NDA 203415 appear to be reliable and acceptable for use in support to the pending application.

Note: The EIR and associated exhibits for this inspection were not available at the time this CIS was written. The general observations described above are based on review of preliminary summary information provided by the ORA investigator. An inspection summary addendum will be generated if conclusions change upon review of the final EIR.

5. Medivation, Inc.
201 Spear Street, Third Floor
San Francisco, CA 94105
Sponsor Inspection

a) What was inspected:
The sponsor, Medivation, Inc., was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. Study CRPC2 was conducted globally, and during this sponsor/monitor inspection clinical site records for the CI sites listed in the table above were focused on. The record review included review of documents associated with the IRB approvals, site and investigator qualifications and site selection, delegation of monitoring activities to contractors and actual monitoring activities, drug accountability records, serious adverse events, and the Sponsor's handling of protocol deviations and violations. In addition, monitoring reports and oversight were reviewed for Sites #801, #302, and #112.

b) General observations/commentary:
Study CRPC2 was found to be generally adequately executed by the Sponsor, Medivation, Inc.; however, a two item Form FDA 483 was issued at the inspection closeout with the following observations:

i. Failure to ensure proper monitoring of a study and ensure that the study was conducted in accordance with the investigational plan [21 CFR 312.50]. Specifically, for:
   a. The Sponsor did not review clinical site monitoring reports within the timeframe required by the investigation plan. While the Monitoring Plan for Study CRPC2 stated that the sponsor was to review final monitoring reports within 30 calendar days of finalization, documentation observed during the inspection demonstrated that multiple monitoring reports were not reviewed within the required time frame (delays observed ranged from nine days to approximately one year). In addition, documentation of sponsor review of final monitoring reports was noted to be absent for three monitoring reports from Site 112.

b. The Monitoring Plan for Study CRPC2 states that monitors are to verify concomitant medication logs at each monitoring visit, but monitors failed to identify in a timely manner the enrollment of subjects (Subjects #300-02, #300-53, and #361-12) who should have been excluded from the study based on concomitant medication usage. Subject #300-02 was taking 20 mg cortancyl daily within four weeks of randomization (in violation of exclusion criterion #10), Subject #300-53 was taking mainserin, a tricyclic antidepressant (in violation of exclusion criterion #17), and Subject #361-12 was taking cyporterone, a steroidal antiandrogen (in violation of exclusion criterion #8).
c. The Protocol and Safety Management Plan Version 1 for Study CRPC2 contained conflicting information regarding who was responsible for reporting of SAEs to IRB/IECs in that the protocol stated the clinical investigator was responsible and the management plan stated the contract research organization to which safety evaluation was delegated, was responsible.
d. The Sponsor and study monitors failed to identify that the race reported for Subject 007-01 was stated incorrectly in the SAE case narrative for this subject as an African American male. The Subject, however, is a White male.

<u>OSI Reviewer Comment:</u> Deficiencies related to less than timely review of monitoring reports by the sponsor may have contributed to findings noted in b. above; however, primary efficacy and safety data from CI sites reviewed during the inspection were still considered reliable. In addition, the concomitant medications listed in b. above were accurately reported in the NDA. While observation c., above could result in deficiencies in SAE reporting to IRBs/IECs, such deficiencies were not observed during the inspection.

ii. Failure to provide to an investigator, prior to the start of an investigation, a brochure containing all of the information required [21 CFR 312.23(a)(5)]. Specifically, the contract research organization (CRO) for Australian sites (b) (4) confirmed receipt of the investigation brochure (IB) by clinical sites through use of a receipt form that required a signature and date, which was then returned to the clinical research organization. For seven Australian sites, the form confirming receipt of the IB by the clinical investigator was not signed until after the Study CRPC2 database lock.

<u>OSI Reviewer Comment:</u> While the Sponsor asserted that the responsibility to distribute the IB to the Australian sites belonged to the CRO to which monitoring of these sites was delegated, this task was not listed in the Transfer of Obligations; therefore, the responsibility remains with the Sponsor, Medivation.

A response from the Sponsor, Medivation, Inc., to the Form FDA 483, Inspectional Observations has not been received.

c) Assessment of data integrity:
The data generated, as it pertains to Study CRPC2 were inspected in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. Not withstanding the Form FDA 483 observations noted above, Study CRPC2 appears to have been conducted adequately by Medivation, Inc. and the data submitted by the Applicant for this study may be used in support of the pending Application.

Note: The EIR and associated exhibits for this inspection were not available at the time this CIS was written. The general observations described above are based on review of preliminary summary information provided by the ORA investigator. An inspection summary addendum will be generated if conclusions change upon review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for the inspections of Medivation, Inc., Dr. Loidl, Dr. Fizazi, and Dr. Goodman, as well as final review of inspectional findings for Dr. Armstrong, the data submitted by the Applicant for Study CRPC2 appear reliable in support of NDA 203415.

The preliminary classification for the inspection of Medivation, Inc. is Voluntary Action Indicated (VAI) based primarily on deficiencies in monitoring practices identified during the inspection.

The preliminary classifications for the inspections of Dr. Loidl, Dr. Fizazi, and Dr. Goodman are No Action Indicated (NAI). The final classification for the inspection of Dr. Armstrong is No Action Indicated (NAI).

Note: All observations noted above related to the inspections of Medivation, Inc., Dr. Goodman, Dr. Fizazi, and Dr. Loidl are based on Form FDA 483s, when issued, and communications with the field investigators who conducted these inspections; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR for these inspections.

{See appended electronic signature page}

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/s/

JEAN M MULINDE
08/14/2012

JANICE K POHLMAN
08/14/2012

Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

IND or NDA	NDA 203415
Brand Name	Xtandi
Generic Name	MDV3100 (enzalutamide)
Sponsor	Medivation, Inc.
Indication	Treatment of patients with castration-resistant prostate cancer who have received docetaxel (b) (4)
Dosage Form	Capsule
Drug Class	Androgen receptor inhibitor; antineoplastic
Therapeutic Dosing Regimen	160 mg q.d. (4 X 40 mg capsules q.d.), with or without food
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	240 mg q.d.
Submission Number and Date	22 May 2012
Review Division	DOP1

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

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No large changes in mean QTc intervals (i.e. >20 ms) were detected following the treatment of MDV3100 160 mg q.d. over 37 weeks of treatment. The largest upper bound of the 2-sided 90% CI for the mean difference between MDV3100 160 mg and placebo was 8.3 ms observed pre-dose at week 13 of treatment.

This is a randomized, double-blind, placebo-controlled, multicenter, Phase 3 study to evaluate the efficacy and safety of MDV3100 in patients with castration-resistant prostate cancer whose disease was progressing after 1 or 2 prior chemotherapy regimens, at least one of which was docetaxel-based. A total of 796 subjects administered MDV3100 160 mg q.d. had safety assessments available for analysis. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for MDV3100 160 mg q.d. (FDA Analysis)

Treatment	Time (week)	ΔΔQTcF (ms)	90% CI (ms)
MDV3100 160 mg q.d.	13	6.5	(4.8;8.3)

QTc interval change from baseline and placebo appears to be concentration-dependent. All concentrations were obtained pre-dose, so the QTc prolongation at C_{max} was not available from the study. However, as the peak-to-trough ratio for MDV3100 is 1.25, the concentration-QTc relationship suggests that exposures similar to those predicted for C_{max} are unlikely to change the conclusion of no significant QTc prolongation for MDV3100 160 mg q.d.

MDV3100 concentrations may increase in patients with severe hepatic impairment or when coadministered with strong CYP2C8 or CYP3A4 inhibitors, but the expected fold-change in C_{max} and AUC are unknown. Clinical trials in patients with mild or moderate hepatic impairment resulted in a 20% increase in MDV3100 exposures and a similar increase in the sum of MDV3100 plus its primary metabolite M2 exposures. Given the concentration-QTc relationship, this increased exposure would not result in large changes in mean QTc intervals (i.e. >20 ms). Additional studies are ongoing to evaluate the impact of severe renal impairment, severe hepatic impairment, and drug-drug interactions on MDV3100 exposures.

2 PROPOSED LABEL

2.1 SPONSOR'S PROPOSED LABEL

12.4 CARDIAC ELECTROPHYSIOLOGY

In the placebo-controlled multicenter phase 3 clinical trial, a formal ECG assessment showed no clinically relevant effect of the therapeutic dose of enzalutamide (160 mg daily).

2.2 QT-IRT'S PROPOSED LABEL

QT-IRT has the following label recommendations which are suggestions only. We defer the final labeling decisions to the review division.

12.6 Cardiac Electrophysiology

The effect of multiple doses of enzalutamide 160 mg on QTc interval was evaluated in 796 patients with castration-resistant prostate cancer. No large changes in the mean QT interval (i.e., >20 ms) from placebo on Fridericia correction method were detected in the study.

3 BACKGROUND

3.1 PRODUCT INFORMATION

MDV3100 is a small molecule with androgen receptor antagonist profile that blocks both androgen binding as well as nuclear translocation, two key aspects of the pathway regulating the growth of prostate cancer cells.

3.2 MARKET APPROVAL STATUS

MDV3100 is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

From eCTD 2.4, non-clinical overview

Cardiovascular	In vitro IK, assay hERG potassium channels expressed in HEK293 cells	MDV3100	3 to70 µM (1.39 to 32.5 µg/mL)	No	Table 2.6.3.4, PRO3100NC91	IC_{50} = 17.6 µM (8.17 µg/mL)
		MDV3100	3 to 60.5 µM (1.39 to 28.1 µg/mL)	Yes	Table 2.6.3.4, PRO3100NC104	IC_{50} = 15.7 µM (7.29 µg/mL)
		M2	3 to 60 µM (1.35 to 27.0 µg/mL)	No	Table 2.6.3.4, PRO3100NC92	IC_{50} = 14.8 µM (6.67 µg/mL)
		M2	3 to 60 µM (1.35 to 27.0 µg/mL)	Yes	Table 2.6.3.4, PRO3100NC107	IC_{50} = 18.6 µM (8.38 µg/mL)
	Cardiovascular determinations in conscious male beagle dogs	MDV3100	0, 5, 15, or 30 mg/kg as a single dose	Yes	Table 2.6.3.4, PRO3100NC94	No changes in blood pressure or heart rate and no abnormal ECG waveforms or arrhythmias were attributable to MDV3100.

3.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.7.4.

Table 2.7.4.1.1.2-1 summarizes the 4 clinical studies that are included in the Summary of Clinical Safety and the integrated safety population. The data cutoff dates for each study (between 26 August 2011 and 07 October 2011) were selected to be close to the (b) (6) cutoff date for the pivotal CRPC2 study and for operational efficiency. However, all of the studies are ongoing with patients continuing to receive MDV3100. Clinical study reports are provided for all of the studies, with the exception of 9785-CL-0111, which has not completed enrollment.

