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RESEARCH**

APPLICATION NUMBER:

203415Orig1s000

MEDICAL REVIEW(S)

Addendum to the Clinical Review

Date	August 29, 2012
From	Yang-Min M. Ning, M.D., Ph.D.
Through	V. Ellen Maher, M.D.
Subject	Radiographic Progression-Free Survival (rPFS) Analysis Results
Clinical Review Completion Date	August 19, 2012
Primary NDA Information (adopted from the previous review cover page)	
Application Type	NDA
Submission Number	203415
Submission Code	None
Letter Date	May 17, 2012
Stamp Date	May 22, 2012
PDUFA Goal Date	Nov. 21, 2012
Efficacy Reviewer	Yangmin M. Ning, M.D., Ph.D.
Safety Reviewer	William Pierce, Pharm. D.
GU Oncology Team Leader	V. Ellen Maher, M.D.
Review Completion Date	August 17, 2012
Established Name	Enzalutamide
Used Trade Name	XTANDI
Therapeutic Class	Androgen Receptor Inhibitor
Applicant	Medivation Inc.
Priority Designation	Priority Review
Formulation:	Capsules of 40 mg for oral administration
Dosing Regimen:	Four 40 mg capsules administered orally once daily with or without food
Proposed Indication:	<i>"For the treatment of patients with castration-resistant prostate cancer who have received docetaxel therapy"</i>
<p>Disclaimer Statement: This clinical review contains assessments and/or conclusions and recommendations written by individual clinical reviewers based on their best clinical interpretation and analyses of the data submitted to the NDA. Such assessments and/or conclusions do not necessarily represent or reflect those from reviewers in other divisions who evaluated the same application from different perspectives, nor do they necessarily represent the final regulatory recommendation and action on this NDA issued by the Review Division and or Office.</p>	

This addendum was generated to provide the rPFS analysis results for Section 6.1.5 of the clinical review dated August 19, 2012.

As described previously in that section, the rPFS analysis was one of the secondary endpoints of the CRPC2 trial. The clinical reviewer and statistical reviewers scrutinized the reported radiographic disease progression (rPD) events in the applicant’s newly submitted rPFS dataset. This dataset was created with implementation of the censoring rules as listed on Page 46 of the clinical review. Those censoring rules were clinically important and were necessary for appropriate determination of the time to progression in study patients who had clinical scenarios that could affect the accuracy and reliability of the rPFS analysis results.

Based on the above rPFS dataset, the reviewers found that approximately 47% of the total events used in the applicant’s original rPFS analysis should have been censored. Compared to the original rPFS dataset, there were more events censored in the placebo arm (62%) than in the MDV3100 arm (38%). This was largely due to the censoring of rPFS events that occurred after subsequent treatment initiation and/or an SRE. Most censored events in the placebo arm appeared at an earlier time (<3-6 months) than those censored in the MDV3100 arm.

Further examinations of the dataset also revealed a small number of patients who had inadequate censoring or had their progression time determined in a manner that differs from that typically used in FDA reviews (e.g., if progression is seen at an unscheduled scan the date of the scan is the date of progression). Those discrepancies are noted (a, b, and c) in the following table that summarizes the rPFS analysis results.

Analyses of Radiographic Progression and rPFS in the CRPC2 Trial

	MDV3100 (N=800)	Placebo (N=399)
Number of Patients with Radiographic Progression ^{a, b} (%)	242 (30%)	74 (19%)
Number of Deaths without Radiographic Progression	49 (6%)	46 (12%)
Number of Patients Censored	509 (64%)	282 (70%)
Radiographic Progression-Free Survival ^c (months) Median (95% CI)	11.0 (10.8, 11.8)	5.6 (5.3, 5.7)
Hazard Ratio (95% CI)	0.40 (0.32, 0.50)	
P value (log-rank)	<0.0001	

- a) *Not including patients with unconfirmed rPD that occurred before or at Week 13 scans. These patients were censored to their randomization date in this analysis.*
- b) *Not including patients who had their first SRE while on study treatment and before the reported rPD date. These patients were censored in this analysis to the date of their last scans without evidence of disease progression or to their randomization date if there were no scans available before the incidence of the first SRE.*
- c) *For patients with rPD detected at unscheduled visits (>Week 13) who did not have an SRE or initiate subsequent antitumor treatment before the rPD detection date, the date of the unscheduled scans was used in this rPFS analysis. The applicant used the date of the next scheduled scans (not conducted) in the updated rPFS analysis.*

Note: Stratified Analysis; p-value <0.0001

The above findings show that treatment with MDV3100 was associated with a statistically significant increase in rPFS when compared with placebo, suggesting that MDV3100 was able to delay mCRPC progression.

In addition, the reviewer evaluated the investigator-reported radiographic response in patients with measurable soft tissue disease at screening. The response was assessed by the investigators according to the RECIST v1.1 criteria as specified in the protocol. Unlike the determination of rPD for the rPFS analysis that required confirmatory scans in the protocol, radiographic response assessment of measurable soft tissue diseases did not necessarily require confirmatory scans or concurrent improvements in bone scans. As such, this evaluation only served as an exploratory analysis to reveal whether MDV3100 was active in shrinking soft tissue metastases of mCRPC treated previously with docetaxel. The results of the response assessment are shown in the following Table (Best Radiographic Response in Measurable Disease).

Best Radiographic Response in Measurable Disease Assessed with RECIST v1.1

	MDV3100 (N=800)	Placebo (N=399)
Number of Patients with Measurable Disease*	446	208
Number of Responders** (%)	137 (31%)	8 (4%)

** with at least one target lesion*

*** Requiring a reduction of $\geq 30\%$ in the sum of diameters of target lesions compared to that at baseline. This evaluation was based on Dataset ADSOFTBN (Analysis of Scans). Patients with unscheduled scans that occurred before the first scheduled, Week 13 scans were excluded from this evaluation.*

Note: All soft disease responses were found to have occurred prior to new treatment initiation.

***Reviewer's Comments:** The findings described in this addendum provide additional evidence of an antitumor effect for MDV3100. This is consistent with the antitumor effects demonstrated in other analyses (time to PSA progression, PSA declines, time to first SRE) as depicted in the August 19, 2012 clinical review of this NDA. Note that in terms of HR and medians, the above rPFS results are very similar to those provided by the applicant in the updated rPFS analysis that employed the clinically important censoring criteria listed in the rPFS part of Section 6.1.5 of the clinical review. The use of the censoring criteria made the current rPFS analysis results more reliable to assess the treatment effect of MDV3100.*

To the reviewer's best knowledge and judgment, all the antitumor evidence demonstrated in this NDA, including tumor responses to and delayed tumor progression by MDV3100, is scientifically fundamental to the detected improvement in overall survival with MDV3100 treatment in the CRPC2 trial. Taken together, this addendum does not change the benefit-risk profile of MDV3100, as assessed in Section 1.2 of the clinical review, for its use in the intended patient population.

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/s/

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08/30/2012

VIRGINIA E MAHER
08/30/2012

Clinical Review

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TABLE OF CONTENTS

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	8
1.1	Recommendation on Regulatory Action	8
1.2	Benefit Risk Analysis	8
1.3	Recommendations for Risk Evaluation and Mitigation Strategies	10
1.4	Recommendations on Post Marketing Requirements/Phase 4 Commitments	10
2	INTRODUCTION AND REGULATORY BACKGROUND	11
2.1	Product Information	11
2.2	Currently Available Treatments for Proposed Indication	12
2.3	Availability of Proposed Active Ingredient in the United States	12
2.4	Important Safety Issues with Consideration to Related Drugs	12
2.5	Summary of Presubmission Regulatory Activity Related to Submission	13
2.6	Other Relevant Background Information	14
3	ETHICS AND GOOD CLINICAL PRACTICES	16
3.1	Submission Quality and Integrity	16
3.2	Compliance with Good Clinical Practices	16
3.3	Financial Disclosures	17
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	18
4.1	Chemistry Manufacturing and Controls	18
4.2	Product Risk Management Plan	18
4.3	Preclinical Pharmacology/Toxicology	18
4.4	Clinical Pharmacology	18
5	SOURCES OF CLINICAL DATA	20
5.1	Tables of Clinical Studies	20
5.2	Review Strategy	21
5.3	Discussion of Individual Studies	22
6	REVIEW OF EFFICACY	22
6.1	Indication	22
6.1.1	Methods	23
6.1.2	Accrual, Demographics, and Analysis Populations	33
6.1.3	Patient Disposition	36
6.1.4	Analysis of Primary Endpoint(s)	39
6.1.5	Analysis of Secondary Endpoints(s)	45
6.1.6	Subpopulations	50
6.1.7	Analysis of Clinical Information Relevant to Dosing Recommendations	53
6.1.8	Discussion of Persistence of Efficacy and/or Tolerance Effects	54
6.1.9	Additional Efficacy Issues/Analyses	54
7	REVIEW OF SAFETY	57
7.1	Methods	60
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	60
7.1.2	Categorization of Adverse Events	63
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence	65

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

7.2	Adequacy of Safety Assessments.....	65
7.2.1	Overall Exposure at Appropriate Doses/Durations	65
7.2.2	Explorations for Dose Response	70
7.2.3	Special Animal and/or In Vitro Testing	70
7.2.4	Routine Clinical Testing.....	70
7.2.5	Metabolic, Clearance, and Interaction Workup.....	70
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class.....	71
7.3	Major Safety Results.....	72
7.3.1	Deaths.....	72
7.3.2	Nonfatal Serious Adverse Events (SAE).....	78
7.3.3	Treatment Discontinuations due to Adverse Events.....	79
7.3.4	Significant Adverse Reactions	80
7.3.5	Review of Specific Primary Safety Concerns	80
7.4	Supportive Safety Results	95
7.4.1	Common Adverse Events.....	95
7.4.2	Laboratory Findings	96
7.4.3	Vital Signs.....	98
7.4.4	Electrocardiograms (ECGs)	99
7.4.5	Immunogenicity	101
7.5	Other Safety Explorations	101
7.5.1	Dose Dependency for Adverse Events	101
7.5.2	Time Dependency for Adverse Events.....	101
7.5.3	Drug-Demographic Interactions.....	103
7.5.4	Drug-Drug Interactions	105
7.6	Additional Safety Evaluations	105
7.6.1	Human Carcinogenicity.....	105
7.6.2	Human Reproduction and Pregnancy Data	105
7.6.3	Pediatrics and Assessment of Effects on Growth.....	106
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound	106
8	POSTMARKET EXPERIENCE.....	106
9	APPENDICES	107
9.1	Literature Review/References.....	107
9.2	Labeling Recommendations.....	107
9.3	Advisory Committee Meeting.....	107

List of Tables

Table 1: Key Information about the Previously Approved Androgen Receptor Inhibitors.....	13
Table 2: Key Regulatory Activities during Clinical Development of MDV3100.....	13
Table 3: Study Sites Identified for Clinical Inspection.....	16
Table 4: Clinical Studies in Support of the NDA for Enzalutamide.....	20
Table 5: Protocol Milestones and Amendments during the CRPC2 Trial.....	24
Table 6: Study Calendar of the CRPC2 Trial (Adapted from Applicant).....	28
Table 7: Geographic Distribution of Study Patients in CRPC2.....	33
Table 8: Baseline Demographics of the Patients in CRPC2.....	33
Table 9: Distribution of Two Stratification Factors in the CRPC2 Trial.....	34
Table 10: Key Baseline Disease Characteristics in the CRPC2 Trial.....	35
Table 11: Prior Use of Cytotoxic Chemotherapy in the CRPC2 Trial.....	35
Table 12: Patients Disposition at the Interim Analysis.....	37
Table 13: Study Treatment Discontinued Solely for Clinical Progression without Evidence of Radiographic Progression or SREs.....	38
Table 14: Concomitant Use of Glucocorticoids and Bisphosphonates/Denosumab.....	38
Table 15: Major Protocol Violations/Deviations in the CRPC2 Trial.....	38
Table 16: Primary Endpoint Analysis Results (ITT).....	40
Table 17: Updated Primary Endpoint Analysis Results in ITT.....	41
Table 18: Sensitivity Analyses of the Impact of the Protocol Violations/Deviations and Clinical Progression Related Discontinuation on Survival.....	41
Table 19: Key Efficacy and Safety Information about Three Products Used for Treatment of mCRPC After Docetaxel Therapy (Reviewer Benefit-Risk Assessment).....	45
Table 20: Incidence and Time to First Skeletal-Related Event While On Study Treatment (ITT).....	47
Table 21: Time to PSA Progression (ITT).....	48
Table 22: Patients with PSA Declines of $\geq 50\%$ from Baseline.....	50
Table 23: Survival Difference in Patients ≥ 75 Years of Age.....	52
Table 24: Survival Difference in Patients Treated with Other Androgen Receptor Antagonists.....	52
Table 25: Impact of Dose Modifications on Overall Survival in the CRPC2 Trial.....	54
Table 26: Distribution of Patients with PSA Progression by 3 Months.....	55
Table 27: Exploratory Analysis of OS from the Landmark of Week 13.....	56
Table 28: Difference in Overall Survival in Patients with No PSA Progression by 3 Months.....	56
Table 29: Clinical Trials Included in the Integrated (Pooled) Safety Analysis.....	61
Table 30: Estimated Total Enzalutamide Exposure.....	62
Table 31: Controlled Terminologies for Clinical Trials in Safety Database.....	63
Table 32: Demographics and Disease Characteristics for the Safety Population.....	66
Table 33: Overall Treatment Duration by Study Arm (in weeks).....	67
Table 34: Treatment Duration by Study Arm (by time categories).....	68
Table 35: Dose Interruptions and Reductions.....	69
Table 36: Deaths and Causes of Death in the CRPC2 Trial.....	72
Table 37: Adverse Events with an Outcome of Death in the CRPC2 Trial*.....	73

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Table 38: Deaths Due to an Adverse Event Within 30 Days of Study Drug*	77
Table 39: Nonfatal SAEs in > 1.0 % and > Placebo*	78
Table 40: Permanent Discontinuation due to Adverse Events (CRPC2 trial)	79
Table 41: Summary of Seizure Cases in Enzalutamide Trials.....	82
Table 42: Fall and Fall-related Injuries by Age and Performance Status	90
Table 43: Spinal Cord Compression and Cauda Equine Syndrome (CRPC2 Trial)	91
Table 44: Nonpathologic Fractures (CRPC2 Trial)	92
Table 45: Adverse Reactions with an Increase of > 2% vs. Placebo*	95
Table 46: Treatment Emergent Laboratory Findings*	96
Table 47: Vital Signs in CRPC2 Study*	99
Table 48: Time to Resolution of Treatment Emergent AEs Leading to Dose Modification ..	102
Table 49: Exploratory Safety Analysis by Age Groups.....	103

List of Figures

Figure 1: Chemical Structure of Enzalutamide.....	11
Figure 2: Study Design of the MDV3100 Trial.....	24
Figure 3: Kaplan-Meier Overall Survival Curves (ITT).....	40
Figure 4: Schematic Diagram Illustrating the Timing of Docetaxel Treatment to Study Treatment (MDV3100 or Placebo)	42
Figure 5: Sensitivity Survival Analysis from the Initiation of Prior Docetaxel Treatment	43
Figure 6: Survival Analysis from the Discontinuation of Prior Docetaxel Treatment	43
Figure 7: Subgroup Analyses of Overall Survival.....	51
Figure 8: Analyses of the Impact of Concomitant Use of Glucocorticoids on Overall Survival	52
Figure 9: K- M Survival Curves of OS from the Week 13 Landmark	56

Commonly Used Abbreviations in this Review

Abbreviation	Full Term
ADT	Androgen Deprivation Therapy
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AR	Adverse Reaction
BPI-SF	Brief Pain Inventory-Short Form
CRF	Case Report Form
DLT	Dose-Limiting Toxicity
GS	Gleason Score
IDMC	Independent Data Monitoring Committee
ITT	Intent-to-Treat
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MTD	Maximum Tolerated Dose
OS	Overall Survival
PCWG2	Prostate Cancer Clinical Trials Working Group 2
rPFS	Radiographic Progression Free Survival
PR	Partial Response
PSA	Prostate Specific Antigen
RECIST	Response evaluation criteria in solid tumors

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical reviewers recommend regular approval of NDA 203415 that provides for the use of enzalutamide for “the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who have previously received docetaxel”.

This recommendation is based on the favorable benefit-risk assessment findings for enzalutamide when studied in the intended patient population. Key review findings in support of this benefit-risk assessment relied on reviewers’ rigorous analyses of the clinical data and reports submitted by the applicant.

Note that to accurately reflect the patient population in which the efficacy and safety of enzalutamide were demonstrated, the reviewers modified the applicant’s proposed indication, as shown on the front page of this review, by adding a key word “metastatic” before castration-resistant prostate cancer (CRPC). The applicant accepted the recommended change.

1.2 Benefit Risk Analysis

The benefit risk profile of enzalutamide (MDV3100/Xtandi) for the intended indication was well demonstrated in a randomized, placebo-controlled Phase 3 trial of the product in patients with mCRPC who had previously received docetaxel-based chemotherapy. The trial had overall survival as the primary endpoint with a prespecified interim analysis plan to detect a 3.7 month improvement in median survival with MDV3100 treatment compared with placebo (target hazard ratio: 0.76, with a two-side alpha level of 0.0244 using the O’Brien-Fleming approach). The trial enrolled 1199 patients, with 800 patients allocated to receive MDV3100 orally at a dose of 160 mg once daily and 399 patients to receive placebo orally once daily. The trial did not enroll patients with a history of seizure or taking medicines known to decrease the seizure threshold. Study treatment continued until patients experienced disease progression (evidence of radiographic progression, a skeletal-related event, or clinical progression), initiation of new treatment for the disease, unacceptable toxicity, or withdrawal.