Table 2: MDV3100 Studies Included in the Summary of Clinical Safety

Study	Phase	Design	MDV3100 Patients	Placebo Patients	MDV3100 Daily Doses Evaluated	Safety Data Cutoff Date
Controlled Study						
CRPC2	3	Randomized, double-blind, placebo-controlled study	800	399	160 mg	(b) (6)
Uncontrolled Open-Label Studies (in Chronological Order of Study Initiation)						
S-3100-1-01	1	Open-label dose escalation study	140	none	30, 60, 150/160[a], 240, 360, 480, and 600 mg	
CRPC-MDA-1	2	Open-label single arm study	60	none	160 mg	26 AUG 2011
9785-CL-0111	1-2	Open-label dose escalation study in Japanese patients	27	none	80, 160, and 240 mg	07 OCT 2011

[a] The daily dose was changed from 150 to 160 mg in this study because of a change from five 30 mg capsules to four 40 mg capsules.

Source: ISS, Table 2.7.4.1.1.2-1, page 10

Study 3100-1-01: A possible dose-dependent increase in nausea was observed in the most commonly reported adverse events. Nausea was reported by 14.3% of patients dosed at 60 mg/day, 19.6% at 150/160 mg/day, 21.7% at 240 mg/day, 45.3% at 360 mg/day, 36.0% at 480 mg/day, and 33.3% at 600 mg/day. A number of the commonly reported adverse events, including edema peripheral, pyrexia, chest pain, back pain, arthralgia, pain in extremity, musculoskeletal pain, headache, dyspnea, cough, anorexia, decreased appetite, and upper respiratory tract infection appear to decrease in incidence with increased dose. No deaths occurred in this study. One patient discontinued because of grade 3 QT prolongation.

Study CRPC-MDA-1: There were no significant changes in vital signs or ECG parameters in this study. There were no reports of QTcF > 500 ms or QTcF prolongation > 16 ms in this study. No deaths were reported in this study.

Reviewer's Comments: Safety data from the controlled study CRPC2 are being discussed in sections 4.2.8.3 and 5.4.1.of this consult review. No deaths, ventricular arrhythmias or clinically relevant ECG changes were reported in the two uncontrolled studies.

3.5 Clinical Pharmacology

Appendix 6.1 summarizes the key features of MDV3100's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 Overview

The QT-IRT agreed to the sponsor's plan to conduct a dedicated QT/QTc substudy of MDV3100 under IND 74563. The sponsor submitted the study report AFFIRM for MDV3100, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

AFFIRM: A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Patients with Progressive Castration-Resistant Prostate Cancer Previously Treated with Docetaxel-Based Chemotherapy

4.2.2 Protocol Number

CRPC2

4.2.3 Study Dates

First Patient Enrolled: 22 September 2009
Last Patient Enrolled: 15 November 2010
Data Cutoff Date: (b) (6)
Study Completion Date: Ongoing

4.2.4 Objectives

Primary objective

- To determine the benefit of MDV3100 as compared to placebo as assessed by overall survival

Secondary Objectives

- To determine the benefit of MDV3100 as compared to placebo as assessed by time to PSA progression;
- To determine the benefit of MDV3100 as compared to placebo as assessed by radiographic progression-free survival;
- To determine the benefit of MDV3100 as compared to placebo as assessed by time to first skeletal-related event
- To determine the benefit of MDV3100 as compared to placebo as assessed on quality of life (Functional Assessment of Cancer Therapy – Prostate [FACT-P]);
- To determine the benefit of MDV3100 as compared to placebo as assessed by pain palliation;
- To determine the benefit of MDV3100 as compared to placebo as assessed by circulating tumor cell count conversion rate;
- To determine the safety of treatment with MDV3100 as compared to placebo;
- To determine the effects of MDV3100 on ECG changes as compared to placebo;
- To establish the covariates that may affect variability in PK parameters;
- To develop a PK model linking MDV3100 exposure with efficacy and safety outcomes.

4.2.5 Study Description

4.2.5.1 Design

The CRPC2 study was a randomized, double-blind, placebo-controlled, multicenter, Phase 3 study to evaluate the efficacy and safety of MDV3100 in patients with castration-resistant prostate cancer whose disease was progressing after 1 or 2 prior chemotherapy

regimens, at least one of which was docetaxel-based. Enrollment of 1170 patients was planned.

4.2.5.2 Controls

The Sponsor used placebo controls.

4.2.5.3 Blinding

The MDV3100 and placebo capsules were identical in regards to appearance, number of capsules/day, and formulation.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

After screening, patients who met eligibility criteria were randomized 2:1 to receive either MDV3100 orally, 160 mg daily, or placebo.

4.2.6.2 Sponsor's Justification for Doses

The results from the Phase 1 dose-escalation study, S-3100-1-01, were used to determine the maximum tolerated dose of MDV3100 and the optimal dose of MDV3100 for future studies in castration-resistant prostate cancer. The maximum tolerated dose was determined to be 240 mg daily, based upon the occurrence of dose-limiting toxicities as well as adverse events of fatigue leading to dose reductions at higher doses. There were 5 dose-limiting toxicities reported in S-3100-1-01, all occurring at doses of 360 mg daily or higher (3 events of seizure, and 1 each of rash and confusion). There was also a dose-dependent increase in adverse events of fatigue leading to dose reduction, with a 2.9% incidence at 240 mg daily, 7.5% incidence at 360 mg daily, and 20.0% incidence at 480 mg daily.

With regards to efficacy, the proportion of patients who had received previous chemotherapy without evidence of progression by any means (PSA, radiographic, or clinical) at 12 and 24 weeks were 54% and 31% for the 150 mg/day dose cohort and 67% and 33% for the 240 mg/day dose cohort, respectively. The proportion of patients showing a 50% decrease from baseline in PSA increased in a dose-dependent manner up to 150 mg/day (33.3% of patients at 30 mg/day, 59.3% at 60 mg/day and 66.7% at 150 mg/day) with no obvious additional benefit recorded for increased doses above 150 mg daily day (58.6% at 240 mg/day, 67.9% at 360 mg/day, 28.6% at 480 mg/day, and 66.7% at 600 mg/day).

Given the comparable efficacy of doses ≥ 150 mg/day, and increasing safety issues at doses ≥ 240 mg/day mg/day, a dose of 160 mg/day was selected for the CRPC2 study.

Reviewer's Comments: The selected dose for this study is acceptable based upon the available safety data from S-3100-1-01 as higher doses resulted in increased adverse event rate with no observed benefit in efficacy. MDV3100 is eliminated primarily by hepatic metabolism (CYP2C8 and CYP3A4/5) and has a half-life of approximately 1 week. Clinical trials in patients with mild or moderate hepatic impairment resulted in a

20% increase in MDV3100 exposures and a similar increase in the sum of MDV3100 plus its primary metabolite M2 exposures. No formal severe renal impairment, severe hepatic impairment or drug-drug interaction studies with MDV3100 have been performed, so a high exposure scenario for MDV3100 cannot be determined.

4.2.6.3 Instructions with Regard to Meals

Doses were administered without regard to food. Doses were to be taken at the same time on each day.

Reviewer's Comment: This ECG substudy was performed within a Phase III trial where MDV3100 was administered with or without food. No clinically significant effect on MDV3100 exposure was observed in a food effect study performed in healthy volunteers.

4.2.6.4 ECG and PK Assessments

A comprehensive evaluation of ECGs was performed in this study. ECGs were obtained in triplicate on Days 1 (pretreatment), 8, 29, and 57. Single ECGs were also collected at Screening, Days 85, 113, 141, 169, and every subsequent 12 weeks, and at the Safety Follow-Up visit.

Samples for PK assessment were collected pre-dose for Days 1, 8, 29, 57, and 85, and every 12 weeks thereafter. Plasma PK samples were analyzed for concentrations of MDV3100 and its metabolites MDPC0001 (M1) and MDPC0002 (M2).

Reviewer's Comments: PK samples were collected only at pre-dose and a full-time course of PK and ECG assessments (e.g., sampling near C_{max}) was not obtained. The peak-to-trough ratio for MDV3100 is 1.25. The reviewer's concentration-ΔΔQTcF model will be used to assess this scenario.

4.2.6.5 Baseline

Baseline measurements were obtained on Day 1 of treatment.

4.2.7 ECG Collection

Standard 12-lead ECGs with rhythm strips were collected from machines provided by the central ECG laboratory. ECGs were obtained after the patient had rested quietly and awake in a fully supine position (or semi-recumbent, if supine not tolerated) for 5–10 minutes. All ECGs were obtained prior to study drug administration on the day of the visit.
All ECGs were read centrally at an ECG laboratory. A formal ECG blinded and independent ECG analysis was conducted with a limited number of skilled readers.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Patient (n: 1199) demographics are summarized in Table 3.

Table 3: Demographics Summary and Baseline Characteristics: Randomized Patients

	MDV3100 (n = 800)	Placebo (n = 399)	Total (n = 1199)
Age (years)			
Mean (SD)	68.8 (7.96)	68.6 (8.39)	68.7 (8.11)
Median	69.0	69.0	69.0
Min, Max	41.0, 92.0	49.0, 89.0	41.0, 92.0
Age group (years)			
< 65	232 (29.0%)	130 (32.6%)	362 (30.2%)
65 to 74	369 (46.1%)	165 (41.4%)	534 (44.5%)
≥ 75	199 (24.9%)	104 (26.1%)	303 (25.3%)
Ethnicity			
Hispanic or Latino	32 (4.0%)	23 (5.8%)	55 (4.6%)
Not Hispanic or Latino	768 (96.0%)	376 (94.2%)	1144 (95.4%)
Race			
American Indian or Alaska Native	1 (0.1%)	1 (0.3%)	2 (0.2%)
Asian	5 (0.6%)	8 (2.0%)	13 (1.1%)
Black or African American	27 (3.4%)	20 (5.0%)	47 (3.9%)
Native Hawaiian or other Pacific Islander	1 (0.1%)	0 (0.0%)	1 (< 0.1%)
White	745 (93.1%)	366 (91.7%)	1111 (92.7%)
Other	21 (2.6%)	4 (1.0%)	25 (2.1%)
Weight (kg)	(n = 793)	(n = 394)	(n = 1187)
Mean (SD)	84.2 (14.51)	85.0 (16.56)	84.5 (15.22)
Median	83.0	83.0	83.0
Min, Max	46.0, 162.7	52.0, 151.7	46.0, 162.7

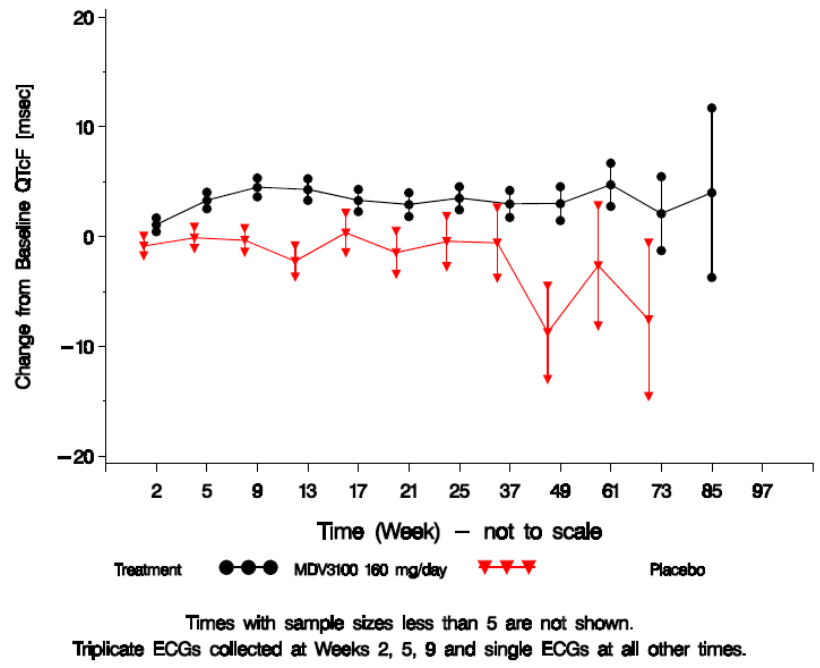
Source: CSR, Table 11.2.1-1

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The QTcF change from baseline for both treatment arms through Week 85 is detailed below in Figure 1. The mean change from baseline placebo-corrected for QTcF interval duration across all 57 days of MDV3100 showed an average increase of 3 ms. The time point analysis for ECG measurements shows a mean placebo corrected change in QTcF of 6.5 ms (90% confidence interval- max 7.5) at Week 13 (n=679) (Table 4). Larger mean increases were observed over the Week 49, 61, 73, and 85 sampling windows (7.4-11.8 ms; 90% confidence interval- max 9.4-17.2), though fewer total assessments were available over these sampling windows (n=257, 134, 56, and 11, respectively) (Table 4).