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Important baseline characteristics at enrollment were balanced between the two arms. Across the arms, all patients had received prior docetaxel-based chemotherapy and 24% had received two cytotoxic chemotherapy regimens. For the two stratification factors, 92% of patients had an ECOG performance status score of 0-1 and 28% had a mean Brief Pain Inventory-Short Form (BPI-SF) score of ≥ 4 . At entry, 59% of patients had radiographic evidence of disease progression and 41% had PSA-only progression. Bone metastases were present in 91% percent of patients and visceral metastases to the lung and/or liver were present in 23% of patients. The total Gleason score of 8-10 at the initial cancer diagnosis was found in 47% of patients.

The interim analysis of overall survival was conducted at the time of 520 events (80% of the events required for the planned final analysis). This analysis showed that overall survival was significantly improved in patients on the MDV3100 arm compared to those on the placebo arm [HR 0.631 (95% CI: 0.529, 0.752), $p < 0.0001$]. The median survival of patients on the MDV3100 arm was 18.4 months (95% CI: 17.3 months, not reached) compared to a median survival of 13.6 months (95% CI: 11.3, 15.8) for those on the placebo arm. As a result, the IDMC recommended that the trial be unblinded and that patients receiving study drug on the placebo arm be offered MDV3100.

The above efficacy findings were sustained in an updated survival analysis (with 93% of the required events for the final analysis) and preserved in a number of sensitivity analyses and subgroup analyses. These findings appear to be supported by the demonstrated antitumor activity of MDV3100 from the analyses of key secondary endpoints, including the prolongation of radiographic progression free survival and PSA progression and the confirmed PSA declines of $\geq 50\%$ in 54% of patients treated with MDV3100. Nevertheless, the analyses of key secondary endpoints are considered exploratory.

The most common adverse reactions ($\geq 5\%$) in patients treated with MDV3100 in the randomized trial were asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, dizziness, spinal cord compression and cauda equina syndrome, muscular weakness, insomnia, lower respiratory infection, hematuria, paresthesia, anxiety, and hypertension. Adverse reactions of \geq Grade 3 occurred in 47% of patients receiving MDV3100 and in 53% of patients receiving placebo. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of patients treated with MDV3100 compared to none (0%) in those treated with placebo. Patients experiencing a seizure during the trial were permanently discontinued from MDV3100 treatment and all seizures resolved.

Taken together, the efficacy and safety findings from this randomized, placebo controlled trial have established a favorable benefit risk profile for MDV3100 for its intended use in patients with mCRPC who have previously received docetaxel. The significant improvement in overall survival with MDV3100 treatment in this patient population represents substantial evidence of clinical benefit in the presence of an acceptable safety profile as listed above. The unique safety signal with this product is the increased risk of developing seizure. Since the Phase 3 trial did not enroll patients at risk for seizure, this unique risk should be further studied in these patients. It will be important to evaluate whether the product's benefit risk profile remains favorable to patients at increased risk for seizures (*See Section 1.4*).

Based on the totality of the data and the review findings, the reviewers concluded that the benefit risk profile of MDV3100 is highly favorable for patients with mCRPC who have previously received docetaxel. This conclusion is substantiated by the benefit risk profile that supported the recent approval of two products used in the same disease setting (*See Reviewer's Comments in Section 6.1.4*). Therefore, regular approval of MDV3100 for the intended indication is highly recommended.

1.3 Recommendations for Risk Evaluation and Mitigation Strategies

No REMS was indicated or recommended based on the safety review findings.

1.4 Recommendations on Post Marketing Requirements/Phase 4 Commitments

A clinical PMR was identified during the review with regard to the observed increased risk of developing seizures with enzalutamide. Since the key trial in support of the proposed indication did not enroll patients with risk factors that may predispose them to seizures, it is important to assess whether the use of enzalutamide in patients with these risk factors is associated with an increase in seizures. If so, the favorable benefit-risk profile of enzalutamide may be altered in this subpopulation. The agreed-upon clinical PMR is as follows:

Because patients at increased risk of developing a seizure were excluded from the randomized clinical trial, convene a panel of experts in oncology and neurology to obtain recommendations regarding which patients at increased risk for seizures are appropriate to participate in a postmarketing safety trial, e.g., patients with a history of seizure (taking/not taking anti-convulsants), 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 increase the seizure threshold, or other risk factors known for the development of

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

seizures. Following the panel's recommendations, conduct a single-arm safety study to assess the risk of seizure with enzalutamide 160 mg/day in at least 350 patients with metastatic castrate-resistant prostate cancer who are at increased risk for seizure. The primary endpoint should be the incidence of seizure. With 350 patients, the trial has 85% power to detect an increase in seizures from ~1% as seen in the randomized clinical trial to 3%. Patients should remain on the study until disease progression, development of a seizure or of an unacceptable adverse reaction. The protocol should contain clear stopping plans for an excessive incidence of seizures.

The timetable submitted on August 9, 2012, by the applicant stated that they will conduct this safety study according to the following schedule:

Expert Panel Recommendations:	December 31, 2012
Final Protocol Submission:	June 30, 2013
Study Completion:	June 30, 2018
Final Report Submission:	March 31, 2019

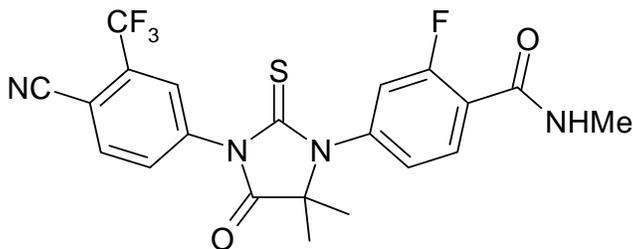
See Section 4.4 for four PMRs pertinent to the clinical pharmacology of enzalutamide and see the clinical pharmacology review for rationales supporting these PMRs.

2 Introduction and Regulatory Background

2.1 Product Information

MDV3100 (enzalutamide) is an androgen receptor inhibitor. The active ingredient is 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide. Its molecular formula is C₂₁H₁₆F₄N₄O₂S, with a molecular weight of 464.44. Its structural formula is shown in Figure 1:

Figure 1: Chemical Structure of Enzalutamide



The active ingredient is a white crystalline non-hygroscopic solid that is practically insoluble in water. The inactive ingredients of the product include caprylocaproyl

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

polyoxyglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, and black iron oxide.

Enzalutamide (XTANDI) is provided as liquid-filled soft gelatin capsules imprinted in black ink with MDV. Each capsule contains 40 mg of enzalutamide as a solution in caprylocaproyl polyoxyglycerides.

Enzalutamide (XTANDI) is administered orally once daily at a recommended dose of 160 mg (four 40 mg capsules administered at the same time).

2.2 Currently Available Treatments for Proposed Indication

Two FDA approved products, cabazitaxel (Jevtana[®]) and abiraterone acetate (Zytiga[™]), are currently marketed in the United States for the treatment of mCRPC progressing on or after docetaxel. See Sections 2.6 and 6.1.4 for more information about the two products relative to this NDA for MDV3100.

There has been off-label use of products such as hormonal agents (including bicalutamide, flutamide, and nilutamide) and cytotoxic agents (including mitoxantrone, cisplatin, carboplatin, cyclophosphamide, ixabepilone, etc) in the above disease setting. Antitumor effects may be observed in some of patients.¹ However, none of them have been shown to improve overall survival or quality of life in patients with mCRPC previously treated with docetaxel.

2.3 Availability of Proposed Active Ingredient in the United States

No products containing the active ingredient of MDV3100 are marketed at the time of this NDA review.

2.4 Important Safety Issues with Consideration to Related Drugs

Three products, including flutamide, bicalutamide, and nilutamide, are related to MDV3100 in terms of mechanism of action. The three nonsteroidal products, classified as an androgen receptor inhibitor, received FDA approval a decade ago for use in combination with androgen deprivation therapy (ADT) for the treatment of hormone-sensitive, metastatic prostate cancer. Table 1 lists key information about the products along with important safety signals reported in their product label. Of note, severe hepatic injury including hepatic failure and hepatic death was observed in patients taking them. No information is available about the incidence of severe hepatic injury is

¹ Aragon-Ching JB and Dahut WL (2007): Chemotherapy in Androgen-Independent Prostate Cancer (AIPC):

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

available. In addition, nilutamide has been well known to cause visual disturbances² (delayed adaptation to darkness).

Table 1: Key Information about the Previously Approved Androgen Receptor Inhibitors

	Flutamide	Nilutamide	Bicalutamide
Approval Year	1989	1995	1996
Indication	<i>“For use in combination with LHRH agonists for the management of locally confined Stage B2-C and Stage D2 metastatic carcinoma of the prostate”</i>	<i>“For use in combination with surgical castration for the treatment of metastatic prostate cancer (Stage D2)”</i>	<i>“for use in combination therapy with a luteinizing hormone-releasing hormone (LHRH) analog for the treatment of Stage D2 metastatic carcinoma of the prostate”</i>
Key Safety Signals Hepatic Injury Hepatic Failure/Death Diarrhea* Visual Disturbance	Reported Reported 8% > the control Not reported	Reported Reported NA 10-50% >the control	Reported Reported 14% < the control** Not reported
Warnings in Product Label Hepatic Injury Interstitial Pneumonitis	Yes No	Yes Yes	Yes No
*Differences in its incidence when compared to the control in randomized clinical trials ** the control contained flutamide Note: This summary is based on information from Drugs@FDA and Dailymed (US National Library of Medicine/NIH/HHS).			

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 2 summarizes key pre-submission regulatory activities with the FDA during the development of MDV3100 for the treatment of patients with mCRPC who received prior docetaxel-based chemotherapy.

Table 2: Key Regulatory Activities during Clinical Development of MDV3100

Feb. 2007	Initial submission of IND 74563 for MDV3100*
2007-2009	Phase 1/2 study**: adequate antitumor activity demonstrated (in both PSA and radiographic evaluations); the MTD was determined to be 240 mg QD.

What’s next after taxane progression? *Cancer Ther.* 5(A): 151–160

2 Anderson J. (2003): The role of antiandrogen monotherapy in the treatment of prostate cancer. *BJU* 91: 455-61

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Feb. 2009	EoPh2 Meeting: proposed to conduct a randomized placebo-controlled trial (CRPC2) in patients with mCRPC previously treated docetaxel-based chemotherapy
Sep. 2009 Nov. 2010	Initiation of CRPC2 with a lower dose schedule: 160 mg QD: intended for an improved risk-benefit profile. Enrollment of patients completed 14 months after the initiation.
March 2011	Proposed amendment for SAP: reducing the target HR from 0.80 to 0.76 and conducting a formal interim analysis at 80% of the targeted deaths required for the final OS analysis.
Sep. 2011	The IDMC recommended unblinding the study after the interim analysis.
Nov. 2011	Fast Track Designation granted for the investigation of MDV3100 for the treatment of patients with mCRPC who have been previously treated with docetaxel-based chemotherapy.
Mar. 2012	Pre-NDA meeting held to discuss critical elements required for the proposed submission of an NDA for MDV3100 for treatment of patients with mCRPC who have received docetaxel therapy. All issues concerning the data submission along with required analyses were well addressed.
Apr. 2012	Submission of a treatment protocol to provide expanded access to MDV3100 treatment use for patients with the above disease. The protocol was found to be safe to proceed after deficiencies and comments from the Agency were satisfactorily addressed.
May 2011	Submission of the NDA, designated for priority review.
* Reported in <i>Science</i> (2009) 324: 787-790 ** Also reported <i>Lancet</i> (2010) 375: 1437-46	

2.6 Other Relevant Background Information

Docetaxel in combination with prednisone has become the standard of care for patients with metastatic castration-resistant prostate cancer (mCRPC) since the FDA approval in 2004. Docetaxel in the combination improves the overall survival of patients with the disease. However, development of resistance to docetaxel treatment or intolerance to the treatment in some patients appears to be inevitable, which is responsible for most disease progression³. The median survival of patients with mCRPC is about 19.2 months based on the updated survival analysis of the TAX327 trial⁴⁻⁵, in which 45% of

3 Seruga B, et al (2011): Drug resistance in metastatic castration resistant prostate cancer. *Nat. Rev. Clin. Oncol.* 8, 12-23

4 Tannock IF, et al (2004): Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502-12.

5 Berthold DR, et al (2008): Docetaxel Plus Prednisone or Mitoxantrone Plus Prednisone for Advanced Prostate Cancer: Updated Survival in the TAX 327 Study. *J Clin Oncol* 26:242-245.

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

patients had a Present Pain Intensity score of >2 or an analgesic score of ≥ 10 , 22% had visceral involvement of the disease, and 13% had a Karnofsky performance-status score of $\leq 70\%$.

There were no proven effective therapies for mCRPC after disease progression on docetaxel or intolerance to docetaxel until the FDA approval of cabazitaxel for the treatment of hormone-refractory metastatic prostate cancer (mCRPC) previously treated with a docetaxel-containing treatment regimen in June of 2010.⁶ In April of 2011, another product, abiraterone acetate, received FDA approval for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel⁷. The approval of both products was based on the demonstrated improvement in overall survival in treated patients, compared with the study control, in their randomized Phase 3 trial. Both products have an acceptable or a favorable benefit-risk profile assessment that supported the approval. See the brief tabular summary of the benefit-risk profile for each product in the reviewer's comments in Section 6.1.4.

The effectiveness of abiraterone acetate in patients with mCRPC provides clinical evidence that impeding the signaling pathway of androgen receptor, from its ligand binding to its transactivation of genes responsible for tumor progression, represents an important approach to development of new products to treat mCRPC. This also provides strong support to years of research suggesting that elevated androgen receptor levels and constitutively activated androgen receptor signaling in tumor cells are responsible for the growth and progression of CRPC⁸⁻⁹ despite castration levels of serum testosterone.

This NDA for MDV3100 provides an additional piece of clinical evidence showing that inhibition of the androgen signaling pathway by an androgen receptor antagonist can be translated into an effective therapy for mCRPC. Unlike abiraterone acetate that acts by decreasing the level of androgens, MDV3100 antagonizes androgens' binding to androgen receptor in the cytoplasm, interferes with its subsequent translocation to the nucleus, and impairs its interaction with androgen response elements and gene transactivation.¹⁰

6 Cabazitaxel Approval Reviews: at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/201023s000TOC.cfm Accessed as of August 8, 2012.

7 Abiraterone Acetate Approval Reviews: at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202379Orig1s000TOC.cfm Accessed as of August 8, 2012.

8 Zhu W, et al (2010): Treatment of castration-resistant prostate cancer: updates on therapeutics targeting the androgen receptor signaling pathway *Am J Ther.* 17(2):176-81.

9 Attard G, et al (2009): Steroid hormone receptors in prostate cancer: a hard habit to break? *Cancer Cell* 16: 458-62

10 Tran C et al (2009): Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science* 324: 787-90

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality and integrity of the submitted data in this NDA were found adequate and acceptable. The applicant submitted safety and efficacy datasets in raw and analysis forms for both the CRPC2 trial and the integrated safety population, allowing the reviewers to examine and verify efficacy and safety findings. Information contained in datasets was found to be consistent information collected in the submitted CRFs. Across the datasets, information is also consistent. However, some clinical or statistical issues were identified during the review and conveyed to the applicant for clarification. As of today, all issues have been addressed and resolved satisfactorily.

3.2 Compliance with Good Clinical Practices

Based on both efficacy and safety reports from each study site that participated in the CRPC2 trial, four sites listed in Table 3 below were selected for clinical inspection.

Table 3: Study Sites Identified for Clinical Inspection

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects Enrolled	Median OS at Site (Range)	Number of SAEs
Site #025 Andrew Armstrong, M.D. Duke University Hospital Medical Center 10 Bryan Searle Dr. 471 Seeley G, Mudd Bldg Durham, NC 27710 Phone: (919) 668-8108 Fax: (919) 668-7117 Email: andrew.armstrong@duke.edu	CRPC2	15	18.2 mos	3

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects Enrolled	Median OS at Site (Range)	Number of SAEs
Site #017 Oscar Goodman Jr., M.D., Ph.D. Nevada Cancer Institute One Breakthrough Way Las Vegas, NV 89135 Phone: (702) 822-5433 Fax: (702) 944-2382 Email: ogoodman@nvcancer.org	CRPC2	7	12.5 mos	11
Site #300 * Karim Fizazi, M.D., Ph.D. Institut Gustave-Roussy 39 Rue Camille Desmoulins Département de Médecine Oncologique de l'IGR Villejuif 94805 France Phone: (33) 142-114317 Fax: (33) 142-115217 Email: fizazi@igr.fr	CRPC2	90	15.8	51
Site #204 Wolfgang Loidl, M.D. Krankenhaus der Barmherzigen Schwestern Linz Seilerstätte 4 Abteilung für Urologie Linz 4010 Austria Phone: (43) 732-76777253 Fax: (43) 732-76777337 Email: wolfgang.loidl@bhs.at	CRPC2	14	Median Estimate Not Yet Met	26

Inspection of the sponsor was also conducted.