Figure 1: Change from Baseline QTcF (ms) with Means± 90% Confidence Interval



Sponsor's crpc2-lab-measurements.pdf, pg 7258

Table 4: Placebo-Corrected Change from Baseline Means and 90% Two-Sided Confidence Intervals QTcF (ms) Electrocardiographic Population

	MDV3100 160 mg/day			
			90% 2-sided C.I.	
Visit	Sample Size	Mean [1]	Lower CI [2]	Upper CI [2]
Week 2	783	2.0	1.3	2.6
Week 5	775	3.4	2.7	4.2
Week 9	726	4.8	4.0	5.7
Week 13	679	6.5	5.6	7.5
Week 17	594	3.0	1.9	4.0
Week 21	560	4.4	3.3	5.5
Week 25	526	3.9	2.9	5.0
Week 37	400	3.6	2.3	4.8
Week 49	257	11.8	10.2	13.3

	MDV3100 160 mg/day			
			90% 2-sided C.I.	
Visit	Sample Size	Mean [1]	Lower CI [2]	Upper CI [2]
Week 61	134	7.4	5.4	9.4
Week 73	56	9.7	6.3	13.0
Week 85	11	9.5	1.8	17.2

Sponsor's crpc2-lab-measurements.pdf, pg 7544-5

4.2.8.2.2 Assay Sensitivity

Reviewer's Comments: Moxifloxacin was not included as a treatment arm in this study.

4.2.8.2.3 Categorical Analysis

The data were presented as the frequency and percent of patients with each type of outlier by treatment group (Table 5). The following criteria ("study endpoints") are defined for this analysis:

- For all QTc (QTcF and QTcB) data: from mean baseline value to determine patients who:
  - attain new QTc values > 500 ms,
  - attain new QTc values > 480 ms,
  - attain new QTc values > 450 ms,
- QTc, categorizations of changes from baseline of >30 to 60 ms,
- QTc categorization of change from baseline of > 60 ms;
- PR change from baseline: more than 25% increase when PR > 200 ms;
- QRS change from baseline: more than 25% increase when QRS > 100 ms;
- HR changes reflecting a more than 25% decrease from baseline to a HR < 50 bpm or a more than 25% increase from baseline reflecting a HR 100 bpm (individually).

Table 5: Time-Averaged Mean Change from Baseline and New Outliers by Treatment Group

Dose	MDV3100 160 mg/day	Placebo
Sample Size	795	395
Heart Rate in bpm (mean change from baseline)	-1.0	1.4
Heart Rate Bradycardic Outliers N (%)	3 (0.4%)	1 (0.3%)
Heart Rate Tachycardic Outliers N (%)	8 (1.0%)	9 (2.3%)
PR in ms (mean change from baseline)	-3.3	-1.2
PR Outliers N (%)	0	0
QRS in ms (mean change from baseline)	-0.9	-0.3
QRS Outliers N (%)	3 (0.4%)	1 (0.3%)
QT in ms (mean change from baseline)	4.4	-2.6
QT new >500 ms N (%)	3 (0.4%)	0
QTcF in ms (mean change from baseline)	2.8	-0.5
QTcF new >500 ms N (%)	2 (0.3%)	0
QTcF new >480 ms N (%)	12 (1.5%)	3 (0.8%)
QTcF 30-60 ms N (%)	35 (4.4%)	5 (1.3%)
QTcF >60 ms N (%)	2 (0.3%)	0

Sponsor's crpc2-lab-measurements.pdf, pg 7555

The outlier analyses revealed no clear imbalance in HR, PR, or QRS between placebo and MDV3100. Outliers for >500 ms, change from baseline of >60 ms, and change from baseline 30-60 ms were more common for MDV3100 compared to placebo.

4.2.8.3 Safety Analysis

Table 6 presents a summary of all deaths occurring in the Safety Population on or prior to the data cutoff date of (b) (6).

Table 6: Deaths and Causes of Death: Safety Population

	MDV3100 (n = 800)	Placebo (n = 399)
Total Number of Deaths on or Prior to Data Cutoff Date[a]	308 (38.5%)	212 (53.1%)
Cause of Death		
Disease progression	274 (34.3%)	192 (48.1%)
Other	22 (2.8%)	13 (3.3%)
Unknown	12 (1.5%)	7 (1.8%)
Deaths Occurring Within 30 Days of the First Dose of Study Drug	2 (0.3%)	1 (0.3%)
Deaths Occurring Within 30 Days of the Last Dose of Study Drug	64 (8.0%)	25 (6.3%)

Source: Table 14.3.2.1.3
[a] The data cutoff date was (b) (6)

Source: CSR, Table 12.3.1.1-1

Table 7: Summary of Deaths within 30 days After 1st Dose and Within 30 days After the last Dose

Death Summary	MDV3100 160mg (n=800)	Placebo (n=399)	Total (n=1199)
Deaths Within 30 days After the First Dose Date of Study Drug	2 (0.3%)	1 (0.3%)	3 (0.3%)
Cause of Death for All Deaths			
DISEASE PROGRESSION	1 (0.1%)	0 (0.0%)	1 (<0.1%)
OTHER	1 (0.1%)	1 (0.3%)	2 (0.2%)
ACUTE MONOCYTIC LEUKEMIA	1 (0.1%)	0 (0.0%)	1 (<0.1%)
EUTHANASIA	0 (0.0%)	1 (0.3%)	1 (<0.1%)
Deaths Within 30 days After the Last Dose Date of Study Drug	64 (8.0%)	25 (6.3%)	89 (7.4%)
Cause of Death for All Deaths			
Note:All deaths occurring at or prior to data analysis cutoff date are included.			
DISEASE PROGRESSION	53 (6.6%)	19 (4.8%)	72 (6.0%)
OTHER	10 (1.3%)	6 (1.5%)	16 (1.3%)
ACUTE LUNG OEDEMA RELATED TO CARDIAC COMORBIDITY AND DIED	1 (0.1%)	0 (0.0%)	1 (<0.1%)
ACUTE MONOCYTIC LEUKEMIA	1 (0.1%)	0 (0.0%)	1 (<0.1%)
AE#36 PNUEMONIA	1 (0.1%)	0 (0.0%)	1 (<0.1%)
CARDIAC FAILURE	1 (0.1%)	0 (0.0%)	1 (<0.1%)
CARDIOGENIC SHOCK OF UNKNOWN ETIOLOGY	0 (0.0%)	1 (0.3%)	1 (<0.1%)
EUTHANASIA	0 (0.0%)	1 (0.3%)	1 (<0.1%)
ISCHEMIC STROKE	0 (0.0%)	1 (0.3%)	1 (<0.1%)
LEUKEMIA	1 (0.1%)	0 (0.0%)	1 (<0.1%)
MYOCARDIAL INFARCTION	0 (0.0%)	1 (0.3%)	1 (<0.1%)
NON-ST ELEVATION MYOCARDIAL INFARCTION	1 (0.1%)	0 (0.0%)	1 (<0.1%)
PULMONARY EMBOLISM	0 (0.0%)	1 (0.3%)	1 (<0.1%)
RESPIRATORY FAILURE	0 (0.0%)	1 (0.3%)	1 (<0.1%)
SEPSIS	1 (0.1%)	0 (0.0%)	1 (<0.1%)
SEPSIS (E. COLI)	1 (0.1%)	0 (0.0%)	1 (<0.1%)
SEPSIS RELATED MULTI ORGAN FAILURE	1 (0.1%)	0 (0.0%)	1 (<0.1%)
STROKE	1 (0.1%)	0 (0.0%)	1 (<0.1%)

Note:All deaths occurring at or prior to data analysis cutoff date are included.

Source: CSR, Table 14.3.2.1.3

Reviewer's Comments: The proportion of patients who died within 30 days of first dose and within 30 days of last dose is similar in the MDV3100 and placebo arms. Three

deaths occurred within 30 days after first dose; 1 in the placebo arm and 2 in the MDV3100 arm all because of disease progression.

All treatment-emergent adverse events (cardiovascular disorders) leading to death are shown in Table 8.

Table 8: Treatment-Emergent Adverse Events (cardiovascular disorders only) Leading to Death: Safety Population

	MDV3100 (n = 800)	Placebo (n = 399)
Treatment-Emergent Adverse Events Resulting in Death	23 (2.9%)	14 (3.5%)
Cardiac Disorders	2 (0.3%)	2 (0.5%)
Acute myocardial infarction	1 (0.1%)	0 (0.0%)
Cardiac failure	1 (0.1%)	0 (0.0%)
Cardiogenic shock	0 (0.0%)	1 (0.3%)
Myocardial infarction	0 (0.0%)	1 (0.3%)

Source: extracted from Table 12.3.1.1-2, CSR page 157.

Reviewer's Comments: There were no reports of ventricular arrhythmias linked to study medication. There were two cardiovascular SAEs reported leading to death in the MDV3100 arm. We reviewed both narratives and we have the following comments:

Subject 2011020243, a 77 year-old male patient in the United States experienced serious adverse events of "non-ST elevation myocardial infarction" and "sepsis." The patient was randomized to the study on 15 FEB 2010 to receive MDV3100. Subject had a past medical history of coronary artery disease s/p bypass graft, hyperlipidemia, atrial fibrillation, congestive heart failure, cardiac stent placement and right bundle branch block. Myocardial infarction took place at study day (b) (6), approximately (b) (6) after initiating study drug and (b) (6) days after discontinuation of study drug due to withdrawal of consent (due to sepsis). Sepsis contributed to death. It seems unlikely that SAE (acute myocardial infarction and death) are linked to MDV3100.

Subject 2011010032, an 85-year-old male patient in the United States experienced serious adverse events of "heart failure" and "stroke". The patient was randomized to the study on 04 MAY 2010 to receive MDV3100. Relevant past medical history included a three vessel coronary artery bypass graft surgery (b) (6) hypertension, hypercholesterolemia, and a deep venous thrombosis of the right arm. On (b) (6) (study day (b) (6)), approximately (b) (6) after initiating study drug, the patient experienced "heart failure" and "stroke". Based on past medical history and the timing of the event (study day (b) (6)) it seems unlikely these serious adverse events were linked to study drug.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The steady-state C_{min} values for MDV3100, M1, and M2 are 11.4 ± 2.95 µg/mL (25.9% CV), 8.44 ± 6.77 µg/mL (80.2% CV), and 13.0 ± 3.78 µg/mL (29.2% CV), respectively.

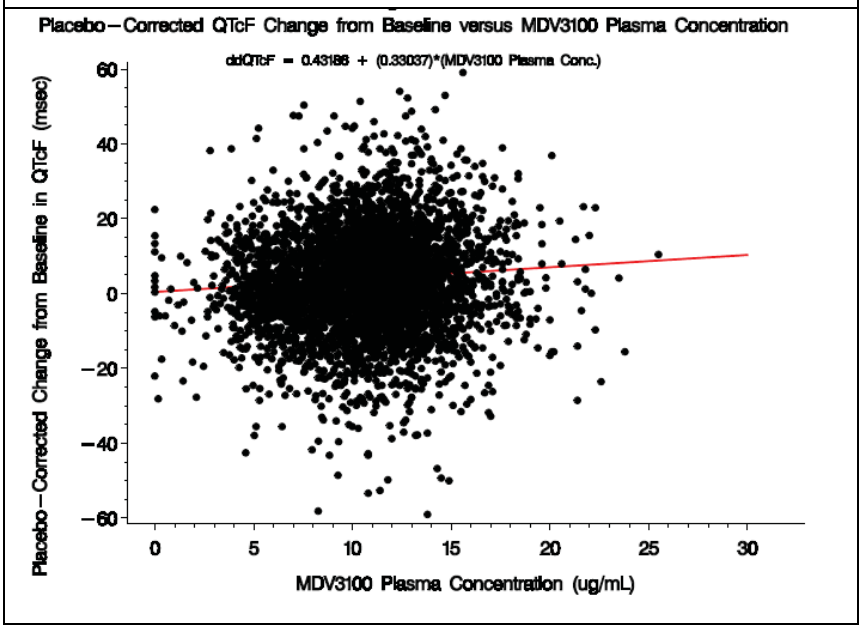
Reviewer's Comments: A PK time course is not available from this study as all samples were obtained pre-dose. No supratherapeutic dose was included in this study.

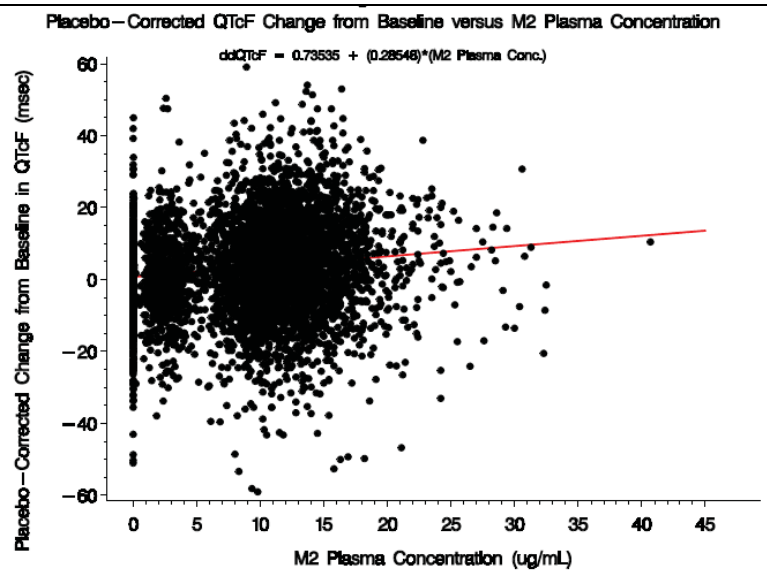
4.2.8.4.2 Exposure-Response Analysis

Figure 2 shows the relationship between ΔΔQTcF and plasma concentration from paired samples for MDV3100 and for M2, respectively. PK-PD model results showing the slopes of the relationships for plasma concentration of MDV3100 or M2 and ΔΔQTcF are in Table 9.

The predicted QTcF change at C_{min} was consistently about 3 ms with upper confidence interval at or <4 ms for both the parent and the metabolite. Since C_{max} was not obtained in the PK analysis in this trial, the value of the C_{min} analysis for determining the effect of MDV3100 on cardiac repolarization should be viewed with caution; however, the mean peak-to-trough ratio at steady-state was previously shown to be 1.25, indicating that the average difference between C_{max} and C_{min} is small (≤ 25%).

Figure 2: ΔΔ QTcF Versus MDV3100 (top) and M2 (bottom)





Sponsor's crpc2-lab-measurements.pdf, pg 7557-8

Table 9: ΔΔQTcF and ΔΔQTcB versus the MDV3100 (top) and M2 (bottom) Plasma Concentration – Estimates from Linear Mixed Model

MDV3100

QTc Parameter	Slope of Plasma Conc. Effect on ΔΔ QTc	Standard Error of Slope of Plasma Conc. Effect on ΔΔ QTc	p-value	Overall Model Fit
QTcF	0.33037	0.07122	<.0001	<.0001
QTcB	0.31722	0.08345	0.0002	<.0001

QTc Parameter	Predicted QTc at Average Cmin 9.033 ug/ml	One-sided Upper 95% Confidence Bound of Predicted QTc [2]
QTcF	3.4161	4.0089
QTcB	1.4825	2.1648

M2

QTc Parameter	Slope of Plasma Conc. Effect on ΔΔ QTc	Standard Error of Slope of Plasma Conc. Effect on ΔΔ QTc	p-value	Overall Model Fit
QTcF	0.28548	0.03921	<.0001	<.0001
QTcB	0.23779	0.04613	<.0001	<.0001

QTc Parameter	Predicted QTc at Average Cmin 8.836 ug/ml	One-sided Upper 95% Confidence Bound of Predicted QTc [2]
QTcF	3.2578	3.8114
QTcB	1.8510	2.4929

Sponsor's crpc2-lab-measurements.pdf, pg 7259-60

Reviewer's Comments: The sponsor identified a significant concentration-ΔΔQTcF relationship during model evaluation. The sponsor's assessment is based on observed C_{min} and does not account for peak-to-trough ratio or the impact of intrinsic/extrinsic factors on drug exposure. The reviewer's independent analysis is presented in Section 5.3.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcB). An individual QT correction (QTcI) was not included in the analysis as an individual baseline QT time course was not collected for this parallel study. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the mixed model of the pooled post-dose data of QTcF and QTcB distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF or QTcB), and the interaction term of RR and correction type. The slopes of QTcF and QTcB versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 10, it appears that QTcF had smaller absolute slopes than QTcB. Therefore, QTcF is a better correction method for the study data.

Table 10: Comparison of QTcB and QTcF Using the Mixed Model

Treatment Groups	Slope of QTcB	Slope of QTcF	P value
MDV3100 160 mg q.d.	-0.080	0.004	0.1309
Placebo	-0.068	0.018	0.0000
All	-0.076	0.008	0.0003

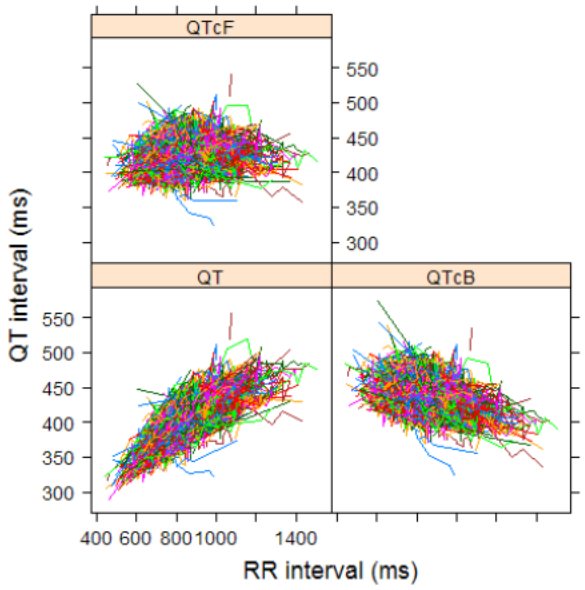
We also confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 11, it also appears that QTcF is the best correction method. Therefore, this reviewer used QTcF for the primary statistical analysis. This is consistent with the sponsor's choice of QTcF for their primary analysis.

Table 11: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	QTcB		QTcF	
Treatment Group	N	MSSS	N	MSSS
MDV3100 160 mg q.d.	796	0.007	796	0.0006
Placebo	395	0.005	395	0.0008
All	1191	0.006	1191	0.0006

The relationship between different correction methods and RR is presented in Figure 3.

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



5.2 Statistical Assessments

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for MDV3100

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes treatment as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables. Due to a limited number of subjects in the MDV3100 treatment arm and placebo arm at later times, the reviewer considered the ΔQTcF and ΔΔQTcF assessments only within the first 37 weeks of treatment. The largest upper bound of the 2-sided 90% CI for the mean difference between MDV3100 160 mg q.d. and placebo was 8.3 ms over the first 37 weeks of treatment.

Table 12: Analysis Results of ΔQTcF and ΔΔQTcF for MDV3100 160 mg q.d.

	MDV3100 160 mg q.d.	Placebo	ΔΔQTcF		
Time (day)	Mean (ms)	Mean (ms)	DF	Diff LS Mean (ms)	90% CI (ms)
2	1.1	-0.9	783	2.0	(0.9;3)
5	3.3	-0.1	810	3.4	(2.2;4.6)
9	4.5	-0.3	735	4.8	(3.5;6.2)
13	4.3	-2.2	563	6.5	(4.8;8.3)
17	3.3	0.3	277	3.0	(0.9;5)
21	2.9	-1.5	201	4.4	(2.1;6.6)

25	3.5	-0.4	143	3.9	(1.4;6.5)
37	3.0	-0.6	62.3	3.6	(0.1;7)
49	3.0	-8.7	32.5	11.8	(7.3;16.3)
61	4.7	-2.6	14.6	7.4	(1.6;13.1)
73	2.1	-7.6	8.8	9.7	(2.3;17.1)

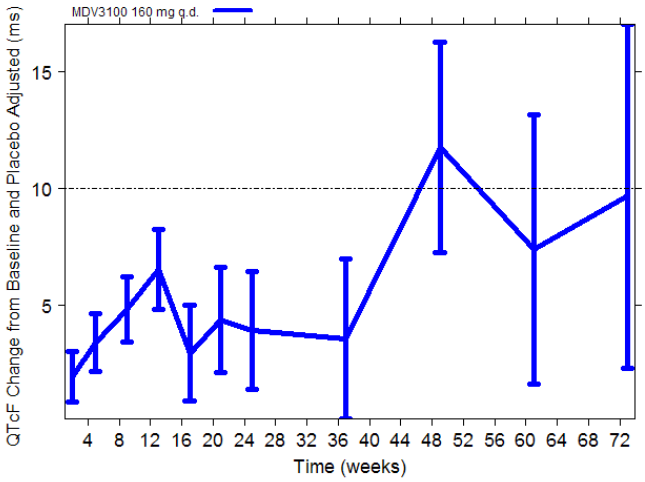
5.2.1.2 Assay Sensitivity Analysis

A moxifloxacin arm was not included in this study.