The Office of Scientific Investigations (OSI) has completed the inspections and concluded that “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”. See detailed summary in the OSI’s inspection report.

3.3 Financial Disclosures

Disclosure of financial interests of the investigators involved in the clinical studies supporting this NDA for MDV3100 was submitted in the FDA form 3454. The

disclosure was certified for the applicant by C Patrick Machado, Chief Business Officer and Chief Financial Officer. Based on the disclosure report, no investigators were required to disclose a proprietary interest in MDV3100, significant equity in the applicant, or the receipt of significant payments of other sorts as defined in 21 CFR 54.2 (f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No issues related to clinical efficacy and safety were identified based on the CMC review findings.

4.2 Product Risk Management Plan

None

4.3 Preclinical Pharmacology/Toxicology

No clinically relevant issues were identified in the pharmacology/toxicology review.

4.4 Clinical Pharmacology

See the final product label that summarizes important clinical pharmacology information about enzalutamide in pharmacokinetics and drug-drug interactions.

The clinical pharmacology reviewers identified four PMRs pertinent to the recommended approval. The four PMRs are as follows:

- 1) 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.

The timetable submitted on August 9, 2012, states that the applicant will conduct this trial according to the following schedule:

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Final Protocol Submission: March 31, 2013
Trial Completion: May 31, 2014
Final Report Submission: November 30, 2014

- 2) 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.

The timetable submitted on August 9, 2012, states that the applicant will conduct this trial according to the following schedule:

Final Protocol Submission: April 30, 2013
Trial Completion: July 31, 2014
Final Report Submission: April 30, 2015

- 3) Conduct drug interaction trials to evaluate the effect of enzalutamide at steady state on the pharmacokinetics of CYP2D6 and CYP1A2 substrates. The proposed trial protocols must be submitted for review prior to initiation of the trials.

The timetable submitted on August 9, 2012, states that the applicant will conduct this trial according to the following schedule:

Final Protocol Submission: July 31, 2013
Trial Completion: December 31, 2014
Final Report Submission: June 30, 2015

- 4) 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.

The timetable submitted on August 9, 2012, states that the applicant will conduct this trial according to the following schedule:

Final Protocol Submission: December 31, 2012
Trial Completion: June 30, 2013
Final Report Submission: December 31, 2013

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Clinical studies related to use of MDV3100 for the proposed indication in the current NDA are listed in Table 4. Important information about their study phase, design and major findings is also summarized.

No additional clinical studies were submitted as supplemental evidence during the review.

Table 4: Clinical Studies in Support of the NDA for Enzalutamide

Phase	Study ID (Period)	Study Population	Key Objectives	Key Design Elements	Major Findings
Phase 1/2	S-3100-1-01 (07/2007-1/2010; ongoing)*	Patients with CRPC (N=140)	Safety and tolerability evaluation; Dosing determination; PK/PD analyses	Open-label, dose-escalation (30, 60,150/160, 240, 360, 480, and 600 mg/day	MTD: 240 mg qd Observed important AEs: Fatigue, rash, and seizure, which appeared to be dose-dependent. PSA declines of $\geq 50\%$ from baseline observed at all dose levels tested, and in 50-60% of the patients Supporting 160 mg qd as the optimal dose for further studies
	CRPC-MDA-1 (02/2010-07/2011; ongoing)	Patients with CRPC (N=60)	MOA: androgen signaling in bone Safety and tolerability evaluation	Open-label Phase 2, with a dose of 160 mg qd	Frequent AEs: fatigue, anorexia, arthralgia, constipation, peripheral edema; no seizures observed as of the study report submission. PSA declines of $\geq 50\%$ from baseline observed in 47% of the patients; Increases in serum and bone marrow androgen levels with the treatment; Reduction in androgen receptor levels in the nucleus.
Phase 3	CRPC2	Patients with mCRPC who	To assess whether	Randomized (2:1), double-	(see detailed review

Phase	Study ID (Period)	Study Population	Key Objectives	Key Design Elements	Major Findings
	(09/2009-cutoff 09/2011)	have received prior docetaxel chemotherapy (N=1199)	MDV3100 improves overall survival	blind, placebo-controlled trial comparing the survival of patients treated with MDV3100 at 160 mg qd or placebo. Treatment continued until documented disease progression, unacceptable toxicity, or initiation of new antitumor therapy.	findings in Sections 6 and 7)
* The applicant specified that the Phase 2 part still is ongoing.					

5.2 Review Strategy

The clinical reviewers focused on the key study (Trial CRPC2) that supports the proposed use of MDV3100 in patients with mCRPC who have previously received docetaxel for metastatic disease. The reviewers evaluated the submitted data and study report, examined both the accuracy and internal consistency of the information contained in relevant datasets against information documented in CRFs and/or case narratives, and verified survival events and censoring with information found across related datasets. Discrepancies or issues indentified during the review were investigated with the statistical reviewers and conveyed to the applicant for clarification and/or correction. Information or data (e.g. rPFS data and analysis) submitted during the review was also examined or verified against that originally submitted information, if applicable, to determine its acceptability, consistency and reliability. The reviewers, with the help of the statistical review team, conducted independent analyses concerning the efficacy of MDV3100 in appropriate analysis populations, mainly the ITT population, subgroup populations, and some exploratory analysis populations as specified in Section 6.1.9.

The reviewers also investigated the consistency of the antitumor activity demonstrated for MDV3100 between the key study and the early Phase 1-2 study in patients with mCRPC who have received prior docetaxel-based chemotherapy. Relevant to the

proposed indication for MDV3100, the reviewers also scrutinized numerous literature publications or reports on product(s) approved or being developed for the same indication in order to better evaluate and understand the clinical relevance of the study findings reported for MDV3100 in this NDA.

5.3 Discussion of Individual Studies

The CRPC2 trial provided key evidence in support of the efficacy claim for MDV3100 in this NDA submission. See Sections 6 and 7 of the review findings.

Study S-3100-1-01 was a combined Phase 1/2 study that revealed considerable antitumor activity for MDV3100 and determined the MTD as 240 mg once daily. However, the results from all the dose levels tested suggested an optimal dose schedule of 160 mg once daily, since dosing at 240 mg or more was associated with increased toxicity (e.g. seizures) without an additional increase in its antitumor activity.¹¹

Study CRPC-MDA-1 was a single-arm, Phase 2 study aimed to investigate pharmacodynamic changes in the androgen receptor signaling pathway with MDV3100 treatment at 160 mg once daily. The results submitted to the NDA appear to provide some support for the claimed mechanism of action. The antitumor activity observed in this study is also consistent with that shown in Study S-3100-1-01.

The safety information from the two Phase 1 and 2 studies will be analyzed in ISS as described in Section 7.

6 Review of Efficacy

6.1 Indication

The initial proposed indication for MDV3100 in this NDA submission was as follows:
“For the treatment of patients with castration-resistant prostate cancer who have received docetaxel (b) (4)”

¹¹ Scher HI, et al (2010): Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. *Lancet* 375: 1437-46

6.1.1 Methods

For the proposed indication for MDV3100 in this NDA, the efficacy review focused on examining both data and reported results from the randomized, placebo-controlled trial (CRPC2).

The reviewer evaluated the original study protocol and its amendments during the trial to assess whether efficacy or safety assessments were affected by the amendments. To evaluate the reliability of important efficacy endpoints, especially for the primary endpoint, the reviewers randomly examined the accuracy of information between CRFs and relevant datasets, and verified the completeness of the datasets and analyses reported by the applicant. The reviewer found no discrepancies that could affect the analyses of the primary endpoint.

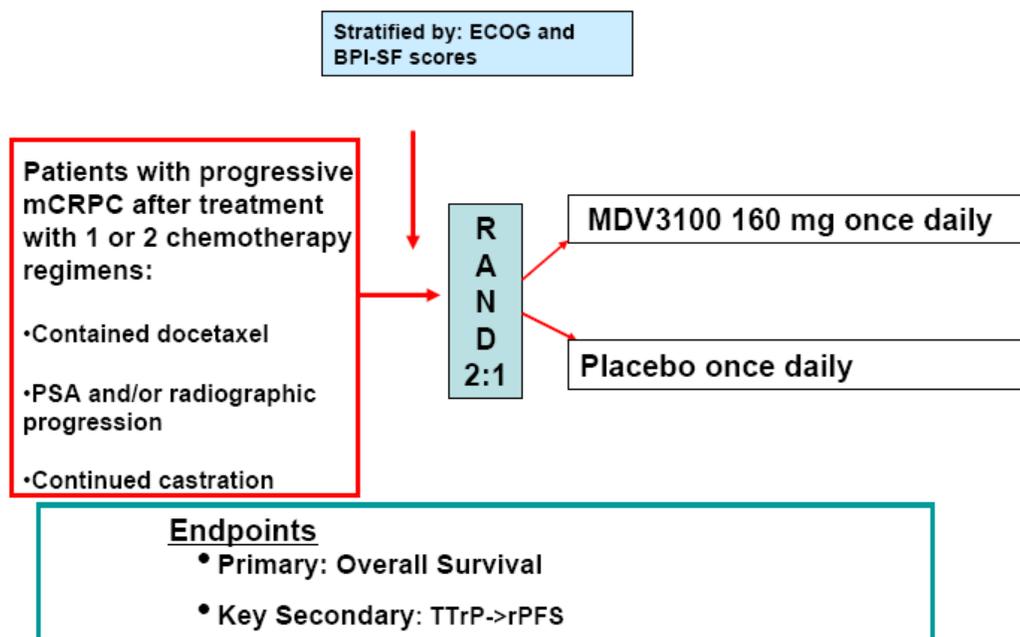
Differences in data tabulations or analyses between this review and the applicant's study report were specified in the review and discussed with the statistical reviewers to resolve or to achieve agreements. Sensitivity analyses were also conducted whenever indicated to assess the reliability of the trial findings and/or conclusions. Clinical importance and implications of the efficacy results were also evaluated and discussed in the reviewer's comments and were based on the reviewer's best medical knowledge and understanding of research on mCRPC.

Protocol Review for Trial CRPC2

Study Design

Trial CRPC2 was a randomized, double-blind, placebo-controlled, multicenter Phase 3 trial to compare the efficacy and safety of once daily dosing of MDV31000 with placebo in patients with mCRPC who had previously received docetaxel-based chemotherapy. Patients had to have documented evidence of disease progression by PSA and/or radiographic scans while maintaining castrate levels of testosterone. Patients were randomized 2:1 to receive either MDV3100 or placebo, as shown in Figure 2. Treatment continued until unacceptable toxicity, disease progression as defined in the protocol, death, or withdrawal. An independent IDMC was formed prior to the study initiation to monitor safety during study and to evaluate efficacy and safety findings from pre-specified analyses.

Figure 2: Study Design of the MDV3100 Trial



Note: BPI-SF scores were determined by averaging the total of the 24 hours worst pain scores collected daily for 7 days prior to randomization.

Protocol Amendments

The trial was planned in May of 2009. Since then, there were 4 protocol amendments as summarized in Table 5.

Table 5: Protocol Milestones and Amendments during the CRPC2 Trial

Milestone	Date	Major Changes or Comments
Original Protocol	05/21/2009	Shortly after the End of Phase 2 meeting with the Agency
Amendments 1	07/30/2009	<ul style="list-style-type: none"> • Decreased the dose schedule from 240 mg/day to 160 mg/day. • Changed in CTCAE version from version 3.0 to version 4.0 for toxicity grading • Clarification of plans for long-term follow-up for survival.
Protocol Initiation	09/22/2009	First patient enrolled
Amendment 2	04/01/2010	<ul style="list-style-type: none"> • Incorporated the European Quality of Life 5-

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Milestone	Date	Major Changes or Comments
		Domain Scale (EQ-5D) assessment in the protocol
Enrollment Completion	11/15/2010	Last patient enrolled
Amendment 3	04/19/2011	<ul style="list-style-type: none"> Reduced the target hazard ratio for the final overall survival analysis from the originally planned 0.80 to 0.76 with a prespecified interim analysis (see Statistical Methods below) Changed one secondary endpoint progression-free survival to radiographic progression-free survival (rPFS) that included radiographic progression and death events Eliminated one originally proposed secondary endpoint: time to radiographic progression
Interim Analysis Report	11/2/2011	<ul style="list-style-type: none"> Positive findings from the interim analysis of the primary endpoint with the data cutoff for the interim analysis was (b) (6) The IDMC reported the findings to the applicant and recommended unblinding the trial and offering MDV3100 to patients actively on placebo The Agency was notified of the findings Nov. 3, 2011. The information was publicly disclosed on the same day.
Database Lock	12/16/2011	<ul style="list-style-type: none"> Before the database lock, the trial blinding was maintained Additional 56 deaths were identified between the interim analysis and the database lock.
NDA-submission	05/22/2012	<ul style="list-style-type: none"> Priority Review designated

Reviewer's Comments: *The above listed amendments had no significant impact on the assessment of the primary endpoint. Note that the key modification of the SAP was introduced 6 months before the interim analysis.*

Trial Objectives**Primary:**

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

Key Secondary:

- To determine the benefit of MDV3100 as compared to placebo as assessed by radiographic progression-free survival (rPFS);
- 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 by time to PSA progression;

Key Inclusion Criteria

Patients with progressive mCRPC who had met all of the following (per the Protocol):

- Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features;
- Ongoing androgen deprivation therapy with a GnRH analogue or orchiectomy (i.e., surgical or medical castration);
- For patients who have not had an orchiectomy, there must be a plan to maintain effective GnRH-analogue therapy for the duration of the trial;
- Serum testosterone level < 1.7 nmol/L (50 ng/dL) at the Screening visit;
- Patients receiving bisphosphonate therapy must have been on stable doses for at least 4 weeks;
- Progressive disease by PSA or imaging after docetaxel-based chemotherapy in the setting of medical or surgical castration. Disease progression for study entry is defined as one or more of the following three criteria:
 - PSA progression defined by a minimum of three rising PSA levels with an interval of ≥ 1 week between each determination. The PSA value at the screening visit should be ≥ 2 ng/ml;
 - Soft tissue disease progression defined by RECIST;
 - Bone disease progression defined by two or more new lesions on bone scan;
- No more than two prior chemotherapy regimens with at least one regimen containing docetaxel;
- ECOG performance status of 0–2;
- Estimated life expectancy of ≥ 6 months;
- Able to swallow the study drug and comply with study requirements;
- Willing and able to give informed consent.

Key Exclusion Criteria (per the protocol)

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

- History of seizure, including any febrile seizure, loss of consciousness, or transient ischemia attack within 12 months of enrollment (Day 1 visit), or any condition that may pre-dispose to seizure (e.g., prior stroke, brain arteriovenous malformation, head trauma with loss of consciousness requiring hospitalization);
- Taking medications known to lower the seizure threshold or prolong the QT interval. Medicines specified in the protocol included: Aminophylline/theophylline; Atypical antipsychotics (e.g., clozapine, olanzapine, risperidone, ziprasidone); Bupropion; Class IA and III antiarrhythmics (e.g., amiodarone, bretylium, disopyramide, ibutilide, procainamide, quinidine, sotalol); Dolasetron; Droperidol; Gatafloxacin/moxifloxacin; Insulin; Lithium; Macrolide antibiotics (e.g., erythromycin, clarithromycin); Pethidine; Phenothiazine antipsychotics (e.g., chlorpromazine, mesoridazine, thioridazine); Pimozide; Tricyclic and tetracyclic antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine); Venlafaxine;
- Metastases in the brain or active epidural disease
- Total bilirubin (Tbili), alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 times the upper limit of normal at the Screening visit
- Use of herbal products that may decrease PSA levels (e.g., saw palmetto) or systemic corticosteroids greater than the equivalent of 10 mg of prednisone/prednisolone per day within 4 weeks of enrollment (Day 1 visit) or plans to initiate treatment with any of these treatments during the study
- Treatment with androgen receptor antagonists (bicalutamide, flutamide, nilutamide), 5- α reductase inhibitors (finasteride, dutasteride), estrogens, or chemotherapy within 4 weeks of enrollment (Day 1 visit) or plans to initiate treatment with any of these treatments during the study
- History of prostate cancer progression on ketoconazole or plans to initiate ketoconazole treatment during the study
- Clinically significant cardiovascular disease such as myocardial infarction within 6 months, uncontrolled angina within 3 months; New York Heart Association (NYHA) class 3 or 4 congestive heart failure; history of clinically significant arrhythmias; prolonged corrected QT interval by the Fridericia correction formula (QTcF) on the screening electrocardiogram (ECG) > 470 msec; hypotension (systolic blood pressure < 86 millimeters of mercury [mmHg] or bradycardia with a heart rate < 50 beats per minute on any ECG taken at the Screening or Study Day 1 visit; and uncontrolled hypertension as indicated by a resting systolic blood pressure > 170 mmHg or diastolic blood pressure > 105 mmHg at the Screening or Study Day 1 visit;

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Reviewer's Comments: Please note that the risk-benefit profile of MDV3100 as described in this review may differ in patients with medical conditions matching the above exclusion criteria.

Study Conduct

Patients found eligible for the trial after the screening assessments received the applicant's approval for enrollment and got their randomization code based on the Interactive Voice Recognition System. The code determined their study treatment assignment and was used on all blinded trial activities. All patients, investigators, and the sponsor's employees involved in the trial were blinded to treatment assignment.

Treatment assessments and safety monitoring were based on the study calendar pre-specified for the protocol, which is shown in Table 6.

Table 6: Study Calendar of the CRPC2 Trial (Adapted from Applicant)

Study Day	Screening Visit	1	8	29	57	85	113	141	169	Safety F/U	Unscheduled Visit ^a
Week	-4 to -1 (28 days)	1	2	5	9	13	17	21	28 and every subsequent 12 weeks	30 Days after last dose ^b	n/a
Window (days)			± 2	± 3	± 3	± 7	± 3	± 3	± 7	± 7	n/a
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	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										
ECOG	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											
Study Drug Treatment ^s		X	X	X	X	X	X	X	X		

Unscheduled visits may be performed 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 comes first.

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

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

- d Vitals signs (blood pressure, heart rate, respiratory rate, temperature) are to be obtained prior to, and 1–2 hours after the administration of study drug for the first 3 visits.
- e A brief physical examination is required at each study visit, with the exception of the Screening visit during which a complete physical examination will be completed.
- f Collect weight at this visit only.
- g Triplicate ECGs are to be obtained on Days 1, 8, 29, and 57. A triplicate ECG constitutes three separate recordings during a 15 minute interval. ECGs will be obtained after the patient has rested quietly and awake in a fully supine position (or semi-recumbent, if supine not tolerated) for 5–10 minutes. All ECGs will be obtained prior to drug administration. In addition, whenever a study procedure coincides with the scheduled timepoint for an ECG triplicate, the study activities must be 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 is required if the patient has a history of anthracycline treatment.
- i Laboratory assessments are to be obtained pre-dose and include serum chemistries and hematology.
- j Collect a blood sample for additional safety testing if indicated.
- k Plasma PK samples to be obtained pre-dose. At each study visit with a PK draw, patients will be asked the time that study drug was taken on the preceding 2 days.
- l At select sites.
- m If there is evidence of progression (as defined in the protocol).
- n Progression at the first reassessment at Week 13 requires a confirmatory scan 6 or more weeks later. Treatment with study medication will continue until the progression has been confirmed AND the patient is scheduled to initiate another systemic antineoplastic therapy.
- o A paper diary must be provided at screening and at the Day 57 visit. Patients will be instructed to complete the diary for 6 days prior to the Day 1 and the Day 85 visits. During the 6-day period, patients will self-report: “worst pain” score over the past 24 hours, use of long-acting narcotic analgesic, use of rescue narcotic, and use of non-steroidal anti-inflammatory drug (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 must be selected for each patient until the Week 13 visit.
- q Serious adverse events will be collected from the time the patient signs the consent form until the Safety Follow-Up visit or until the initiation of another anti-neoplastic therapy whichever occurs first. Non-serious adverse events will be collected from the time of first study drug dosing until the Safety Follow-Up visit or the initiation of another anti-neoplastic therapy, whichever occurs first.
- r All patients MUST undergo long-term follow-up to assess for survival, subsequent antineoplastic therapy, skeletal-related events, and radiographic progression.
- s For study visit days, patients will self administer study drug at the clinic upon instruction from the staff.

Adapted from the CRPC2 protocol

Note: The long-term follow-up occurred every 12 weeks +/- 7 days after the last safety assessment, which was scheduled 30 days after the last dose of study treatment.

Treatment Plan

Randomized patients received 4 capsules of study treatment once daily, taken as close to the same time each day as possible. No double dosing (e.g. taking 8 capsules) was allowed if dosing on the prior day was missed.

Patients experiencing a toxicity of \geq Grade 3 that was not ameliorated with adequate medical intervention had study treatment interrupted until the toxicity decreased to \leq

Grade 2 in severity. Thereafter, patients could resume on study treatment at a reduced dose with the written approval from the applicant or sponsor.

During the trial, patients should continue ADT, but should not take medicines known to lower the seizure threshold or prolong the QTc interval, as specified in the exclusion criteria. In addition, the following medicines were prohibited per the protocol.

- Chemotherapeutic and biologic agents;
- Systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone/prednisolone (unless needed for stress steroids or to treat presumed adrenal insufficiency);
- Androgen-receptor antagonists (bicalutamide, flutamide, nilutamide); Estrogens; 5 α -reductase inhibitors (finasteride, dutasteride);
- Herbal medications that may affect PSA levels (i.e., saw palmetto);
- Androgens (testosterone, dihydroepiandrosterone [DHEA], etc.).

Efficacy Assessments

For the primary endpoint, overall survival was defined as time from randomization to death due to any cause. Patients who did not reach the endpoint were censored to the date last known to be alive.

For the following secondary endpoints, assessment was dependent on the study calendar and varied with the definition for each of them:

- a) Radiographic progression-free survival (rPFS) was defined as time from randomization to the earliest objective evidence of radiographic progression or death due to any cause. Radiographic progression was assessed by the investigator according to the definition of 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. Patients who did not reach the endpoint were right censored at their last assessment. (See more protocol-specified censoring rules in Statistical Methods)
- b) Time to first skeletal-related event was defined as time from randomization to the occurrence of the first skeletal-related event. 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.
- c) Time to PSA progression was defined as time from randomization to PSA progression. PSA progression was defined according to the consensus

guidelines of the Prostate Cancer Clinical Trials Working Group 2 (PCWG2). For patients with PSA declines at Week 13, the PSA progression date was defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir was documented, which was confirmed by a second consecutive value obtained 3 or more weeks later. For patients with no PSA declines at Week 13, the PSA progression date was defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the baseline was documented, which was confirmed by a second consecutive value 3 or more weeks later. Patients who did not have PSA progression at the time of analysis were censored to the date of their last PSA assessment.

***Reviewer's Comments:** The above secondary endpoints are clinically important in terms of assessing the antitumor effects of MDV3100. However, there has not been a good correlation of rPFS or time to PSA progression with a clinical benefit such as overall survival. The role of rPFS may be more difficult to characterize in patients with progressive mCRPC who have previously been treated with docetaxel because of the increased tumor burden after disease progression on docetaxel.*

The protocol-specified definition of radiographic disease progression was based on the 2008 Prostate Cancer Clinical Trials Working Group (PCWG2) recommendations¹². However, the censoring rules specified in the clinical protocol were insufficient to assure a reliable assessment of the treatment effect of MDV3100 on rPFS. Except for the requirement for confirmatory scans for radiographic progression detected at Week 13, the protocol did not include censoring rules for important clinical scenarios that may affect the accuracy and or reliability of radiographic progression interpretation. For example, the protocol did not state how to determine radiographic progression time for the rPFS analysis in patients who before the analysis, had radiographic progression reported before the first scheduled scans at Week 13, experienced an SRE, discontinued study treatment due solely to clinical progression, initiated subsequent antitumor therapies, or underwent radiation or surgical therapy involving the bone.

Statistical Methods

The initial trial sample size estimation was to require approximately 1080 patients and 786 events (deaths). This was calculated under the following assumptions: a median overall survival of 15 months for the MDV3100 arm and a median overall survival of 12 months for the placebo arm. Using a two-sided log-rank test with a 0.05 level of significance, the trial had 85% power to detect the above three month difference in median survival.

12 Scher HI et al (2008): Design and End Points of Clinical Trials for Patients with Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 26:1148-1159

In April of 2011, the applicant modified the above assumptions and also pre-specified an interim analysis plan. The statistical modification provided approximately 90% power to detect a 3.7 month difference in median survival (the target hazard ratio of 0.76) using a two-sided log-rank test with a 0.05 level of significance. The pre-specified interim analysis plan was to perform an overall survival analysis at the time of approximately 520 events (80% of the 650 targeted events for the planned final analysis, with a two-side alpha level of 0.0244 using the O'Brien-Fleming approach) with a stratified log rank test. Findings from this interim analysis, performed by an independent statistician, were presented to the IDMC. The IDMC was then asked to make recommendations about continuation of the double-blind, randomized trial.

To determine the duration of the secondary endpoint rPFS, the protocol's statistical analysis plan specified censoring or progression time-defining rules for the following situations (*adopted from the SAP*):

- No baseline assessments: **censoring** to date of randomization
- Lost to follow-up since randomization: **censoring** to date of randomization
- Disease progression or death after two or more consecutive missed radiographic assessments: **censoring** to date of last radiographic assessment showing no evidence of disease progression that is before the first missed radiographic assessment or data analysis cutoff date, whichever occurs first
- Not known to have progressed or died at the data analysis cutoff date (this includes patients who were known to have progressed or died after the data analysis cutoff date): **censoring** to date of last radiographic assessment showing no evidence of disease progression or data analysis cutoff date, whichever occurs first.
- Disease progression between two scheduled radiographic assessments: **Progressed** on date of next scheduled radiographic assessment showing disease progression or date of death
- Death between two scheduled radiographic assessments: **progressed** on date of death
- Death before first radiographic assessment: **progressed** on date of death

All randomized patients constituted the intent-to-treat (ITT) population, regardless of whether the actual assigned study treatment was received or not. Primary efficacy analyses were conducted in the ITT population. In contrast, the safety population consisted of patients who receive at least one dose of study treatment.

See the statistical review of this NDA for detailed statistical plans.

6.1.2 Accrual, Demographics, and Analysis Populations

From September of 2009 to November of 2010, the trial enrolled 1199 patients from 156 study centers in 15 countries, with 800 patients allocated to the MDV3100 arm and 399 to the placebo arm. Twenty-four percent of the patients were recruited from the United States. Their enrollment by geographic region is summarized in Table 7.

Table 7: Geographic Distribution of Study Patients in CRPC2

Geographic Region	MDV3100 (N=800)	Placebo (N=399)
USA Canada	181 (22.6%) 82 (10.3%)	107 (26.8%) 25 (6.3%)
Europe*	461 (57.6%)	223 (55.9%)
Rest of the world	76 (9.5%)	44 (11.0%)
* Majority of patients from France. Other patients from Austria, Belgium, Germany, Italy, Netherlands, Poland, Spain, United Kingdom		

The patient demographics are summarized in Table 8. The median age was 69 years. Ninety-three percent of the patients were White, and 4% were Black.

Table 8: Baseline Demographics of the Patients in CRPC2

	MDV3100 (N=800)	Placebo (N=399)
Age		
Median (yrs) (range)	69 (41, 92)	69 (49, 89)
Age Group		
< 65	232 (29%)	130 (33%)
65 to 74	369 (46%)	165 (41%)
≥ 75	199 (25%)	104 (26%)
Race		
Caucasian	745 (93%)	366 (92%)
Black	27 (3%)	20 (5%)
Asian	5 (1%)	8 (2%)
Other	23 (3%)	5 (1%)

Table 9 shows the distribution of the two stratification factors used for randomization in the study population. As expected, these factors were well balanced between the arms.

Table 9: Distribution of Two Stratification Factors in the CRPC2 Trial

	MDV3100 (N=800)	Placebo (N=399)
BPI-SF Pain Score*(Mean)		
≥4	225 ^a (28%)	115 (29%)
<4 but >0	429 (54%)	199 (50%)
=0	146 (18%)	85 (21%)
ECOG Score at Enrollment		
0	298 (37%)	156 (39%)
1	432 (54%)	211 (53%)
2	70 (9%)	32 (8%)
<p>*Baseline BPI-SF pain score of ≥4 (Average of patient’s reported scores over the 7 days prior to randomization). ^a The sponsor’s tabulation had a total number of 226. The difference was due to inclusion of Patient 017-06 who actually had an averaged weekly BPI score of 3.2 instead of the score of 4.0, which was the last 24-hour worst pain score reported at the first clinic visit (Day 1).</p>		

Baseline disease characteristics for the randomized patients were also balanced between the two arms. Key disease characteristics are summarized in Table 10. As shown in the table, 59% of patients had radiographic evidence of disease progression and 41% had PSA-only progression at enrollment. Most patients, 91% had metastases in bone while 23% had visceral involvement in the lung and/or liver. The percentage of patients with visceral involvement was 4% more in the MDV3100 arm than that in the placebo arm, which may favor the placebo arm in terms of prognosis. In addition, 47% of patients had a total Gleason score of 8-10 at their cancer diagnosis.

Important baseline laboratory parameters were also examined and found to be balanced between the arms. These included levels of baseline hemoglobin, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and alkaline phosphatase (ALP). In both arms, the median hemoglobin level was 12.0 g/dL (range: 6.3, 15.6), the median ALP level 114 IU/L (range: 28, 5676), and the median LDH level 211 IU/L (range: 78, 5978).

Table 10: Key Baseline Disease Characteristics in the CRPC2 Trial

	MDV3100 (N=800)	Placebo (N=399)
Disease Progression Type		
PSA-only Progression	326 (41%)	164 (41%)
Radiographic Progression*	470 (59%)	234 (59%)
Disease Metastasis Site		
Bone	730 (92%)	364 (92%)
Lymph Node	442 (56%)	219 (55%)
Viscera (Liver, Lung)	196 (25%)	82 (21%)
Total Gleason Score at Diagnosis		
≤7	359 (45%)	175 (44%)
≥8	366 (46%)	193 (48%)
Missing	75 (9%)	31 (8%)
Serum PSA Level (ng/mL)		
Median (range)	108 (0.4, 11794)	128 (0.6, 19000)

* Some had concurrent PSA progression.

All patients had received prior docetaxel-based therapy and 24% of them had received two cytotoxic chemotherapy regimens. Table 11 summarizes the prior use of chemotherapy regimens and information about prior exposure to docetaxel, including the cumulative dose of docetaxel and the docetaxel treatment timing relevant to the initiation of study treatment. As shown, patients enrolled in the trial had comparable exposure to docetaxel between the arms prior to enrollment.

Table 11: Prior Use of Cytotoxic Chemotherapy in the CRPC2 Trial

	MDV3100 (N=800)	Placebo (N=399)
Number of Regimens		
1	72%	74%
2	25%	24%
≥3*	3%	2%
Prior Docetaxel Usage and Timing to Enrollment		
Total Docetaxel Dose ^a	600 mg	600 mg
Median (range)	(25, 2520)	(75, 2175)

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Time from the FIRST docetaxel treatment to study initiation ^b (mos) Median (range)	13.6 (2.5, 95.9)	13.1 (1.8, 97.8)
Time from the LAST docetaxel treatment to study initiation ^b (mos) Median (range)	6.1 (1, 80.8)	5.8 (0.9, 94.3)
<i>*Representing a protocol deviation</i>		
<i>a: Reported in 86% patients</i>		
<i>b: Reported in ALL patients</i>		
<i>Note: Prior docetaxel usage information was collected retrospectively.</i>		

Prior use of the previously approved androgen receptor antagonists was examined and found to be balanced between the two arms. Across the arms, 85% of patients used bicalutamide, 14% used flutamide, and 10% used nilutamide.

Analysis Population: All randomized patients consisted of the ITT population used for key efficacy analyses of overall survival, as described in Section 6.1.4. Populations used for sensitivity analyses or exploratory analyses were determined as appropriate to each analysis. For subgroup analyses, the distribution of baseline characteristics was used.

Reviewer Comments:

All baseline characteristics listed above were balanced between the two arms. This is particularly important for some key characteristics including baseline pain level, performance status, type of disease progression at enrollment, and percentages of patients with visceral involvement of the disease. Also, prior docetaxel usage was similar between the two arms.

6.1.3 Patient Disposition

Patient disposition at the time of interim analysis was examined and the results are shown in Table 12. Twenty-nine percent of patients were actively on MDV3100 treatment compared with 5% actively on placebo. In contrast, 74% of patients in the placebo arm discontinued study treatment because of disease progression, approximately 20% higher than the percentage (55%) of patients in the MDV3100 arm who discontinued study treatment secondary to disease progression. Key reasons for treatment discontinuation were summarized along with percentages of patients for each reason. Interestingly, 10% of patients from the placebo arm discontinued study treatment because of adverse events compared to 8% of patients from the MDV3100 arm. On the

other hand, more patients (in percentage) withdrew from the placebo arm than from the MDV3100 arm.

Table 12: Patients Disposition at the Interim Analysis

	MDV3100 (N=800)	Placebo (N=399)
On Treatment	232 (29%)	19 (5%)
Treatment Discontinued	569 (71%)	380 (95%)
Reasons for Discontinuation of Study Treatment		
Disease Progression*	441 (55%)	296 (74%)
Radiographic Progression ^a	246 (31%)	180 (45%)
Clinical Progression	231 (29%)	159 (40%)
Skeletal Related Event	81 (10%)	39 (10%)
Death	17 (2%)	6 (2%)
Adverse Events	61 (8%)	39 (10%)
Withdrawal	23 (3%)	23 (6%)
Protocol Violation	1 (0.1%)	1 (0.3%)
Other**	26 (3%)	15 (4%)
<p><i>* At the time of study treatment discontinuation, some patients had >1 of the three types of disease progression listed below. For those patients, they were counted only once in determining the total number of patients with Disease Progression. Nevertheless, the numbers of patients with each type of disease progression were tabulated as reported and patients could be counted more than once.</i></p> <p><i>^a Patients who continued study treatment following detection of radiographic progression, but who discontinued the treatment thereafter due to other reasons were not included among those having “Radiographic Progression” as the cause of treatment discontinuation in this tabulation.</i></p> <p><i>** The majority of the patients listed in this category had their treatment discontinued for increases in serum PSA level.</i></p>		

Table 13 lists the number of patients discontinued solely due to “Clinical Progression” as assessed by the investigator in the absence of evidence of radiographic progression or an SRE. The effect of these “Clinical Progression” events on overall survival will be examined in Section 6.1.4. Since determination of “Clinical Progression” was based on best clinical judgment or experience, this might be subject to bias and or to variations of the investigator’s clinical assessment skills.