5.2.1.3 Graph of ΔΔQTcF Over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups. (Note: CIs are all unadjusted)

Figure 4: Mean and 90% CI ΔΔQTcF Timecourse



5.2.1.4 Categorical Analysis

Table 13 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. Twenty seven (3.4%) and 7 (1.8%) subject's QTcF was above 480 ms in the MDV3100 and placebo treatment arms, respectively.

Table 13: Categorical Analysis for QTcF

	Total N		Value<=450 ms		450 ms<Value<=480 ms	
Treatment Group	# Subj.	# Obs.	# Subj. (%)	# Obs. (%)	# Subj. (%)	# Obs. (%)
Baseline	1206	1206	1115 (92 5%)	1115 (92.5%)	173 (7.0%)	173 (7.0%)
Placebo	395	1851	327 (82.8%)	1686 (91.1%)	61 (15.4%)	157 (8.5%)
MDV3100 160 mg q.d.	796	5490	597 (75%)	4903 (89.3%)	172 (21.6%)	541 (9.9%)

Table 14 lists the categorical analysis results for ΔQTcF. Three subjects' change from baseline was above 60 ms in the MDV3100 treatment arm.

Table 14: Categorical Analysis of ΔQTcF

	Total N		Value<=30 ms		30 ms<Value<=60 ms	
Treatment Group	# **Subj.**	# **Obs.**	# **Subj.**	# **Obs.**	# **Subj.**	# **Obs.**
Placebo	395	1851	378 (95.7%)	1831 (98.9%)	17 (4.3%)	20 (1.1%)
MDV3100 160 mg q.d.	796	5490	688 (86.4%)	5327 (97%)	105 (13.2%)	159 (2.9%)

The ΔQTcF outlier analysis presented above should be interpreted with caution given the high variability in the placebo ΔQTcF values and sparse sampling. While there were more subjects in the MDV3100 treatment arm with ΔQTcF 30 - ≤60 ms (13% versus 4%) this is due to a mean 5-10 ms shift in ΔQTcF on average for subjects in the MDV3100 treatment arm compared to subjects in the placebo arm. For example, if a more granular analysis is performed looking at the percent of subjects with ΔQTcF increases over 10 ms increments, it is observed that the percentage of subjects with 20 - ≤30 ms ΔQTcF in the placebo treatment (n=33, 8.4%) is similar to the percentage of subjects with 30 - ≤40 ms ΔQTcF in the MDV3100 treatment arm (n=78, 9.8%). Similar results are observed over other 10 ms increments between the two treatment arms.

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 15. The largest upper limits of 90% CI for the HR mean differences between MDV3100 160 mg q.d. and placebo was 2 bpm over the first 37 weeks of treatment.

Table 15: Analysis Results of ΔHR and ΔΔHR for MDV3100 160 mg q.d.

	MDV3100 160 mg q.d.	Placebo	ΔΔHR		
Time (week)	Mean (bpm)	Mean (bpm)	DF	Diff LS Mean (bpm)	90% CI (bpm)
2	-1.3	1.0	729	-2.3	(-3.1;-1.6)
5	-1.0	1.4	671	-2.3	(-3.2;-1.4)
9	-1.2	1.1	621	-2.3	(-3.2;-1.3)
13	-1.3	2.2	518	-3.4	(-4.6;-2.3)
17	-2.3	1.5	235	-3.8	(-5.3;-2.4)
21	-1.9	2.4	152	-4.3	(-6;-2.6)
25	-1.7	3.1	117	-4.8	(-6.8;-2.8)
37	-1.8	-1.3	54.1	-0.4	(-2.8;2)
49	-1.5	1.2	27.2	-2.7	(-6.3;0.8)
61	-2.1	0.0	11.1	-2.1	(-8.9;4.7)
73	-3.7	0.1	5.4	-3.8	(-15.3;7.7)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 16. The largest upper limits of 90% CI for the PR mean differences between MDV3100 160 mg q.d. and placebo was 2.7 ms over the first 37 weeks of treatment.

Table 16: Analysis Results of ΔPR and ΔΔPR for MDV3100 160 mg q.d.

	MDV3100 160 mg q.d.	Placebo	ΔΔPR		
Time (week)	Mean (ms)	Mean (ms)	DF	Diff LS Mean (ms)	90% CI (ms)
2	0.4	-0.9	633	1.3	(0.2;2.3)
5	-4.4	-0.8	719	-3.6	(-4.7;-2.5)
9	-6.0	-1.8	592	-4.2	(-5.4;-3)
13	-5.7	-2.4	477	-3.2	(-4.9;-1.6)
17	-6.8	-2.0	224	-4.8	(-6.9;-2.8)
21	-5.6	-2.1	142	-3.5	(-6;-0.9)
25	-5.5	-4.1	103	-1.4	(-5.5;2.7)
37	-5.2	1.3	46.8	-6.6	(-12.5;-0.6)
49	-5.1	-7.2	24.9	2.1	(-4.9;9.1)
61	-5.7	-2.0	10.5	-3.7	(-18.3;10.9)
73	-4.6	9.2	6.4	-13.8	(-23.5;-4.2)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 17. The largest upper limits of 90% CI for the QRS mean differences between MDV3100 160 mg q.d. and placebo was 1.5 ms over the first 37 weeks of treatment. There are 16.5% subjects who experienced QRS interval greater than 110 ms in MDV3100 160 mg q.d.

Table 17: Analysis Results of ΔQRS and ΔΔQRS for MDV3100 160 mg q.d.

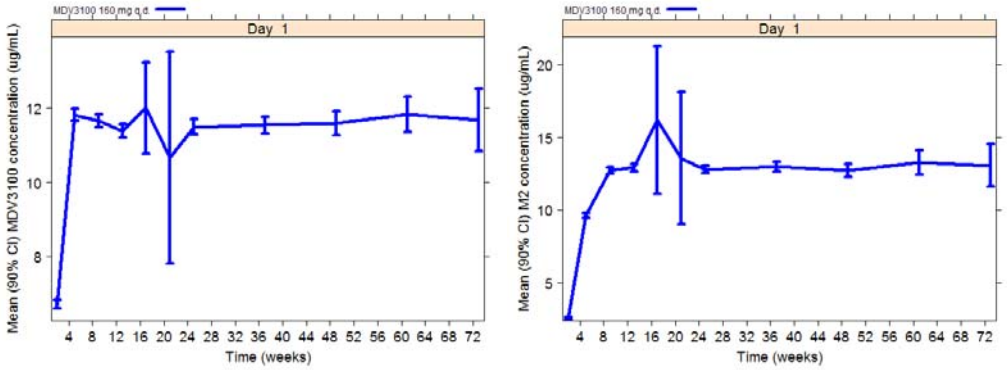
	MDV3100 160 mg q.d.	Placebo	ΔΔQRS		
Time (week)	Mean (ms)	Mean (ms)	DF	Diff LS Mean (ms)	90% CI (ms)
2	-0.2	-0.2	822	-0.1	(-0.5;0.4)
5	-1.1	-0.2	782	-0.9	(-1.5;-0.4)
9	-1.2	-0.4	676	-0.8	(-1.4;-0.2)
13	-1.3	0.2	527	-1.5	(-2.3;-0.7)
17	-1.1	0.1	274	-1.2	(-2.1;-0.2)
21	-0.7	0.1	152	-0.9	(-2.1;0.3)
25	-0.7	-0.2	139	-0.4	(-1.6;0.7)
37	-0.3	-0.4	60	0.0	(-1.5;1.5)
49	-0.4	-3.8	25	3.5	(-0.6;7.5)

61	0.6	-3.5	11.5	4.1	(-0.7;8.9)
73	0.7	-1.7	6.6	2.4	(-3.2;8)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

Mean C_{min} MDV3100 and M2 concentrations over 73 weeks are illustrated in Figure 5. A similar profile was observed for metabolite M1 (not shown). For a majority of the assessment period (>8 weeks) the ratio of MDV3100 and M2 exposures were similar. As such, individual contribution to QT prolongation of MDV3100 and its metabolites can not be determined from the available data. Therefore, the concentration-ΔΔQTcF assessment will only use MDV3100 concentrations.

Figure 5: Mean MDV3100 (left) and M2 (right) C_{min} over 73 Weeks for 160 mg q.d. mg (blue line)



The relationship between ΔΔQTcF and MDV3100 concentrations was investigated by linear mixed-effects modeling. The following three linear models were considered:

Model 1 is a linear model with an intercept

Model 2 is a linear model with mean intercept fixed to 0 (with variability)

Model 3 is a linear model with no intercept

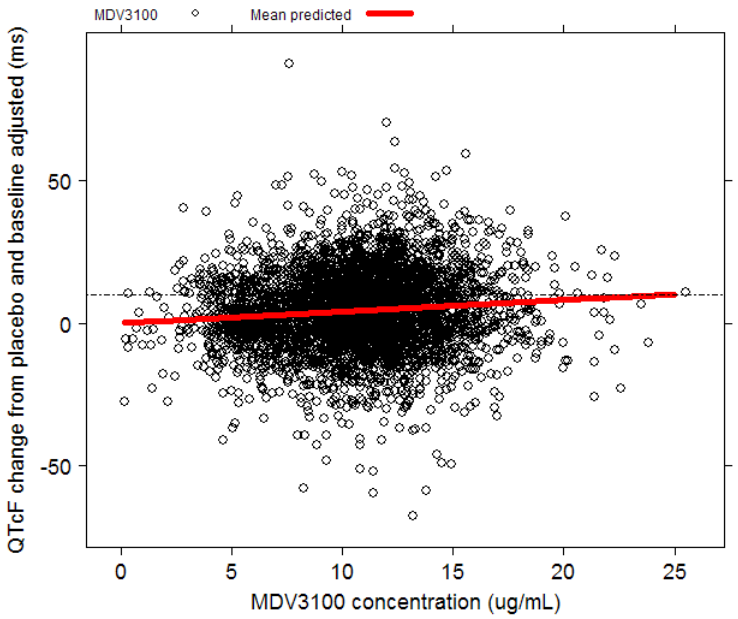
In all three models a significant slope was identified. Model 2 was used for further analysis since the model with fixed intercept was found to fit the data best. Table 18 summarizes the results of the MDV3100-ΔΔQTcF analyses.

Table 18: Exposure-Response Analysis of MDV3100 Associated with ΔΔQTcF Prolongation

Parameter	Estimate	P-value	Inter-individual Variability (%)
ΔΔQTcF = Intercept + slope * MDV3100 Concentration			
Intercept (ms)	0		1.9
Slope (ms per ug/mL)	0.41 (0.35; 0.46)	<.0001	0.3
Residual Variability (ms)	10.5		

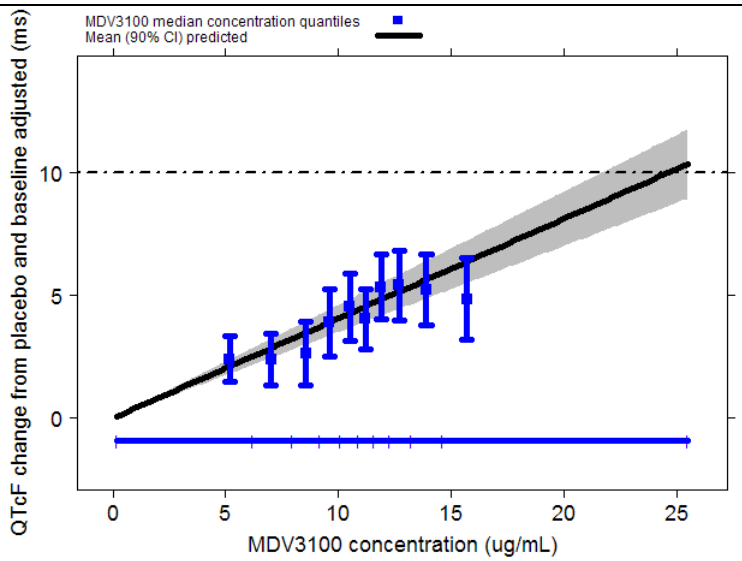
The exposure-response relationship between ΔΔQTcF and MDV3100 concentrations is visualized in Figure 6.