Table 13: Study Treatment Discontinued Solely for Clinical Progression without Evidence of Radiographic Progression or SREs

	MDV3100 (N=800)	Placebo (N=399)
Investigator-Assessed Clinical Progression*	140 (18%)	94 (24%)
<i>* Not including patients with clinical progression who had concurrent evidence of radiographic or an SRE.</i>		

In addition, concomitant use of glucocorticoids and bisphosphonates/denosumab during the trial was also tabulated since products may affect the efficacy and or safety results of the trial. As specified in Section 6.1.2, use of these products was not required in the trial. The tabulation as shown in Table 14 indicates that approximately 46% of patients used systemic glucocorticoids and or bisphosphonates/denosumab and that the usage of either one was also balanced between the arms.

Table 14: Concomitant Use of Glucocorticoids and Bisphosphonates/Denosumab

	MDV3100 (N=800)	Placebo (N=399)
Glucocorticoids*	47.9%	45.6%
Bisphosphonates/Denosumab	47.9%	45.9%
<i>*Includes only systemic use</i>		

Fourteen percent of patients had major protocol violations and/or deviations in the trial. As shown in Table 15, the incidence of the violations/deviations types was similar for each type as listed.

Table 15: Major Protocol Violations/Deviations in the CRPC2 Trial

Type	MDV3100 (N=800)	Placebo (N=399)
Number with at least 1 deviation	117 (14.6%)	50 (12.5%)

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Eligibility criteria unmet	60 (7.5%)	30 (7.5%)
Not discontinued per the protocol	4 (0.5%)	0 (0%)
Use of protocol-prohibited concomitant medication	56 (7.0%)	22 (5.5%)
• Chemotherapy*	7 (1.0%)	3 (1.0%)
Wrong treatment/dose	1 (0.1%)	0 (0.0%)

* Including cabazitaxel, docetaxel, carboplatin, cisplatin, cyclophosphamide, and investigational product (undefined)

During the trial, 2 patients (IDs 032-02 and 502-04) were unblinded regarding their treatment assignment through the IVRS/IWRS for determination of their subsequent clinical study. The un-blinding was conveyed to the sponsor and investigators prior to database lock. All other patients remained blinded to the sponsor and investigators before the interim analysis.

Reviewer Comments:

Sensitivity Analyses listed in Section 6.1.4 examined the impact of the protocol deviations/violations and the “Clinical Progression”-related treatment discontinuation on primary overall survival results. A subgroup analysis shown in Section 6.1.6 evaluated differences between the two arms in patients with/without systemic glucocorticoid use during the trial. Given that the use of bisphosphonates and or denosumab between the arms was similar during the trial, time to first SRE was evaluated in Section 6.1.5. As a standard care for patients with mCRPC, use of bisphosphonates and or denosumab appears low in the trial. This may be associated with differences in patients’ management across the 15 countries in which the trial was conducted, or with other factors that affect utilization of this standard care in patients with mCRPC.

6.1.4 Analysis of Primary Endpoint(s)

Analysis of Primary Endpoint

Analysis of the primary endpoint overall survival was conducted according to the pre-specified interim analysis plan with a total of 520 events. The data cutoff date for the analysis was (b) (6)

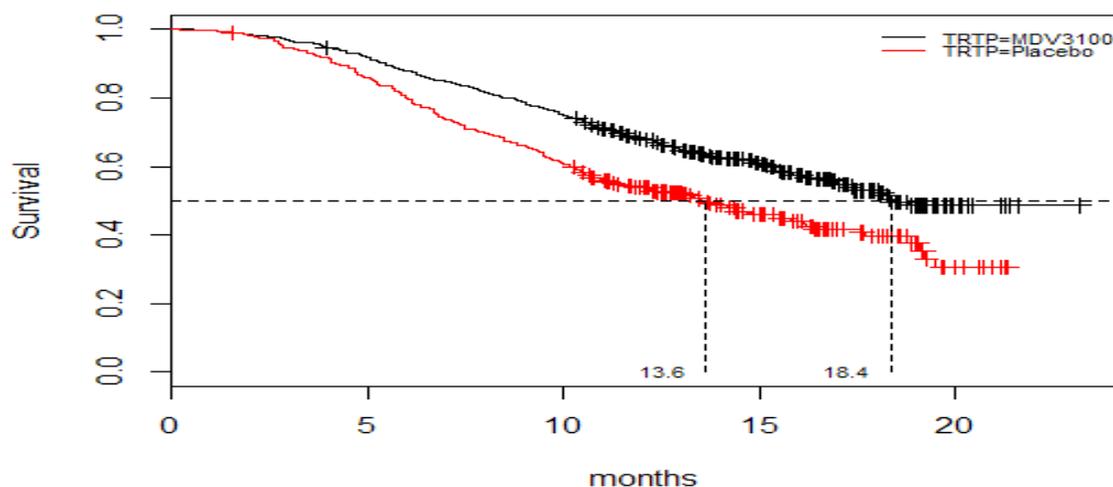
The interim analysis showed a statistically significant improvement in overall survival in patients on the MDV3100 arm compared to patients on the placebo arm [stratified HR 0.631 (95% CI: 0.529, 0.752), p<0.0001].

Table 16 summarizes the results and Figure 3 shows the Kaplan-Meier overall survival curves from this analysis. The median survival time was 18.4 months in the MDV3100 arm compared to a median survival of 13.6 months in the placebo arm.

Table 16: Primary Endpoint Analysis Results (ITT)

	MDV3100 (N=800)	Placebo (N=399)
Number of Deaths (%)	308 (38.5%)	212 (53.1%)
Median Survival (months) (95% CI)	18.4 (17.3, NR)	13.6 (11.3, 15.8)
p value ^a	< 0.0001	
Hazard Ratio (95% CI) ^b	0.63 (0.53, 0.75)	
^a P-value is derived from a log-rank test stratified by ECOG performance status score (0-1 vs. 2) and mean pain score (< 4 vs. > or equal to 4)		
^b Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors MDV3100		
NR = not reached		

Figure 3: Kaplan-Meier Overall Survival Curves (ITT)



With the interim analysis results, the IDMC recommended that the trial be unblinded and that MDV3100 be offered to patients randomized to the placebo arm. In addition, patients receiving MDV3100 was transitioned to the open-label portion of the trial.

An updated survival analysis of overall survival was conducted with an additional 56 deaths that occurred between the interim analysis and the database lock. The results, as shown in Table 17, are almost same as the results from the interim analysis. Of note, the median survival times in both arms became slightly shorter when compared to the results in Table 16.

Table 17: Updated Primary Endpoint Analysis Results in ITT

	MDV3100 (N=800)	Placebo (N=399)
Deaths (%)	344 (43%)	232 (58%)
Median Survival (months) (95% CI)	17.8 (16.7, 18.8)	13.3 (11.2, 14.1)
Hazard Ratio (95% CI)	0.62 (0.52, 0.73)	

Sensitivity Analyses of the Primary Endpoint

To examine whether the protocol violations/deviations as listed in Table 15 and the study treatment discontinuations due solely to “clinical progression” (as listed in Table 12) affect the reliability of the above survival results, two sensitivity analyses were conducted with exclusion of those patients from the interim analysis. As shown in

Table 18, the hazard ratios from the two sensitivity analyses were similar to that of the interim analysis, suggesting that the survival benefit demonstrated was sustained despite the protocol violations/deviations and the treatment discontinuations due solely to clinical progression.

Table 18: Sensitivity Analyses of the Impact of the Protocol Violations/Deviations and Clinical Progression Related Discontinuation on Survival

	HR* (95%CI)	P Value
ITT (Index)	0.63 (0.53, 0.75)	<0.0001
Excluding Patients with Major Protocol Violation/Deviation	0.67 (0.55, 0.81)	<0.0001
Excluding Patients Discontinued Solely Due to Clinical Progression	0.59 (0.49, 0.70)	<0.0001

*HR<1 favors MDV3100

All the patients in the trial received prior docetaxel treatment for their mCRPC. As shown in Table 11, the exposure to docetaxel and the timing of docetaxel usage relative to study treatment initiation appear comparable between the two arms. As such, two more sensitivity analyses were performed to test the robustness of the

interim analysis results. One analysis was to explore survival differences between the arms from docetaxel treatment initiation to the occurrence of either death or censoring; the other one was from docetaxel discontinuation (last dose) to either death or censoring in the trial. Figure 4 provides a schematic diagram to illustrate the time points (first and last docetaxel doses) used for the two sensitivity analyses.

Figure 4: Schematic Diagram Illustrating the Timing of Docetaxel Treatment to Study Treatment (MDV3100 or Placebo)

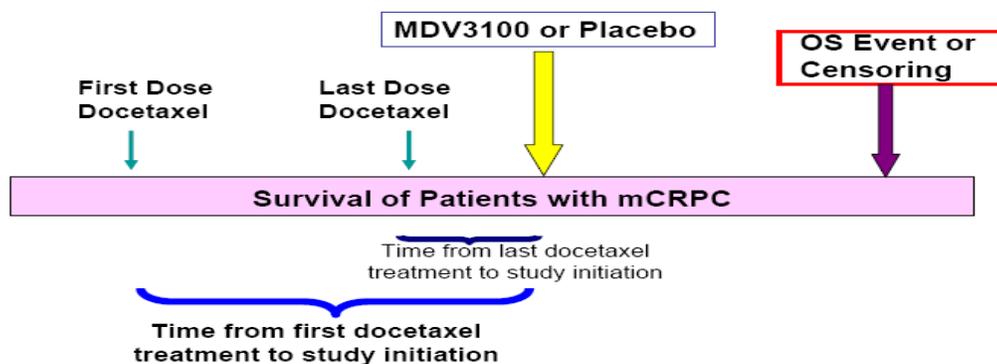
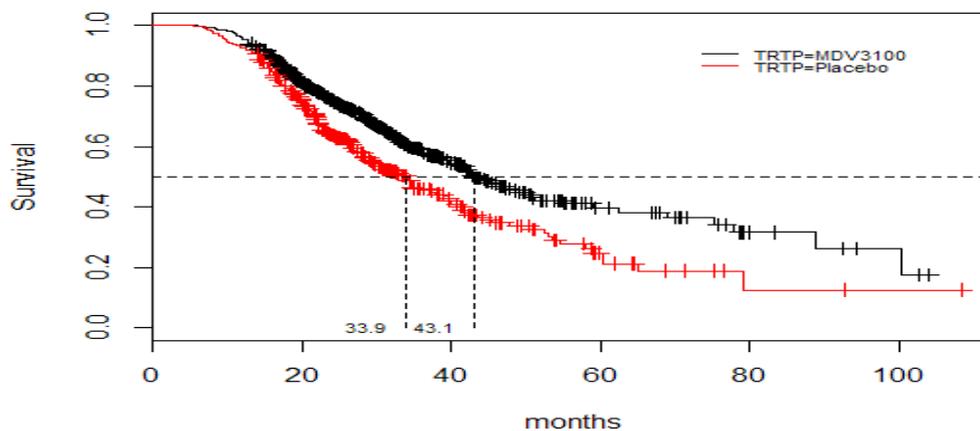


Figure 5 shows the results of overall survival from the initiation of prior docetaxel treatment in the ITT population. The estimated median overall survival was 43 months (95% CI: 40 to 50) for patients on the MDV3100 arm compared to a median overall survival of 34 months (95% CI: 29- 38) for patients on the placebo arm. The hazard ratio was 0.67 (95% CI: 0.6, 0.8), suggestive of the preserved survival advantage with MDV3100 treatment.

Figure 5: Sensitivity Survival Analysis from the Initiation of Prior Docetaxel Treatment



HR: 0.67 (95%CI: 0.6, 0.8)

Median Survival in the MDV3100 Arm: 43 months (95% CI: 40, 50)

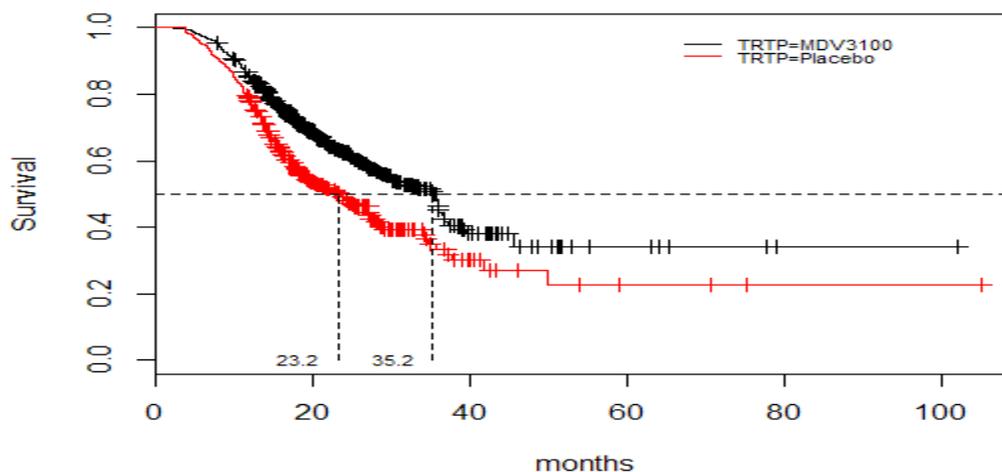
Median Survival in the Placebo Arm: 34 months (95% CI: 29, 38)

Figure 6 shows the results from the time of the last docetaxel treatment in the ITT population. The estimated median overall survival was 35 months (95% CI: 30, 36) in the MDV3100 arm and 23 months (95% CI: 19, 27) in the placebo arm. The hazard ratio was 0.67 (95% CI: 0.5, 0.8), suggesting that the survival benefit with MDV3100 treatment was also maintained from the last dose of prior docetaxel use.

Figure 6: Survival Analysis from the Discontinuation of Prior Docetaxel Treatment

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy



HR: 0.67 (95%CI: 0.5, 0.8)

Median Survival in the MDV3100 Arm: 35 months (95%CI: 30, 36)
Median Survival in the Placebo Arm: 23 months (95%CI: 19, 27)

Although the study patients in the trial represent a selected population, the results from the two exploratory sensitivity analyses also provide important information about how long patients with mCRPC may survive from either initiation or discontinuation of prior docetaxel treatment. Most importantly, the results show that the survival advantage with MDV3100 treatment was preserved irrespective of prior docetaxel use.

Reviewer's Comments

The above primary endpoint analyses, including the pre-specified interim analysis, updated survival analysis and four sensitivity analyses, demonstrate that treatment with MDV3100, as compared with placebo, led to superior survival in patients with mCRPC who received prior docetaxel treatment. The improvement in median overall survival was approximately 4 months with MDV3100 treatment.

Table 19 summarizes the efficacy findings along with key safety information from the CRPC2 trial and lists relevant information from two other products approved for the treatment of patients with mCRPC who have received prior docetaxel. In the reviewer's assessment, the benefit-risk profile of MDV3100 in the same disease setting appears to be greatly favorable relevant to that of the other products. Please note that neither improvements in median overall survival nor incidence rates of adverse reactions as listed in this table should be compared directly to each other because of the inherent issues with cross-study comparisons.

Table 19: Key Efficacy and Safety Information about Three Products Used for Treatment of mCRPC After Docetaxel Therapy (Reviewer Benefit-Risk Assessment)

	<i>Cabazitaxel</i>	<i>Abiraterone</i>	<i>Enzalutamide (MDV3100)</i>
Approval Year	2010	2011	
Drug Class	<i>Cytotoxic</i>	<i>Hormonal</i>	<i>Hormonal</i>
Trial Demonstrating Clinical Benefit	<i>EFC6193</i>	<i>COU-AA-301</i>	<i>CRPC2</i>
<i>Study Disease Setting</i>	<i>mCRPC s/p Docetaxel</i>	<i>mCRPC s/p Docetaxel</i>	<i>mCRPC s/p Docetaxel</i>
<i>Study Control*</i>	<i>Mitoxantrone</i>	<i>Placebo</i>	<i>Placebo</i>
<i>Study Size (# to treatment arm)</i>	<i>755 (378)</i>	<i>1195 (797)</i>	<i>1199 (800)</i>
Survival Difference** HR (95% CI)	<i>0.70 (0.59-0.83)</i>	<i>0.65 (0.543, 0.768)</i>	<i>0.63 (0.53, 0.75)</i>
<i>Improvement in Median OS (mos)</i>	<i>2.4</i>	<i>3.9</i>	<i>4.8</i>
Key Toxicity Profile***			
<i>Infusion Reaction/ Boxed Warnings</i>	<i>Yes</i>	<i>N/A</i>	<i>N/A</i>
Severe Toxicity (Grade 3/4)			
<i>Neutropenia (%)</i>	<i>82%</i>	<i>NS</i>	<i>1%</i>
<i>Febrile Neutropenia (%)</i>	<i>7%</i>	<i>NS</i>	<i>NS</i>
<i>Infection or UTI (%)</i>	<i>2%</i>	<i>2%</i>	<i>1%</i>
<i>Fluid Retention/Edema (%)</i>	<i><1%</i>	<i>2%</i>	<i>1%</i>
<i>Hepatic ALT/AST (%)</i>	<i>1%</i>	<i>2%</i>	<i>0.3%</i>
<i>Seizure (%)</i>	<i>NS</i>	<i>NS</i>	<i>1%</i>
Adverse Reaction of Interest (Grade 3/4)			
<i>Hypokalemia (%)</i>	<i>NS</i>	<i>5%</i>	<i>NS</i>
<i>Hypertension (%)</i>	<i>NS</i>	<i>1%</i>	<i>2%</i>
<i>Adrenocortical Insufficiency</i>	<i>NS</i>	<i><1%</i>	<i>NS</i>
<p>* Use of glucocorticoids varied among the trials ** Compared to Study Control in each trial. Inherent bias prevents from inter-trial comparisons. *** Based on information from the active treatment arm only. N/A denotes "not applicable" NS denotes "not specified", meaning not found in relevant product's label or the review.</p>			

6.1.5 Analysis of Secondary Endpoints(s)

The following analyses of key secondary endpoints were performed based on the clinical relevance of the endpoints and listed according to the sequence specified in the study protocol.

Radiographic Progression-Free Survival

Radiographic progression-free survival (rPFS) was defined as the time interval from randomization to the earliest evidence of radiographic progression or death due to any cause. This endpoint was introduced in Protocol Amendment 3 to replace the originally used composite endpoint of progression-free survival that included radiographic progression, skeletal-related events, and death. See Section 6.1.1 for more information about how to assess this endpoint along with the censoring rules specified in the statistical analysis plan.

Radiographic disease progression was assessed and reported by the investigator according to the PCWG2 guidelines. There were no central reviews or audit findings of reported radiographic progression. During the review, a number of discrepancies were identified concerning appropriate determination of radiographic progression events and the progression date. These discrepancies were largely related to lack of required confirmation for radiographic progression detected at the Week 13 scans, lack of censoring of radiographic progression reported before the first scheduled Week 13 scans, and lack of censoring of radiographic progression for important clinical situations including new treatment initiation, incidence of an SRE, or use of radiation or surgical therapy involving bone. As such, a new dataset was requested for clarification and a reanalysis of rPFS using additional censoring rules for radiographic progression (rPD) events **occurring on or before the previously reported overall rPD dates**. These censoring rules were as follows:

- Censoring to the last scans without evidence of disease progression for rPD events that were not confirmed per the protocol. This censoring rule was also applied to patients whose confirmation scans occurred after new treatment initiation, an SRE, or surgical or radiation therapy for prostate cancer (see below).
- Censoring to the last bone scan without evidence of disease progression for pathological SREs or non-pathological SREs because of the impact of the SRE events on bone scan interpretation.
- Censoring to the last scans without evidence of disease progression for patients whose new treatment started before study treatment discontinuation or before the previously reported overall progression dates.
- Censoring to the last scans without evidence of disease progression for patients who had surgical or radiation therapy performed for prostate cancer related lesions or other disorders that most likely affected bone scan interpretation.

On August 7, 2012, the applicant provided a new rPFS dataset and a reanalysis of rPFS. The reviewer's examination of the new dataset identified a number of cases that had inadequate censoring or had their progression time determined in a manner that differs from that typically used in FDA reviews (e.g., if progression is seen at an unscheduled

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

scan the date of the scan is the date of progression). The review of the rPFS data is currently ongoing. The reviewers' preliminary analysis showed that treatment with MDV3100 was associated with an increase in rPFS when compared with placebo. As a result, an addendum will be provided to this clinical review to show the final rPFS analysis findings.

Time to First Skeletal-Related Event

Time to first skeletal-related event (TTFSRE) was defined as the time from randomization to the occurrence of the first skeletal-related event. Please refer to Section 6.1.1 for the definition of SRE.

To examine the treatment effect of MDV3100 on TTFSRE and the incidence of SREs, patients with an SRE that occurred while receiving study treatment were tabulated and analyzed for differences in TTFSRE between the two arms. The results are shown in Table 20. There was no difference in the overall incidence of SREs between the two arms; however, the difference in TTFSRE suggests that treatment with MDV3100 may delay the occurrence of an SRE.

Table 20: Incidence and Time to First Skeletal-Related Event While On Study Treatment (ITT)

	MDV3100 (N=800)	Placebo (N=399)
Number of SRE Events* (%)	167 (21%)	82 (21%)
Number of Spinal Cord Compression	39 (5%)	16 (4%)
Time to First Skeletal-Related Event (months) Median (95% CI)	4.3 (3.6, 5.3)	2.5 (1.8, 2.8)
Hazard Ratio**(95% CI)	0.47 (0.36, 0.63)	
* Not including patients with an SRE that occurred after discontinuation of study treatment and/or initiation of new treatment. Note that concurrent use of bisphosphonates or denosumab after study treatment discontinuation and or initiation of new treatment could confound the assessment of TTFSRE. ** Stratified Analysis, p-value<0.0001		

Reviewer's Note: Patients with an SRE that occurred after study treatment discontinuation and/or new treatment initiation during the trial were not included in

the above analysis, since inclusion of these patients would confound assessment of the treatment effect of MDV3100 on SRE prevention or delay in its occurrence. It is important to note that approximately 50% of enrolled patients received bisphosphonates or denosumab during the trial. Nevertheless, there was not an imbalance in overall use of bisphosphonates or denosumab between the two arms (See information in Section 6.1.2.)

Time-to-PSA progression

Time to PSA progression was defined as the time from randomization to the first documented date of PSA progression, as assessed using the PCWG 2 criteria for PSA progression as described in Section 6.1.1. Accordingly, PSA progression could only be declared on or after the Week 13 PSA assessment and required a confirmation assessment performed ≥ 3 weeks after the initial evidence showing PSA progression.

Table 21 shows the number of patients with confirmed PSA progression at the time of interim analysis. Patients whose confirmatory PSA progression assessment occurred during new treatment, initiated after study treatment discontinuation, were excluded from this tabulation because the new treatment could confound the confirmatory assessment result.

Table 21 also shows the result of the time to PSA progression analysis based on the number of confirmed PSA progression events and the first date when PSA progression occurred. Patients who did not have a PSA progression event at the time of the interim analysis were censored to the date of the last assessment showing no evidence of PSA progression.

Table 21: Time to PSA Progression (ITT)

	MDV3100 (N=800)	Placebo (N=399)
Number of Patients with Confirmed PSA Progression* (%)	388 (21%)	177 (21%)
Number of Patients Censored	412 (5%)	222 (4%)
Time to PSA Progression (months) Median (95% CI)	8.3 (7.4, 8.3)	3.6 (2.9, 3.7)

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Hazard Ratio**(95% CI)	0.294 (0.242, 0.356)
<i>* Not including patients whose confirmatory PSA progression assessment occurred after new treatment initiation</i>	
<i>** Stratified Analysis; p-value <0.0001</i>	

Rate of PSA Declines

As discussed in the Section 6.1.1 protocol review, PSA response was assessed based on the central laboratory measurement of PSA levels during the trial and a response with a $\geq 50\%$ decline from baseline required a PSA confirmation performed 3 or more weeks later.

Similar to the requirements for assessment of PSA progression, patients eligible for PSA response evaluation should also require PSA assessment at Week 13 or after based on the pre-specified study schedules in the protocol. Post-baseline PSA values obtained before Week 13 represented non-scheduled assessments and should not be included in the PSA response evaluation. A total of 86% of patients had PSA values at the scheduled Week 13 assessment, consisting of a population (N=1032) evaluable for PSA response rate. Table 22 summarizes patients with PSA declines of $\geq 50\%$ while receiving study treatment. Fifty-four percent of patients on the MDV3100 arm had confirmed PSA declines of $\geq 50\%$ as compared to 2% of patients on the placebo arm. Of these patients, approximately a half had PSA declines of 90% or more. These PSA response rates appear comparable with the responses rates observed in the early Phase 1-2 study (see Section 5) in patients with metastatic CRPC who received prior chemotherapy, thus corroborating the previously observed antitumor effect of MDV3100 in patients with CRPC.

Table 22: Patients with PSA Declines of $\geq 50\%$ from Baseline

	MDV3100 (N=800)	Placebo (N=399)
Number of Patients with Week 13 PSA Assessment (evaluable population)	N=719	N=313
Number of Patients with the PSA response* (%)	418 (58%)	11 (4%)
Confirmed PSA Declines of $\geq 50\%$ (%)	390 (54%)	5 (2%)
Confirmed PSA Declines of $\geq 90\%$ (%)	181 (25%)	3 (1%)

* Including all patients with at least one PSA decline of $\geq 50\%$ while receiving study treatment without new treatment, but excluding patients with a PSA response detected prior to Week 13.

Reviewer Comments:

The above analyses of key secondary endpoints provide supportive evidence showing considerable antitumor effects for MDV3100. However, none of them have been correlated with an improvement in overall survival in patients with mCRPC. The results described in this section are considered exploratory.

6.1.6 Subpopulations

Based on the baseline characteristics listed in Section 6.1.2, a number of subgroup analyses were performed to examine the consistency of the overall survival benefit of MDV3100 in various subpopulations that may affect the interpretation of the primary endpoint analysis results. The results of the subgroup analyses, as shown in Figure 7, were generally consistent in all subgroups except for the subgroups ECOG score 2 and visceral involvement of the disease. In these 2 subgroups, the upper limit of the 95% confidence intervals for the HRs were >1.0 . This may be related to the small number of patients (10% in the ECOG 2 subgroup and 23% in the visceral involvement subgroup) and/or the poor prognosis in patients with these subgroup characteristics.

In the trial, 25% of patients were ≥ 75 years old. Table 23 shows differences in survival between the two arms in this subgroup. The hazard ratio is very similar to that found in the other two age groups as shown in Figure 7, suggesting that MDV3100 exerted similar treatment effects in elderly and younger patients.

The majority of patients in the trial also received prior hormonal therapy with one or more androgen receptor antagonist including bicalutamide, flutamide, and/or nilutamide. Table 24 shows the subgroup analysis results in those patients. For patients who received prior treatment with bicalutamide, the survival benefit of MDV3100 was well preserved; whereas for patients who received flutamide or nilutamide, the upper

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

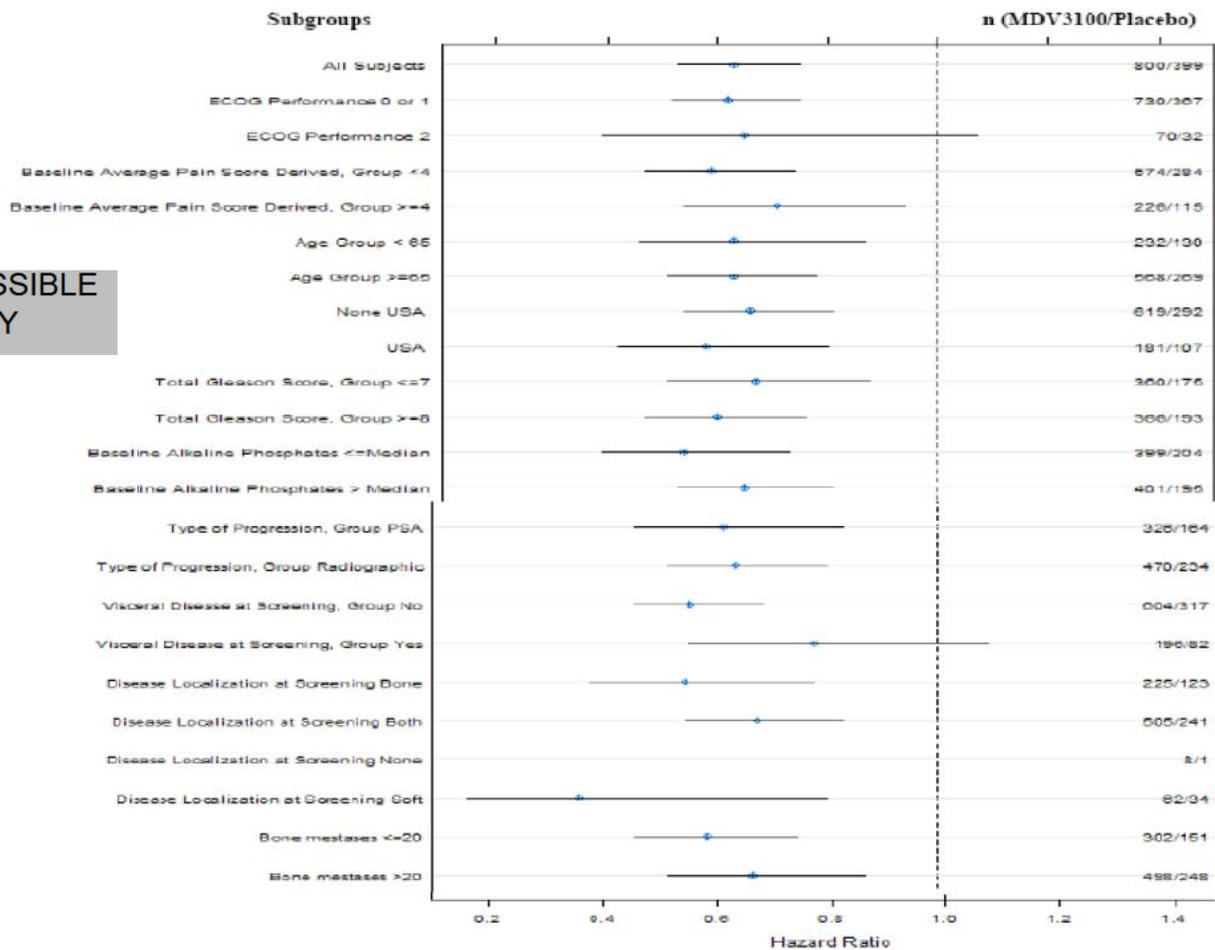
Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

limit of 95% confidence interval for each hazard ratio was above 1.0 (although the HR itself was <1.0). This may be related to the small number of patients in the flutamide and nilutamide subgroups. Overall, the results suggest that the MDV3100 treatment effect was preserved in patients who had received the currently marketed androgen receptor antagonists.

In addition, Figure 8 shows that the MDV3100 survival advantage was found in both patients receiving and not receiving glucocorticoids during the trial. Of note, patients in both arms who used glucocorticoids had a median survival time shorter than the median survival time in patients who did not use glucocorticoids. The reason for the observed differences remains unclear. It may be associated with a possibility that patients receiving glucocorticoids in the trial had other poor prognostic factors.

Figure 7: Subgroup Analyses of Overall Survival

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Note: No adjustment for multiple comparisons

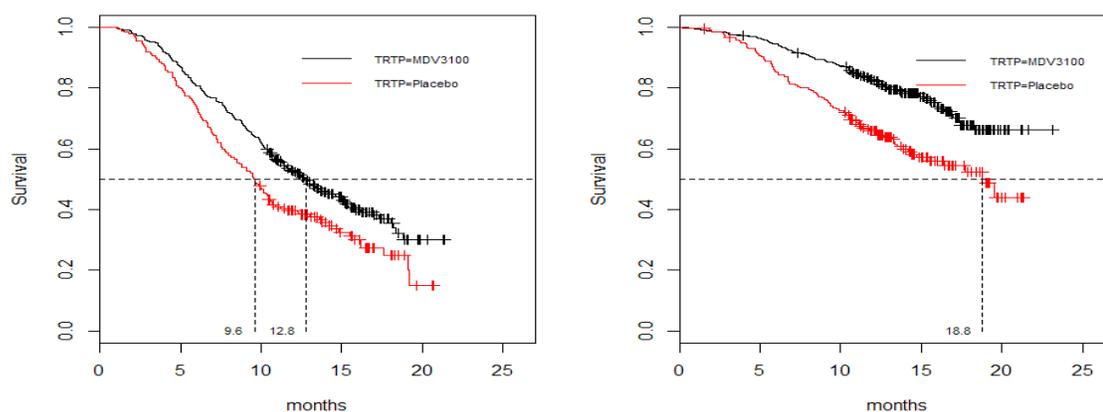
Table 23: Survival Difference in Patients ≥ 75 Years of Age

	MDV3100 (N=800)	Placebo (N=399)
Number of Patients ≥ 75 Years of Age	N=199	N=104
Median Survival (months) (95% CI)	18.2 (15.4, NE)	13.3 (9.8, 17.6)
Hazard Ratio* (95% CI)	0.65 (0.46, 0.91)	
* HR in the ITT was 0.63 (95% CI: 0.53, 0.75)		

Table 24: Survival Difference in Patients Treated with Other Androgen Receptor Antagonists

Subgroup (prior use)		Hazard Ratio	HR Lower CL	HR Upper CL	MDV310 0 (N)	Placebo (N)
Bicalutamide	No	0.56	0.34	0.91	131	50
	Yes	0.65	0.54	0.78	669	349
Nilutamide	No	0.61	0.50	0.73	726	357
	Yes	0.93	0.52	1.68	74	42
Flutamide	No	0.60	0.50	0.73	688	339
	Yes	0.87	0.52	1.44	112	60

Figure 8: Analyses of the Impact of Concomitant Use of Glucocorticoids on Overall Survival



Left Panel: Patients who used glucocorticoids in the trial: HR: 0.70 (95%CI: 0.56, 0.87)

Right Panel: Patients who did not use glucocorticoids in the trial: HR: 0.49 (95%CI: 0.37, 0.66)

***Reviewer Comments:** The above subgroup analysis results are generally consistent with the results observed in the ITT population. Some of the subgroup results appear to be clinically important, e.g. the sustained survival benefit of MDV3100 in patients treated with bicalutamide, a product commonly used for treatment of patients with prostate cancer. Such information may help providers and patients to make sound treatment decisions. Regardless, the subgroup analysis results are exploratory.*

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

As discussed in Section 5, the MTD determined from the Phase 1/2 study was 240 mg once daily. However, the dosing schedule used in the CRPC2 trial was 160 mg once daily. This was due to the applicant's concern about the risk of seizure at the 240 mg dose. The efficacy and safety results from the CRPC2 trial support the use of the 160 mg once daily schedule. Use of MDV3100 at a dose >160 mg once daily is not recommended.