Figure 6: Observed ΔΔQTcF Versus MDV3100 Concentrations Together with the Population Predictions (solid red line)



The goodness-of-fit plot in Figure 7 shows the observed median-quantile MDV3100 concentrations and associated mean (90% CI) ΔΔQTcF together with the mean (90% CI) predicted ΔΔQTcF.

Figure 7: Observed Median-Quantile MDV3100 Concentration and Associated Mean (90% CI) ΔΔQTcF (colored dots) Together with the Mean (90% CI) Predicted ΔΔQTcF (black line with shaded grey area)



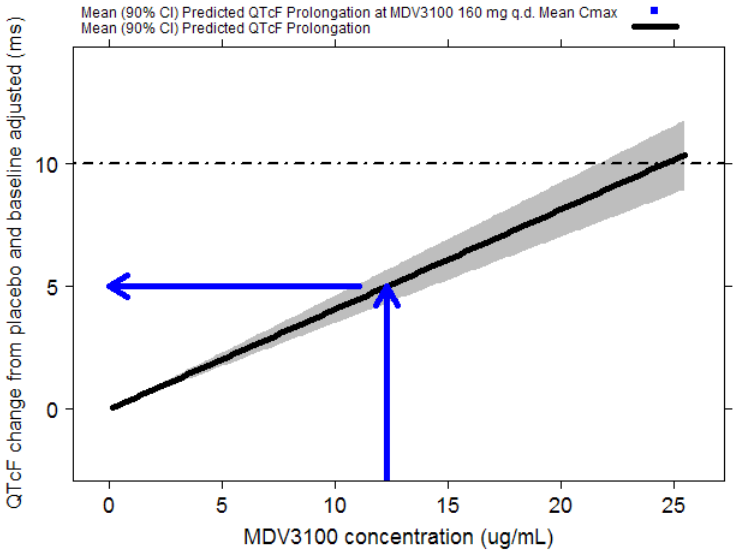
The predicted ΔΔQTcF at the geometric mean C_{min} for MDV3100 160-mg can be found in Table 19 and is visualized in Figure 8. In addition, the anticipated ΔΔQTcF at C_{max} was determined using the observed peak-to-trough ratio from S-3100-1-01 (C_{min}: 12.8 µg/mL; C_{max}: 15.4 µg/mL) and by extrapolating the MDV3100 concentration-ΔΔQTcF relationship (Table 19).

Table 19: Predicted ΔΔQTcF Interval at Geometric Mean Peak MDV3100 Concentration Using Model 2.

Treatment	Concentration	Predicted ΔΔQTcF	90% CI
MDV3100 160 mg q.d., predose	12.3 µg/mL	5.0	(4.3; 5.7)
MDV3100 160 mg q.d., C_{max}	*15.4 µg/mL*	*6.3*	*(5.4; 7.2)*

[*] *Predicted based on sponsor's peak-to-trough ratio results from S-3100-1-01*

Figure 8: Mean (90% CI) Predicted ΔΔQTcF at Geometric Mean C_{min}



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

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

5.4.2 ECG assessments

Waveforms were reviewed in the ECG warehouse. Measurements were performed on the 'global' presentation of superimposed representative (median) PQRST complexes from all leads. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

The sponsor's outlier analysis (see Table 5) reports that no subject with a PR > 200 ms had a change from baseline >25%. Incidence of subjects who experienced a QRS increase over baseline of more than 25%, with baseline QRS values > 100 ms, was similar to the placebo group. Therefore no clinically relevant PR and QRS changes were observed in this study.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic Dose	160 mg/day orally, with or without food	
Maximum Tolerated Dose	240 mg/day orally	
Maximum Dose Tested	Single Dose	600 mg (as a split dose: 300 mg in the morning and 300 mg in the evening)
	Multiple Dose	600 mg/day for 28 days (given as 300 mg BID)
Exposures Achieved at Therapeutic Dose	Single Dose Mean ± SD (%CV)	S-3100-1-01 (150 mg) • C_{max}: 3.36 ± 0.78 µg/mL (23%CV); • AUC_{0-inf}: 334 ± 50.0 µg·h/mL (15%CV)
	Multiple Dose Mean ± SD (%CV)	S-3100-1-01 (150 mg/day) • C_{max}: 14.5 ± 3.3 µg/mL (23%CV); • $AUC_{0-\tau}$: 300 ± 68 µg·h/mL (23%CV) CRPC2 (160 mg/day) At steady state, the mean predose C_{min} values for MDV3100 and the active metabolite (M2) are 11.4 µg/mL (26%CV) and 13.0 µg/mL (29%CV), respectively. The steady-state C_{min} values for MDV3100 in individual patients remained constant beyond Day 28 of chronic therapy, suggesting time-linear PK once steady state is achieved.
Range of Linear PK	No major deviations from dose proportionality are observed over the dose range 30 to 600 mg.	
Accumulation Index at Steady State [a]	With daily oral administration, MDV3100 accumulates 8.3-fold relative to a single dose.	
Absorption	Absolute Bioavailability	Based on a mass balance study in humans, oral absorption of MDV3100 is estimated to be at least 84.2%.
	Absorption	MDV3100 readily crosses Caco-2 cell monolayers by passive diffusion and is not a substrate of the efflux transporter P-gp.
	Median t_{max} (range)	1 hour (range: 0.4 to 4 hours after a single dose).
	Biopharmaceutics Classification System	Low solubility, high permeability Class 2 compound.
Distribution	V/F Mean ± SD (%CV)	110 ± 32 L (29%CV).
	% Plasma Protein Bound	97% to 98% bound to plasma proteins, primarily albumin. Metabolite M1 is 98% bound to plasma proteins. Metabolite M2 is 95% bound to plasma proteins.
	Blood-Brain Barrier	Studies in rodents indicate that MDV3100 and metabolite M2 readily cross the blood-brain barrier.
Metabolism	MDV3100 is cleared slowly via hepatic metabolism. There are 2 major metabolites in human plasma: an active metabolite (M2) that demonstrates key primary pharmacodynamics of similar potency to MDV3100 and an inactive metabolite (M1). The 2 major metabolites in human plasma are also present in rats and dogs (i.e., the toxicology species). In vitro studies show that MDV3100 is metabolized by CYP2C8 and CYP3A4/5, both of which play a role in the formation of metabolite M2. MDV3100 is not metabolized in vitro by CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C18, CYP2C19, CYP2D6, or CYP2E1.	
Elimination	Route	Following oral administration of ^{14}C-MDV3100, 84.6% of the dose is recovered though Day 77 postdose: 71.0% is recovered in urine (primarily M1, with trace amount of MDV3100 and M2), and 13.6% is recovered in feces (0.39% of dose as MDV3100)
	Terminal $t_{1/2}$ Mean ± SD (Range)	5.8 ± 1.6 days (2.8 to 10.2 days). The terminal $t_{1/2}$ does not appear to be affected by dose size. Due to the long $t_{1/2}$, it takes a month to reach steady state, and the daily fluctuation in plasma concentrations is low (mean peak-to-trough ratio of 1.25).
	CL/F Mean ± SD (%CV)	0.564 ± 0.169 L/h (30%CV).
	CL_R	Negligible.
Intrinsic Factors	Age	Differences in PK based on age have not been formally evaluated. The PK of MDV3100 has not been evaluated in pediatric patients.
	Race	Differences in PK based on race are unknown.
	Weight	With a fixed dose of 160 mg/day, the effect of body weight on exposure is small, and correction of dosing based on body weight is not indicated.
	Gender	The PK of MDV3100 has not been evaluated in women.
	Renal Impairment	No formal renal impairment study for MDV3100 has been completed. Patients with serum creatinine > 177 µmol/L (2 mg/dL) were excluded from clinical trials. MDV3100 has not been evaluated in patients with severe renal impairment (CrCL < 30 mL/min) or end-stage renal disease, and caution is advised when treating these patients. It is unlikely that MDV3100 will be significantly removed by intermittent hemodialysis or continuous ambulatory peritoneal dialysis.
	Hepatic Impairment	No formal hepatic impairment study for MDV3100 has been completed. Patients with impaired hepatic function (total bilirubin, ALT, and/or AST > 2x ULN) were excluded from clinical trials. Because MDV3100 is eliminated primarily by hepatic metabolism and has a $t_{1/2}$ of approximately 1 week, hepatic impairment is likely to affect exposures to MDV3100 and/or metabolite M2. Caution is advised when treating patients with liver disease.

Extrinsic Factors	Clinical Drug Interactions	No formal drug-drug interaction studies have been completed with MDV3100.
	Potential for MDV3100 to Increase Exposures to Other Drugs	In vitro studies show that MDV3100 and/or metabolite M2 are potential inhibitors of CYP2C8 and CYP2C19 with lesser potential for inhibitory effects on CYP2B6 and CYP2C9. Substrates of CYP2B6, CYP2C8, CYP2C9, and CYP2C19 that have a narrow therapeutic index (e.g., paclitaxel, phenytoin, warfarin) should be used with caution. In vitro studies show that MDV3100 and metabolite M2 are potential inhibitors of the efflux transporter P-gp. Co-administration of MDV3100 with P-gp substrates may increase the plasma concentrations of the P-gp substrate. Use caution when co-administering sensitive P-gp substrates (e.g., colchicine, dabigatran etexilate, digoxin) during MDV3100 treatment.
	Potential for MDV3100 to Decrease Exposures to Other Drugs	In vitro studies show that MDV3100 is an inducer of CYP3A4. Induction of CYP3A occurs via activation of the nuclear PXR, which is expected to result in co-induction of CYP2C. Co-administration of MDV3100 with CYP3A or CYP2C substrates may reduce oral bioavailability and/or accelerate elimination of these substrates.
	Potential for Other Drugs to Affect MDV3100 Exposures	In vitro studies show that MDV3100 is metabolized by CYP2C8 and CYP3A4/5. Strong inhibitors or inducers of these enzymes may affect MDV3100 exposures. Use caution when co-administering strong inhibitors of CYP2C8 (e.g., gemfibrozil) or CYP3A4/5 (e.g., clarithromycin, itraconazole, ketoconazole) during MDV3100 treatment, as MDV3100 concentrations may increase. Use caution when co-administering strong inducers of CYP2C8 (e.g., rifampin) or CYP3A4/5 (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) during MDV3100 treatment, as MDV3100 concentrations may decrease.
	Food Effects	Food has no clinically significant effect on the extent of absorption. In clinical trials, MDV3100 was administered without regard to food.