The other question is whether dose delay or reductions affect the efficacy of MDV3100 in the intended patient population. During the CRPC2 trial, 10% of patients had dose delays and/or reductions due to adverse reactions. The reviewer examined whether the MDV3100 survival effect was negatively affected with these dose modifications. Table 25 shows survival differences between the two arms in the 10% of patients. The results suggest that the survival benefit of MDV3100 was maintained in these patients when compared to placebo.

The antitumor activity of MDV3100 also appears to have remained in patients with dose reductions. Of the 18 patients with dose reductions in the trial, 9 had a dose-reduction duration time of >30 days. Seven of the 9 patients had PSA declines of 50% or more. Having considered that 44% of patients treated with 60 mg MDV3100 once daily in the Phase 1/2 study had PSA declines of 50% or more, the estimated PSA response rate of approximately 40% in the patients with dose reductions highly suggests that dose reductions are unlikely to mitigate the antitumor activity of MDV3100 in patients whose disease responds to the treatment.

Taken together, the current recommended starting dose and schedule and the recommendations concerning dose interruption/reduction are acceptable.

Table 25: Impact of Dose Modifications on Overall Survival in the CRPC2 Trial

	MDV3100 (N=800)	Placebo (N=399)
Number of Patients with Dose Delay (%)	97 (12.1%)	61 (15.3%)
Number of Patients with Dose Reduction*	18 (2.3%)	11 (2.8%)
Overall Survival (months) Median (95% CI)	12.9	9.4
Hazard Ratio*(95% CI)	0.569 (0.379, 0.955)	

* All patients with dose reduction had dose delays.

6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

In the CRPC2 trial, the median treatment duration in the MDV3100 arm was about 7 months (see Section 7.2.1). Of patients whose disease responded to MDV3100 treatment, as evidenced by a PSA decline of $\geq 50\%$, 265 of them remained responding for >7 months. One third of the 265 patients had a PSA response duration of 12-22 months. These 265 patients represent 68% of the 390 patients who had confirmed PSA responses (Table 22). The prolonged response in some responding patients highly suggests that the antitumor activity MDV3100 can be persistent. Nevertheless, it remains to be investigated as to why patients respond to MDV3100 or why some respond for a long time. On other hand, why responding patients become resistant to the treatment with time is also an important question for scientists to address. So far, no evidence has suggested that tolerance to MDV3100 may be responsible for loss of antitumor activity with continued treatment.

6.1.9 Additional Efficacy Issues/Analyses

Exploratory Analyses of the Relationship of PSA Progression by 3 Months with Overall Survival

Retrospective studies with data pooled from a number of the CALGB or SWOG trials suggested that PSA progression at or by 3 months was adversely associated with survival in patients with metastatic CRPC.^{13, 14} This investigational surrogate also

13 Hussain M. et al (2009): Prostate-Specific Antigen Progression Predicts Overall Survival in Patients With Metastatic Prostate Cancer: Data from Southwest Oncology Group Trials 9346 (Intergroup Study 0162) and 9916. *J Clin Oncol* 27:2450-2456.

14 Halabi S. et al (2009): Progression-Free Survival as a Predictor of Overall Survival in Men With Castrate-Resistant Prostate Cancer. *J Clin Oncol* 27:2766-2771.

appears to be predictive of overall survival in patients treated with docetaxel-based therapy, since patients with PSA progression by 3 months in the S9916 trial had a median survival time of 11 months when compared with a median survival of 18 months in patients with no PSA progression by 3 months [adjusted HR 2.06 (95% CI, 1.69 to 2.51), nominal $p < 0.001$].

To explore whether this investigational surrogate has a role in patients who have had prior docetaxel-based chemotherapy, the reviewer evaluated the number of patients with PSA progression by 3 months in the CRPC2 trial and examined its association with overall survival without respective to treatment assignment in patients with mCRPC who had received prior docetaxel.

Table 26 shows the distribution of patients with and without the PSA progression by 3 months in the sub-population of patients who had the landmark Week 13 PSA assessment, which was required for determination of the status of PSA progression by 3 months for the purposes of performing exploratory analyses. This also means that patients in the sub-population survived to the landmark survival time of 3 months.

Table 26: Distribution of Patients with PSA Progression by 3 Months

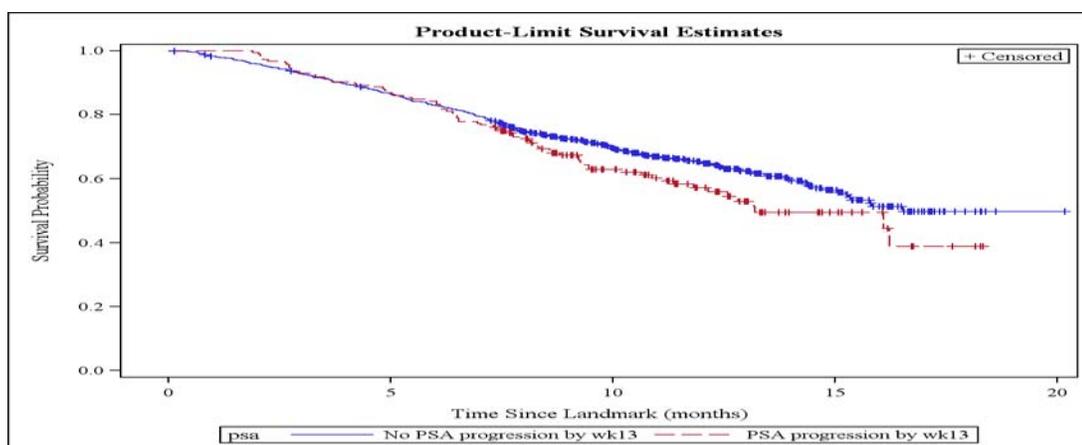
	MDV3100 (N=800)	Placebo (N=399)
Number of Patients with PSA Assessment at Week 13*	N=693	N=299
Number of Patients with PSA Progression by 3 Months (%)	59 (9%)	125 (42%)
Number of Patients without PSA Progression by 3 Months (%)	634 (91%)	174 (58%)
<i>* Representing the sub-population for the following exploratory analyses</i>		

Table 27 and Fig. 9 show the results of the landmark analysis of overall survival from Week 13 in patients with and without PSA progression by Week 13, regardless of arm. As shown, PSA progression by 3 months was associated with a median post-landmark survival time of 13.2 months as compared with a median post-landmark survival time of 16.5 months in patients without PSA progression by 3 months [HR 0.81, nominal $p=0.10$]. The survival difference suggests that PSA progression by 3 months is a negative surrogate in the post-docetaxel setting. On the other hand, the difference in the median survival times appears to favor patients without PSA progression by 3 months, suggesting that no PSA progression by 3 months may be a positive surrogate in the same disease setting.

Table 27: Exploratory Analysis of OS from the Landmark of Week 13

	No PSA Progression by Week 13	PSA Progression by Week 13
Number of Evaluable Patients at Week 13	808	184
Number of Deaths	279 (35%)	77 (42%)
Median (months since landmark), (95% CI)	16.5 (15.2, NR)	13.2 (11.4, NR)
HR (95% CI)	0.81 (0.63, 1.04)	
Log rank p-value (nominal)	0.10	

Figure 9: K- M Survival Curves of OS from the Week 13 Landmark



The reviewers also examined differences in survival between the MDV3100 and placebo arms in patients who had no evidence of PSA progression by 3 months. As shown in Table 28, findings from this exploratory subgroup analysis favor MDV3100 treatment when compared to placebo.

Table 28: Difference in Overall Survival in Patients with No PSA Progression by 3 Months

Number of Patients with No PSA Progression by 3 Months (%)	MDV3100 (N=634)	Placebo (N=174)
Number of Death (%)	196 (31%)	83(48%)
Median Survival (months since landmark) (95% CI)	NR (15.4, NR)	13.4 (10.1, 16.5)
Hazard Ratio (95% CI)	0.55 (0.43, 0.72)	
Nominal P value	<0.0001	

Reviewer's Comments: *The results from the analyses described in this section (6.1.9) are exploratory, since these analyses were performed simply from an investigational perspective to explore the role of a potential surrogate, PSA progression by 3 months in patients with mCRPC who received prior docetaxel. The subpopulation used in the analyses may have imbalances in baseline characteristics that could confound the interpretation of the above findings. In addition, some patients who lived >3 months but missed the scheduled Week 13 assessment were not included in the analyses. There were no evaluations of potential interactions and no adjustment for multiplicity. On the other hand, findings from the landmark analyses appear to suggest that PSA progression by 3 month may be associated with a shorter survival time in patients with mCRPC who had received prior docetaxel. Although the absence of PSA progression by 3 months seems to be associated with a favorable survival outcome in the same disease setting, more research would be needed to assess whether reduction in the number of patients with PSA progression by 3 months may serve as a suitable surrogate to estimate treatment effects of investigational products at early stages of clinical development..*

7 Review of Safety

Safety Summary

In this NDA, the Applicant submitted safety data from 1199 castrate resistant prostate cancer (CRPC) patients (i.e., 800 enzalutamide; 399 placebo) who were enrolled and received at least one dose of study therapy in the CRCP2 (a.k.a. AFFIRM) randomized, controlled, clinical trial. The safety analysis database also included three open-label trials that enrolled and treated an additional 242 CRPC patients with enzalutamide at doses of 30 mg – 600 mg administered orally (PO) once a day (QD). Out of these 242 patients, 125 patients received the proposed 160 mg or a comparable 150 mg PO QD enzalutamide dose [i.e., 150-160 mg integrated (pooled) safety analysis population, (n=925)]. The median exposure of enzalutamide in these trials was approximately 35 weeks. The number of patients and duration of exposure to enzalutamide was adequate for this NDA safety review.

Key findings from the CRPC2 randomized controlled trial:

- Deaths: Deaths were less common on the enzalutamide arm compared to the placebo arm (62% versus 50%, respectively).

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

- Deaths due to Adverse Events (AEs): Fatal AEs were less common on the enzalutamide arm compared to the placebo arm, with 3.3% of the patients receiving
- Deaths due to Adverse Events (AEs): Fatal AEs were less common on the enzalutamide arm compared to the placebo arm, with 3.3% of the patients receiving enzalutamide experiencing fatal AEs compared to 3.8% of the placebo-treated patients. Fatal infections (primarily sepsis) occurred in 1% of the enzalutamide patients compared to 0.3% of the placebo patients. There were a small number of fatal cardiac AE deaths and these were less common on the enzalutamide arm compared to placebo (0.4% vs. 0.5%, respectively). There were no deaths due to hepatotoxicity reported in enzalutamide-treated patients.
- Serious Adverse Events (SAEs) and Dose Modifications: The incidence of SAEs, permanent and temporary discontinuation of therapy, and dose reduction were all higher on the placebo arm compared to the either enzalutamide treatment group.
- Grade 3 and 4 Adverse Reactions (ARs): Grade 3 and 4 ARs were reported among 47% of enzalutamide-treated patients and 53% of placebo-treated patients. The most common Grade 3 and 4 ARs (> 2% and > placebo) reported in patients receiving enzalutamide were spinal cord compression and cauda equina syndrome, back pain, arthralgia, hypertension, and lower respiratory tract infections.
- Seizures: Seizures were identified as a potential dose-dependent AR in early enzalutamide clinical and nonclinical trials. The proposed mechanism of action is related to off target inhibition of the GABA gated chloride channel. At the proposed dose, seven (0.9%) seizures occurred on the enzalutamide arm compared to no (0%) seizures on the placebo arm. Two seizure-related safety issues remain poorly characterized:

Patients at high risk for seizure: The CRPC2 trial excluded patients at high risk from seizure. There is no clinical trial information available related to the safety of enzalutamide in this subpopulation. However, enzalutamide may be used in patients at high-risk for seizure and it will be important to determine if these patients are at increased risk.

Retreatment of patients who experience a seizure: There is no clinical trial experience in which patients who have had a seizure while on enzalutamide therapy are subsequently retreated. All of the patients who experienced a seizure were permanently discontinued. It is unclear if a reduced dose of

enzalutamide with or without medications for seizure prophylaxis could be used to prevent recurrent seizures in patients where continuation of enzalutamide therapy is indicated.

- Common ARs: Ninety-eight percent of the patients on both arms experienced at least one AE. The most common ARs ($\geq 5\%$ and $> 2\%$ compared to placebo) reported in patients receiving enzalutamide were asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, dizziness, spinal cord compression and cauda equina syndrome, muscular weakness, insomnia, lower respiratory infection, hematuria, paresthesia, anxiety, and hypertension.
- Other ARs of interest: The following ARs were also more common on the enzalutamide arm compared to placebo:

Falls and fall-related injuries: Falls or injuries related to falls occurred in 4.6% of the patients treated with enzalutamide compared to 1.3% of the patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in patients treated with enzalutamide and included non-pathologic fractures, joint injuries, and hematomas.

Nonpathologic fractures: Nonpathologic fractures occurred in 4.0% (1.4% Grade 3) of the enzalutamide-treated patients compared to 0.8% (0.3% Grade 4) of the placebo-treated patients. A 3-fold increase in the incidence of nonpathologic fracture was found in an exploratory analysis comparing the enzalutamide treatment arm compared to the placebo arm when nonpathologic fracture AEs reported as SREs were censored (i.e., 2.5% vs. 0.8%, respectively). Bone preserving therapies such as bisphosphonates or denosumab appeared to be underutilized in this mCRPC population.

Spinal Cord Compression and Cauda Equine Syndrome: Grade 3-4 spinal cord compression and cauda equina syndrome occurred in 6.6% of enzalutamide-treated patients and in 3.8% of placebo-treated patients. A majority of the events occurred while patients were receiving enzalutamide therapy.

Hallucinations: There was a 3-fold increase in Grade 1 and 2 hallucinations and delusions not directly attributed to opioid medications in the enzalutamide-

treated patients compared to placebo (1.5% vs. 0.5%). A majority of the hallucinations were visual.

Neutropenia: Neutropenia occurred in 15% of patients on enzalutamide (1% Grade 3-4) and in 6% of patients on placebo (0% Grade 3-4).

ECG and QTc prolongation: The Applicant conducted a thorough QT/QTc substudy reviewed by the FDA's Interdisciplinary Review Team (IRT) for QT studies. The IRT team review concluded that there was no significant QTc prolongation for enzalutamide at the 160 mg PO QD dose.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

7.1.1.1 Original NDA submission

The integrated safety summary (ISS) submitted in the original NDA application includes 1426 castrate-resistant prostate cancer (CRPC) patients who received at least one dose of study drug in the randomized, controlled, double-blind clinical trial (CRPC2, a.k.a. AFFIRM) or in one of the three uncontrolled open-label clinical trials (i.e., S-3100-1-01, CRPC-MDA-1, and 9785-CL-0111). The S-3100-1-01, CRPC-MDA-1, and CRPC2 clinical studies were conducted by Medivation and the 9875-CL-0111 was conducted by Astellas Pharma, Inc. In these trials, a total of 1027 patients were treated with enzalutamide at doses ranging from 30 mg to 600 mg administered orally (PO) once a day (QD), and 399 subjects were treated with matching placebo (PO QD). A brief description of the clinical trial designs and the safety cutoff dates for each trial (original NDA submission) are listed in Table 29.

Table 29: Clinical Trials Included in the Integrated (Pooled) Safety Analysis

Study	Study Design	# of Enzalutamide Patients	# of Placebo Patients	Enzalutamide Doses	Safety Cutoff Date
Controlled Study					
CRPC2 (a.k.a. AFFIRM)	Randomized, double-blind, placebo-controlled study	800	399	160 mg	25 Sep 2011
Uncontrolled Open-Label Studies					
S-3100-1-01 1	Open-label dose escalation study	140	None	30, 60, 150/160, 240, 360, 480, and 600 mg	25 Sep 2011
CRPC-MDA-1	Open-label single arm study	60	None	160 mg	26 Aug 2011
9785-CL-0111	Open-label dose escalation study (Japan)	27	None	80, 160, 240 mg	07 Oct 2011

7.1.1.2 Sixty (60)-Day Safety Update

On July 20, 2012, the Applicant submitted a 60-day safety update to the NDA. The safety cutoff date for the 60-day safety update was January 31, 2012 and was consistent for the clinical trials included in the pooled safety analyses. The 60-day safety update included approximately four months of additional safety data for each of the clinical trials listed in Table 29 above. For the pooled safety analysis, an additional 16 patients were treated with 160 mg PO QD enzalutamide in the 9785-CL-011 clinical trial, which increased the number of patients in the integrated (pooled) 150-160 mg safety analysis population from 909 to 925 patients.