[a] Accumulation Index = Ratio of 24-hour AUC on Day 84 to Day 1; calculated as $AUC_{0-\tau}/AUC_{24}$.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the plasma concentration versus time curve; AUC_{inf}, AUC from time zero to infinity; $AUC_{0-\tau}$, AUC from time zero to 24 hours after dosing at steady state; BID, twice per day; C_{max}, maximum observed plasma concentration; C_{min}, observed plasma concentration in a pre-dose sample; CL/F, apparent total plasma clearance; CrCL, creatinine clearance; CYP, cytochrome P450; mg/day, milligrams per day; mL/min, milliliters per minutes; P-gp, permeability glycoprotein; PK, pharmacokinetics; PXR, pregnane X receptor; SD, standard deviation; $t_{1/2}$, half-life; t_{max}, time to maximum plasma concentration; V/F, apparent volume of distribution; %CV, percent coefficient of verification; µg/mL, micrograms per milliliter; µg·h/mL, microgram hours per milliliter.

Sponsor's investigator-brochure-v5-23mar2012.pdf, page 46-49

6.2 SCHEDULE OF ASSESSMENTS

Study Day	Screening Visit	1	8	29	57	85	113	141	169	Safety F/U	Unscheduled Visit[a]	Long-Term F/U
Week	−4 to −1 (28 days)	1	2	5	9	13	17	21	25 and every subsequent 12 weeks	30 Days after last dose[b]	n/a	Every 12 weeks
Window (days)			± 2	± 3	± 3	± 7	± 3	± 3	± 7	± 7	n/a	± 7
Informed Consent	X											
Medical History	X											
Inclusion/Exclusion Criteria	X	X										
Randomization (IVRS)[c]		X										
Vital Signs[d]	X	X[d]	X[d]	X[d]	X	X	X	X	X	X	X	
Physical Examination, Weight[e]	X[f]	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG	X	X[g]	X[g]	X[g]	X[g]	X	X	X	X	X	X	
MUGA/Echocardiogram[h]	X											
Clinical Labs[i]	X	X[j]	X	X	X	X	X	X	X	X	X	
PSA	X	X				X	X	X	X	X		
PK[k]		X	X	X	X	X			X		X	
CTCs, Molecular Profiling, and Bone Turnover Markers[l]	X	X			X	X			X[m]			
CT/MRI and Bone Scan	X					X[n]			X			
CXR or Chest CT	X											
Eastern Cooperative Oncology Group	X	X	X	X	X	X	X	X	X	X	X	
Provide Pain Diary[o]	X[p]				X							
Collect Pain Diary and Brief Pain Inventory – Short Form		X				X						
Brief Fatigue Inventory and Fatigue Severity Assessment		X										
FACT-P		X				X	X	X	X			
EQ-5D[1]		X				X			X			
Adverse Events[q]		X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Dispensing		X		X		X	X		X			
Long-Term F/U Assessments[r]												X
Study Drug Treatment[s]		X	X	X	X	X	X	X	X			

Source: Apendix 16.1.1

[a] Unscheduled visits were at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request or if deemed necessary by the Investigator.

[b] Or before the initiation of another systemic antineoplastic therapy, whichever occurred first.

[c] ECOG performance status from the Day 1 visit and the average of the patient's reported daily pain scores were required to randomize the patient in IVRS.

[d] Vital signs (blood pressure, heart rate, respiratory rate, temperature) were obtained prior to, and 1–2 hours after the administration of study drug for the first 3 visits.

[e] A brief physical examination was required at each study visit, with the exception of the Screening visit during which a complete physical examination was completed.

[f] Weight collected at this visit only.

[g] Triplicate ECGs were obtained on Days 1, 8, 29, and 57. A triplicate ECG constituted 3 separate recordings during a 15 minute interval. ECGs were obtained after the patient had rested quietly and was awake in a fully supine position (or semi-recumbent, if supine not tolerated) for 5–10 minutes. ECGs were obtained prior to drug administration. In addition, whenever a study procedure coincided with the scheduled time point for an ECG triplicate, the study activities were undertaken in a fixed sequence: ECGs first, vital signs second, and any type of blood draw as the last assessment.

[h] A MUGA scan or echocardiogram was required if the patient had a history of anthracycline treatment.

[i] Laboratory assessments were obtained predose and include serum chemistries and hematology.

[j] A blood sample for additional safety testing was collected if indicated.

[k] Plasma PK samples were obtained predose. At each study visit with a PK draw, patients were asked the time that study drug was taken on the preceding 2 days.

[l] At select sites.

[m] If there was evidence of progression.

[n] Progression at the first tumor assessment at Week 13 required a confirmatory scan 6 or more weeks later. Treatment with study medication continued until the progression had been confirmed AND the patient was scheduled to initiate another systemic antineoplastic therapy.

[o] A paper diary was provided at screening and at the Day 57 visit. Patients were instructed to complete the diary for 6 days prior to the Day 1 and the Day 85 visits. During the 6-day period, patients self-reported: "worst pain" score over the past 24 hours, use of long-acting narcotic analgesic, use of rescue narcotic, and use of NSAID.

[p] A single type of long-acting narcotic analgesic, a single type of rescue narcotic, and a single type of non-steroidal anti-inflammatory drug was selected for each patient until the Week 13 visit.

[q] Serious adverse events were collected from the time the patient signed the consent form until the Safety Follow-Up visit or until the initiation of another anti-neoplastic therapy whichever occurred first. Non-serious adverse events were collected from the time of first study drug dosing until the Safety Follow-Up visit or the initiation of another antineoplastic therapy, whichever occurred first.

[r] All patients underwent long-term follow-up to assess for survival, subsequent antineoplastic therapy, skeletal-related events, and radiographic progression.

[s] For study visit days, patients self administered study drug at the clinic upon instruction from the staff.

Sponsor's crpc2-report-body.pdf, page 38-39

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

/s/

JEFFRY FLORIAN
08/13/2012

KEVIN M KRUDYS
08/13/2012

MONICA L FISZMAN
08/13/2012

NORMAN L STOCKBRIDGE
08/13/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 203415 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Xtandi Established/Proper Name: enzalutamide Dosage Form: Capsules Strengths: 40 mg		
Applicant: Medivation, Inc. Agent for Applicant (if applicable):		
Date of Application: May 21, 2012 Date of Receipt: May 22, 2012 Date clock started after UN:		
PDUFA Goal Date: November 22, 2012	Action Goal Date (if different): August 31, 2012	
Filing Date: July 21, 2012	Date of Filing Meeting: June 15, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): For the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted

Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐

Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 074563	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
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***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
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 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***				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
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 Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

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).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
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:	**X**			

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

☒ legible ☒ 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 #				
Applications in "the Program" (PDUFA V) (NME NDAs/Original BLAs)	**YES**	**NO**	**NA**	**Comment**
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			**X**	
• If yes, were all of them submitted on time?				
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			**X**	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			**X**	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
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)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
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)?	X			
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)?	X			

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***	X			
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, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			
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.***			X	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**

PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			Waiver
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
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."***	X			Accepted by DMEPA
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***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels			

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			
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.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				

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

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			QT-IRT and OSI
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 3/17/09 and 9/28/09 (CMC) ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 3/30/12 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 15, 2012

BLA/NDA/Supp #: NDA 203415

PROPRIETARY NAME: Xtandi

ESTABLISHED/PROPER NAME: enzalutamide

DOSAGE FORM/STRENGTH: Capsules, 40 mg

APPLICANT: Medivation, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): For the treatment of patients with metastatic

BACKGROUND: This is a new molecular entity (NME) NDA. The application was submitted on May 21, 2012 (receipt date of May 22, 2012). Priority review was designated, however, the Division plans to expedite the review and take action by August 31, 2012.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Christy Cottrell	Y
	CPMS/TL:	Alice Kacuba	N
Cross-Discipline Team Leader (CDTL)	Ellen Maher		Y
Clinical	Reviewer:	Max Ning and Bill Pierce	Y
	TL:	Ellen Maher	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Jeanne Fourie Zirkelbach	Y
	TL:	Qi Liu	Y – phone
Biostatistics	Reviewer:	Stella Karuri	Y
	TL:	Shenghui Tang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Brian Chiu	Y
	TL:	Todd Palmby	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Debasis Ghosh and Gaetan Ladouceur	Y
	TL:	Janice Brown	Y
Quality Microbiology *(for sterile products)*	Reviewer:	John Metcalfe	Y
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Kim DeFronzo	N
	TL:	Todd Bridges	N
OSE/DRISK (REMS)	Reviewer:	Cynthia LaCivita	N
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	DJ Maranthe (Pharmacometrics) Tzu-Yun McDowell, Cunlin Wang Margaret Rand, Bob Pratt		Y N N
Other attendees	Susan Jenney, Amna Ibrahim, Debbie Mesmer, Robert Justice, Richard Pazdur, Liang Zhou, Anne Pilaro		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: None	☐ Not Applicable
CLINICAL **Comments**: None	☐ 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:***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: Expedited review – no time for ODAC; nothing controversial

o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: None	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: None	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: None	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: None	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Richard Pazdur

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): July 10, 2012

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

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. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review

ACTIONS ITEMS

☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day

	filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in "the Program")
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

CHRISTY L COTTRELL
08/09/2012

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

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 203415

Application Type: New NDA

Name of Drug: Xtandi (enzalutamide) Capsules

Applicant: Medivation, Inc.

Submission Date: May 21, 2012

Receipt Date: May 22, 2012

1.0 Regulatory History and Applicant's Main Proposals

This application provides for a new NDA indicated for the treatment of patients with castration-resistant prostate cancer who have received docetaxel (b) (4)

2.0 Review of the Prescribing Information (PI)

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

3.0 Conclusions/Recommendations

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

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. These deficiencies will be corrected by the Division during labeling negotiations.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

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

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

NO 4. White space must be present before each major heading in HL.

Comment: *Insert a space before the Adverse Reactions heading.*

NO 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *In the Contraindications section, the cross reference should just be (4). Since there is only one Contraindication, it does not need a subsection number.*

YES 6. Section headings are presented in the following order in HL:

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

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

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

Comment: *"For Oral Administration should be moved up so it appears on the same line as the product title. The "F", "O" and "A" should be changed to lower case.*

Initial U.S. Approval

NO

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

Comment: *Proposed labeling has "Month Year". This should be changed to 4-digit year only.*

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

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

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

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

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(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, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment: *Per the Label Review Tool, the Contraindications section in Highlights should state "Pregnancy" with a cross-reference to (4) and (8.1). The proposed labeling lists Pregnancy as section 4.1. Since there is only one contraindication, there should not be a separate subsection for Pregnancy and the cross reference should be (4).*

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment: *The proposed labeling states SUSPECTED DRUG ADVERSE REACTIONS. The word "DRUG" should be removed. In addition, the proposed labeling states "…or the FDA at 1-800…". The word "the" before FDA should be removed.*

Patient Counseling Information Statement

YES 26. Must include <u>one</u> of the following three **bolded** verbatim statements (without quotation marks):

<u>If a product **does not** have FDA-approved patient labeling</u>:

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

<u>If a product **has** FDA-approved patient labeling</u>:

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

Comment: *Since there is proposed Patient Labeling, the statement should be "See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."*

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment: *Section 12.4 Cardiac Electrophysiology in the proposed labeling should be changed to Section number 12.6, as 12.4 and 12.5 are reserved per the Label Review Tool.*

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment: *The proposed labeling does not capitalize "Full Prescribing Information". The first letters of each word should be capitalized.*

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment: *An additional space must be added after each section and subsection number so that the space is the size of two letter "m".*

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Selected Requirements of Prescribing Information (SRPI)

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

Comment: *Section 12.4 Cardiac Electrophysiology in the proposed labeling must be changed to Section 12.6, as 12.4 and 12.5 are reserved.*

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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

/s/

CHRISTY L COTTRELL
08/03/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	July 11, 2012
Reviewer:	Kimberly DeFronzo, RPh, MS, MBA Division of Medication Error Prevention and Analysis
Team Leader:	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Division Director:	Carol A. Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Xtandi (Enzalutamide) Capsules 40 mg
Application Type/Number:	NDA 203415
Applicant:	Medivation, Inc.
OSE RCM #:	2012-1216

***** This document contains proprietary and confidential information that should not be released to the public.*****

Contents

1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Xtandi (Enzalutamide) Capsules, NDA 203415, for areas of vulnerability that could lead to medication errors.

Xtandi (Enzalutamide) is a new molecular entity (NME) not approved in any country.

1.1 REGULATORY HISTORY

On Nov. 11, 2011, this product was granted Fast Track status for being a potent, novel androgen receptor (AR) signaling inhibitor that has a mechanism of action different from the commonly used, classic AR antagonists, including bicalutamide, flutamide and nilutamide.

1.2 PRODUCT INFORMATION

The following product information is provided in the May 21, 2012 submission.

- **Active Ingredient:** Enzalutamide
- **Indication of Use:** For the treatment of patients with castration-resistant prostate cancer who have received docetaxel (b) (4).
- **Route of Administration:** Oral
- **Dosage Form:** Capsules
- **Strengths:** 40 mg
- **Dose and Frequency:** 160 mg or 4 capsules once daily with or without food. No dose adjustment is necessary in the elderly. No formal renal or hepatic impairment study has been completed.
- **How Supplied:** As white to off-white oblong soft gelatin capsules imprinted in black ink with "MDV" in bottles of 120 capsules.
- **Storage:** Store capsules at controlled room temperature 20°C-25°C (68°F-77°F) with excursions to 15°C-30°C (59°F-86°F) permitted.
- **Container and Closure System:** Drug product will be packaged and supplied in 300-cc, (b) (4) opaque high density polyethylene (HDPE) bottles with (b) (4) closures lined with induction seals.

2 METHODS AND MATERIALS REVIEWED

Using the principals of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container label (electronic submission) submitted on May 21, 2012 (Appendix A)
- Carton labeling (electronic submission) submitted on May 21, 2012 (Appendix B)
- Insert labeling, including Patient Information, submitted on May 21, 2012 (no image)

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

The proposed recommended dose of 160 mg requires the patient to ingest four (4) of the 40 mg strength capsules daily. While this potential "pill burden" may be of a consideration for the elderly or patients with swallowing difficulties, the ingestion of multiple pills is not uncommon in oncology patient populations (e.g., Zytiga dosing is 4 tablets once daily). Although it would be preferable to decrease the number of capsules per day for patient compliance and to reduce the risk of dosing confusion, DMEPA finds this dosing proposal acceptable for approval since it is in line with available therapies and the Applicant is unlikely to develop alternative strengths at this stage of product development.

The Applicant also indicates that Xtandi capsules will be imprinted with the letters "MDV" using black ink. We acknowledge the proposed imprint marking complies with 21 CFR 206.10(a), by permitting the unique identification of the drug product and the manufacturer or distributor of the product. However, since the imprint "MDV" is an abbreviation for their company name "Medivation", we were concerned that this imprint may be repeated on other solid oral dosage forms the Applicant may develop in the future. DMEPA contacted the Applicant and received confirmation via email on July 3, 2012, that the imprint "MDV" will be used only on the enzalutamide capsules. Thus, we find this "MDV" imprint acceptable since it will remain a unique identifier for this product.

Additionally, DMEPA identified deficiencies in the container label, carton labeling, and the insert labeling. These deficiencies include:

- Inadequate prominence of important information
- Layout and format of information that can be optimized

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Unclear and/or missing important label and labeling statements
- Repetitive information that crowds or detracts important information

We provide recommendations in Section 5 to correct these deficiencies and minimize the risk of medication errors.

4 CONCLUSIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information to promote the safe use of the product.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Container Label

1. Revise the dosage form statement so that the font size of the word "capsules" is the same as the active ingredient "enzalutamide".
2. Ensure the statement "enzalutamide capsules" has a prominence commensurate with the prominence of the proprietary name, including typography (size, font, etc.), layout, contrast, and other printing features, as per 21 CFR 201.10(g)(2).
3. Remove the statement [redacted] (b) (4) " since it is redundant information.
4. Delete the graphic to the right of the proprietary name as it may be misinterpreted as the letter 'l', resulting in a new ending to the name and causing confusion with the proprietary name.
5. Add the statement "Swallow capsules whole. Do not chew, dissolve, or open the capsules." in a prominent location under the dosage form information.
6. To accommodate for other important information on the container label and carton labeling, retain only the one Manufacturer's contact information that is responsible for regulatory compliance.
7. Relocate the "Keep this and all medication out of the reach of children" statement to the bottom right hand corner of the principal display panel.

8. The statement of strength [redacted]. This is not the customary location and may hinder a provider's ability to quickly and easily identify this information on the label. Relocate the statement of product strength to follow the dosage form. The proprietary name, active ingredient, dosage form and product strength should be presented as follows:

Xtandi
(Enzalutamide Capsules)
40 mg

9. The net quantity statement is missing. Please add this information but ensure that the net quantity statement is positioned away from the product strength to avoid confusion with the strength.

B. Carton Labeling

1. See comments 1-6 above.
2. Remove the word [redacted] that follows the product strength since it is redundant information.

C. Insert Labeling

1. The Dosage and Administration section in the Full Prescribing Information should include the additional information "four 40 mg capsules" similar to what is found under the same section in the Highlights of Prescribing Information. Revise the statement in <u>both</u> Dosage and Administration sections to read: "The recommended dose of Xtandi is 160 mg (four 40 mg capsules) administered orally once daily."

2. Revise the Dosage and Administration section in the Full Prescribing Information and the Patient Counseling Information section to include the following statements, which are currently in the Patient Information section: "Swallow capsules whole. Do not chew, dissolve, or open the capsules."

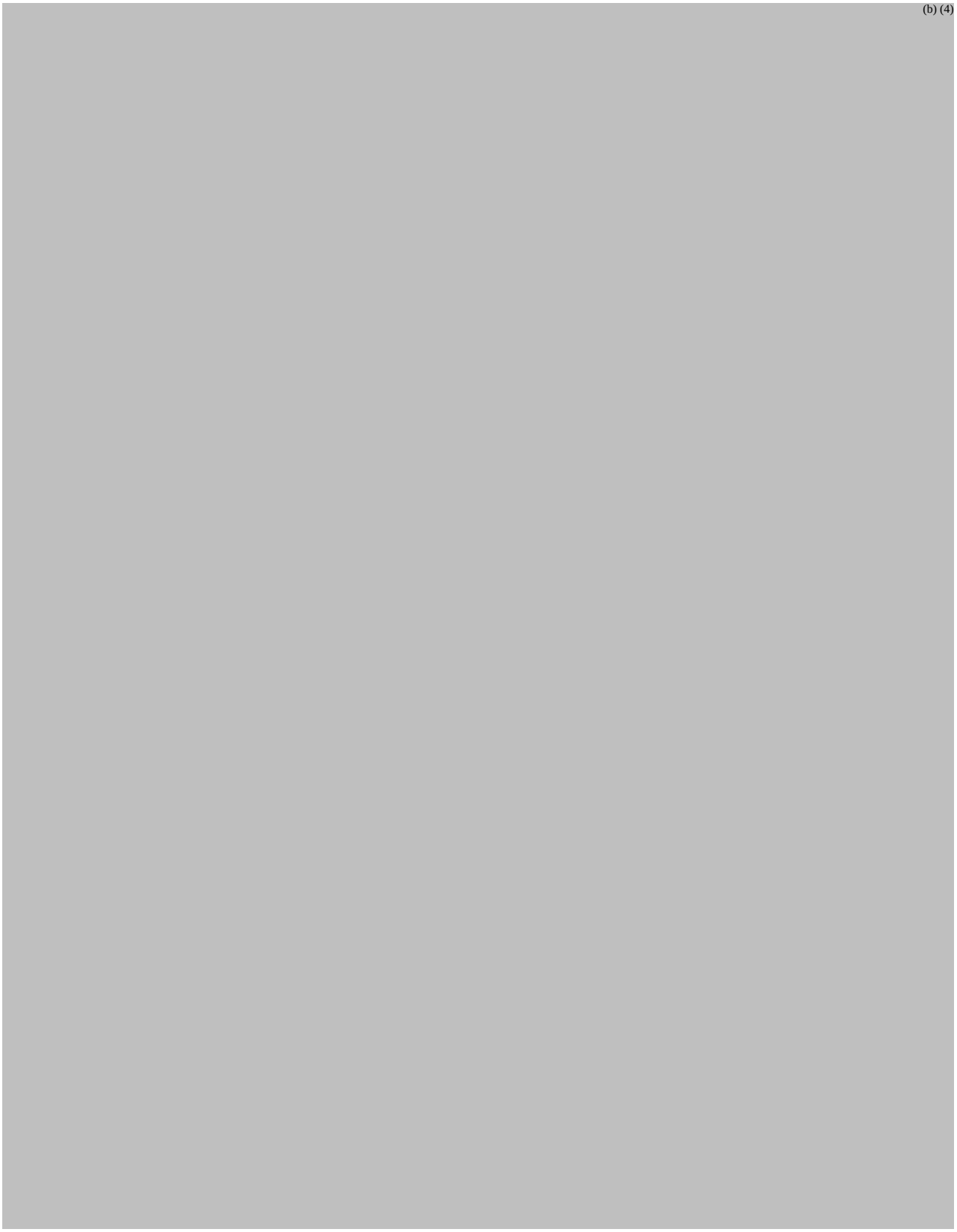
3. We recommend [redacted] in the Storage section in both the Full Prescribing Information and the Patient Information sections since [redacted], especially with temperature ranges. Therefore, we recommend revising the storage condition to read "Store …at 20ºC **to** 25ºC (68ºF **to** 77ºF) with excursions to 15ºC **to** 30ºC (59ºF **to** 86ºF) permitted]…"

4. Under the Patient Information section, relocate the statement "Tradename is not for use in women[redacted]" from the subheading "What is Tradename?" to the subheading of "Who should not take Tradename?", since it is a more appropriate placement of this type of information.

If you have further questions or need clarifications, please contact Frances Fahnbulleh, OSE Project Manager, at 301-796-0942.

APPENDICES

(b) (4)



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/s/

KIMBERLY A DE FRONZO
07/11/2012

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