The major safety results in this review were updated to use the most complete and up-to-date safety database. All other safety analyses of CRPC2 used updated data unless otherwise noted in the review. For the pooled 150-160 mg safety population and the CRPC2 trial (i.e., both enzalutamide treatment groups), the original analyses for enzalutamide dose modifications and exposure were maintained since these parameters did not change significantly in the safety update. For both enzalutamide treatment groups, AEs leading to permanent discontinuation did not increase more than 0.5%, no new AEs lead to temporary interruption of therapy in > 1% of the study patients, and no new AEs lead to a dose reduction. For the 60-day safety update, the median enzalutamide exposure remained 36 weeks for the CRPC2 trial, and remained similar for the 150-160 mg pooled safety population (i.e., changed from 35 to 34 weeks). There was a significant increase in the number of patients exposed to enzalutamide for longer than 12 months [i.e., 24% to 32% (n= +82 patients)].

An additional 125 deaths were reported in the 60-day safety update. Ninety occurred in enzalutamide-treated patients with 74 due to progression of disease (PD). Three additional patient deaths were attributed to AEs with one death each due to septic shock, myocardial infarction, and general physical health deterioration (with disease progression).

7.1.1.3 Additional Applicant Response to FDA Information Request (June 27, 2012)

During this review, FDA became aware of other completed and ongoing clinical trials administering enzalutamide to patients at the proposed dose that were not discussed in the original NDA submission. FDA requested a concise safety and exposure assessment based on all of the current worldwide clinical trial knowledge for enzalutamide. Table 31 shows the sponsor analysis of total enzalutamide exposure in all of the available clinical trials.

Table 30: Estimated Total Enzalutamide Exposure

(All Completed and Ongoing Trials as of June 14, 2012) (Copied from Applicant submission)

	Number of Subjects Exposed to Enzalutamide < 150 mg (N = 36)	Number of Subjects Exposed to Enzalutamide 150–160 mg (N = 2108)	Number of Subjects Exposed to Enzalutamide > 160 mg (N = 82)
Time on Study Drug Category			
≤ 2 Months	4 (11%)	380 (18%)	21 (26%)
> 2 – < 6 Months	17 (47%)	843 (40%)	29 (35%)
≥ 6 – <12 Months	4 (11%)	496 (24%)	12 (15%)
≥ 12 Months	11(31%)	389 (18%)	20 (24%)

Notes:

Time on study drug defined as (date of last dose - date of first dose + 1) / 30.4375. If patient is still on study drug at analysis data cutoff then time on study drug is censored at date of data cutoff.

Exposure is calculated based upon dose assigned at randomization or study entry.

Studies include: S3100-1-01, CRPC-MDA-1, CRPC2, MDV3100-03 (PREVAIL), MDV3100-05, MDV3100-06, MDV3100-07, MDV3100-08, 9875-CL-0111, 9875-CL-0222 (TERRAIN), 9785-CL-0321, 9785-CL-0401, 9785-CL-0007, 9785-CL-0121, 9785-CL-0001, 9785-CL-0006, 9785-CL-0009.

Single dose healthy volunteer studies: MDV3100-05, 9785-CL-0001, 9785-CL-0006, 9785-CL-0009.

Data cut-off date is 14JUN2012 except 9875-CL-0111 study data cutoff is 31 JAN2012.

Source: Clinical database from respective studies.

Out of the 2108 patients who have been exposed to enzalutamide at the 150-160 mg dose:

- 925 were included in this NDA
- 897 are in the ongoing blinded, placebo-controlled trials MDV3100-03 (a.k.a., PREVAIL; n=843) and 9875-CL-0222 (a.k.a., TERRAIN; n=54) clinical trials (estimated)
- 140 were in completed single dose studies
- 21 patients are CRPC2 placebo arm crossovers

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

- 14 were from the completed 9785-CL-0007 drug interaction trial
- Approximately 111 patients are in the ongoing open-label trials listed in the Table 31 notes above.

The Applicant's internal safety review committee reviewed the available safety data using safety cutoff dates ranging from May 7, 2012 to June 7, 2012, depending on the specific clinical trial being evaluated. The Applicant stated that the safety data was consistent with the safety data in this NDA, no new safety signals were detected, and there had been no new reports of seizures since the January 31, 2012 60-day safety cutoff date in this NDA.

FDA requested line listings for expedited IND safety reports from these trials for this NDA review. A majority of the 7-day and initial 15-day SAE reports from trials not included in this NDA were from trial MDV3100-03 (14 out of 16). The MDV3100-03 trial is monitored by an Independent Data Monitoring Committee (IDMC) that reviews unblinded ongoing safety data and meets every 4 months. The last meeting was held in June 2012; the IDMC recommended that the MDV3100-03 study continue as planned. There were no additional seizure SAEs reported in this data.

7.1.2 Categorization of Adverse Events

The Applicant defined Treatment Emergent Adverse Events (TEAEs) as events reported after the first dose of study therapy that occurred up to 30 days after the last dose of study therapy.

The Applicant originally coded adverse event (AEs) for these trials using earlier versions of the MedDRA dictionary, and recoded the ISS data submitted in this NDA using MedDRA Version 14.1. This resulted in minor differences in AE terms and frequencies when comparing the original study reports to the integrated safety data for this NDA. Earlier versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) were also used to grade the severity of AEs. The minor differences in control terminologies were not expected to significantly impact the interpretation of the overall safety results. The previous versions of the MedDRA and CTCAE terminologies used in the clinical trials included in the pooled 150-160 mg safety analyses are listed in Table 31.

Table 31: Controlled Terminologies for Clinical Trials in Safety Database

Clinical Trial	MedDRA Dictionary Version	CTCAE Version
Integrated Safety Database (ISS)	14.1	NA
CRPC2	12.0	4.0
S-3100-1-01	10.0	3.0

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Clinical Trial	MedDRA Dictionary Version	CTCAE Version
CRPC-MDA-1	12.0	4.0
9875-CL-0111	12.1	4.0

AEs were recorded on electronic case report forms (eCRFs). Investigators were informed to provide data on AE causality defined as “unrelated”, “unlikely”, “possible”, “probable”, or “definite”. When available, the AE outcomes were also provided and described as “recovered/resolved”, “recovered/resolved with sequelae”, “not recovered/not resolved”, “fatal”, or “unknown”.

To verify the accuracy of the AE coding process, a side-by-side comparison of verbatim terms recorded from randomly selected CRFs were compared to MedDRA Lower Level Terms (LLTs) in the adverse event dataset (ADAE) to AE data in the electronic Case Report Forms (eCRFs) for CRPC2 or case narratives for the uncontrolled studies (if available). Nearly all of the AE terms reviewed were accurately coded in the ADAE dataset; no major discrepancies were identified. The Contract Resource Organization (CRO) data quality procedures and monitoring audited the case report forms (CRFs) and queried investigators to resolve potential data recording issues. The few minor discrepancies that were identified were not significant with regards to the overall integrity of the AE database.

Reviewer Comment: The approach used by Investigators to report fractures and spinal cord compression appears to be inconsistent in at least some cases. Comparable events that lead to study drug discontinuation were reported as serious adverse events (SAEs) (Patient #043-04) or were not reported as an AE/SAE but documented as progression of disease (PD) from an Skeletal Related Event (SRE) (Patients #006-03; #257-09). Other Grade 3 events were reported as both an AE and PD from an SRE (Patient #105-01). In the CRPC2 trial, these events were required to be recorded as SREs in the SRE datasets (i.e., ADTESRE and ADSRE). There were a higher number of events in the SRE datasets compared to the AE (ADAE) data. This supports the Applicant’s assertion that the most complete data for all fracture events (pathologic and nonpathologic) is the SRE CRF, rather than the AE CRF or AE datasets, but also makes interpretation of fracture data difficult. FDA analyses of fractures focused on the nonpathologic fractures reported as AEs in the CRPC2 trial. Fractures reported as AEs and specifically identified by the Investigator as pathologic in the verbatim or coded terms were censored from FDA nonpathologic fracture analyses.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data from the randomized, controlled trial (i.e., CRPC2, a.k.a., AFFIRM) is the primary focus of the FDA safety review. Patients treated with doses of 150 or 160 mg of enzalutamide in the pooled safety analysis population were also evaluated since this is or is approximately equal to the proposed dose of enzalutamide. Inclusion of these patients provides an additional 109 patients in the original NDA submission, and 125 patients in the 60-day safety update (n=909 and 925 patients, respectively). The enzalutamide product and the recommended dose (b) (4)

(b) (4) 160 mg PO QD dose due to a (b) (4)
(b) (4) 40 mg soft capsule. (b) (4)

(b) (4) There were no changes to the composition of the enzalutamide drug substance with this product change. Based on the comparable dose and product, overlapping pharmacokinetic exposure characteristics, and that the patients treated at the 150 mg dose were treated in the United States, the patient exposure from the 150 mg dose in S-3100-1-01 was pooled with the 160 mg enzalutamide exposures in the other trials in the integrated 150-160 mg safety analysis.

In addition, in the original NDA submission, safety data from an additional 118 other patients who received enzalutamide doses of < 150 mg (n= 33 patients) or > 160 mg PO QD (n=85 patients) in the pooled safety trials was reviewed to assess dose response relationships for adverse reactions (ARs) that occurred at the 150-160 mg dose.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations

7.2.1.1 Drug Exposure at Appropriate Dose and Schedule

The pooled safety analysis population provided by the Applicant in the original NDA includes a total of 909 patients who received at least one dose of enzalutamide PO QD at the 150 mg or 160 mg dose level. Of the 909 patients treated at this dose, 800 of these patients were treated with 160 mg of enzalutamide in the CRPC2 trial and 109 patients were treated with 150 mg (n=28) or 160 mg (n = 81) in one of the other three open-label studies. In the CRPC2 trial, 399 patients also received matched placebo, and were used for comparison to the CRPC2 analysis population.

7.2.1.2 Demographics of Safety Population

The baseline demographics and baseline disease characteristics for the patients treated with enzalutamide in the CRPC2 trial and the 150-160 mg pooled safety analysis population were comparable. Table 32 shows the demographics and baseline disease characteristics for these study groups.

Table 32: Demographics and Disease Characteristics for the Safety Population

	CRPC2 (160 mg) (N=800)	CRPC2 (Placebo) (N=399)	Safety Analysis Population (Pooled) (150-160 mg) (N=925)^a
Demographic Characteristics			
Age			
Median (yrs) (range)	69 (41, 92)	69 (49, 89)	69 (39, 93)
Age Group			
< 65	232 (29%)	130 (33%)	274 (30%)
65 to 74	369 (46%)	165 (41%)	414 (45%)
≥ 75	199 (25%)	104 (26%)	237 (26%)
Race			
Caucasian	745 (93%)	366 (92%)	826 (89%)
Black	27 (3%)	20 (5%)	31 (3%)
Asian	5 (1%)	8 (2%)	44 (5%)
Other	23 (3%)	5 (1%)	24 (3%)
Baseline Performance Status			
ECOG Score			
0	298 (37%)	156 (39%)	354 (38%)
1	432 (54%)	211 (53%)	498 (54%)
2	70 (9%)	32 (8%)	73 (8%)
Baseline Disease Characteristics			
Total Gleason Score			
≤7	359 (45%)	130 (33%)	403 (44%)
≥8	366 (46%)	165 (41%)	442 (48%)
Missing	75 (9%)	104 (26%)	80 (8%)
Serum PSA Level (ng / mL)			
Median (range)	108 (0.4, 11794)	128 (0.6, 19000)	99 (0.2, 11794)
Prior Exposure to Docetaxel			
Yes	800 (100%)	399 (100%)	893 (97%)
No	0 (0%)	0 (0%)	32 (4%)

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

	CRPC2 (160 mg) (N=800)	CRPC2 (Placebo) (N=399)	Safety Analysis Population (Pooled) (150-160 mg) (N=925)^a
Other Key Baseline Characteristics			
Creatinine (µmol/mL)			
Median (range)	80 (43, 771)	79 (36, 179)	80 (41, 771)
Prior History of Cardiovascular Disease^b			
Yes	136 (17%)	71 (18%)	160 (17%)
No	664 (83%)	328 (82%)	765 (83%)
Prior History of Hypertension			
Yes	425 (53%)	219 (55%)	502 (54%)
No	375 (47%)	180 (45%)	423 (46%)

^a Safety cutoff date: 31 Jan 2012

^b Applicant defined cardiovascular disease as a history of arterial thromboembolic events such as coronary artery disease, acute coronary syndromes, and peripheral vascular disease.

7.2.1.3 Treatment Duration

Table 33 shows the overall duration of treatment for patients who received 150-160 mg of enzalutamide, 160 mg of enzalutamide on CRPC2, or matching placebo. The data cutoff for these analyses is [REDACTED]^{(b) (6)}. The median overall duration of treatment for patients treated with enzalutamide on the CRPC2 trial was approximately nine cycles of 28 days in duration (i.e., 36 weeks). The placebo arm of the CRPC2 trial had a median duration of treatment of 13 weeks, which is approximately 2.5-fold less than the duration of therapy for patients in the enzalutamide treatment arm.

Table 33: Overall Treatment Duration by Study Arm (in weeks)

	CRPC2 (160 mg) (N=800)	CRPC2 (Placebo) (N=399)	Safety Analysis Population (Pooled) (150-160 mg) (N=909)
Treatment Duration (in weeks)			
Median	36.3	13.0	34.7
Mean	37.1	18.8	36.6
Range	0.1 – 100.6	0.7 – 89.9	0.1 – 196.9

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Table 34 shows the total number of patients exposed to 150-160 mg of enzalutamide, 160 mg of enzalutamide on CRPC2, or placebo on CRPC2 for durations of < 2 months, 2 - 6 months, 6 - 12 month, and > 12 months.

Table 34: Treatment Duration by Study Arm (by time categories)

	CRPC2 (160 mg) (N=800)	CRPC2 (Placebo) (N=399)	Safety Analysis Population (Pooled) (150-160 mg) (N=909)
Treatment Time (in months)			
≤ 2 months	73 (9.1%)	74 (18.5%)	95 (3.9%)
> 2 months and < 6 months	238 (29.8%)	254 (63.7%)	288 (23.3%)
≥ 6 months and < 12 months	291 (36.4%)	53 (13.3%)	306 (37.2%)
≥ 12 months	198 (24.8%)	18 (4.5%)	220 (35.6%)

A higher percentage of patients on the placebo arm discontinued therapy earlier than patients on the enzalutamide arm, with less than 20% of the patients remaining on placebo beyond 6 months, and less than 5% beyond one year. In the CRPC2 trial, 89 patients (11.1%) on the treatment arm, and six patients (1.5%) on the placebo arm, who were continuing treatment were censored at the safety cutoff date after receiving between 6 and 12 months of therapy.

Reviewer Comment: At the proposed dose, the overall exposure of enzalutamide was adequate to assess safety in mCRPC patients previously treated with docetaxel-based chemotherapy. With the 60-day safety update (cutoff date 31 Jan 2012), over 500 patients (58%) were treated for a duration of greater than 6 months, and 300 (32%) patients were treated for a duration of greater than 12 months in the pooled 150-160 mg safety analysis population (n=925).

7.2.1.4 Treatment Compliance

The Applicant calculated treatment compliance by using the number of capsules taken during the study divided by the expected number of capsules, multiplied by 100%. Capsules that were not returned were considered to have been taken, leading to an overestimate of treatment compliance (values > 100%) in approximately 40% of patients in the CRPC2 trial. The Applicant reported that only 1% of the patients in the trial had overall compliance of < 80%.

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Reviewer Comment: The results of this calculation are difficult to interpret due to the overestimate of treatment compliance based on the Applicant's assumptions. In the Applicant's analysis of protocol violations in the CRPC2 trial, noncompliance was listed as a minor protocol violation, and occurred in less than 1% of the patients on the enzalutamide arm compared to 1.3% on the placebo arm. The safety data related to exposure and dose modifications do not suggest that treatment compliance is a significant issue for patients who are taking enzalutamide on the proposed once a day schedule.

7.2.1.5 Dose Delays and Dose Discontinuations

Table 35 shows the dose delays and dose reductions for patients treated on the CRPC2 trial and for the 150-160 mg safety analysis population.

Table 35: Dose Interruptions and Reductions

	CRPC2 (160 mg) (N=800)	CRPC2 (Placebo) (N=399)	Safety Analysis Population (Pooled) (150-160 mg) (N=909)
	N (%)	N (%)	N (%)
Dose Interruptions	97 (12.1%)	61 (15.3%)	115 (12.7%)
1	74 (9.3%)	47 (11.8%)	84 (9.2%)
2	13 (1.6%)	10 (2.5%)	16 (1.8%)
≥ 3	10 (1.3%)	4 (1.0%)	15 (1.7%)
Number of Dose Reductions*	18 (2.3%)	11 (2.8%)	22 (2.4%)
1	14 (1.8%)	7 (1.8%)	16 (1.8%)
2	3 (0.4%)	1 (0.3%)	5 (0.6%)
≥ 3	1 (0.1%)	3 (0.8%)	1 (<0.1%)
Patients Treated at Reduced Doses			
120 mg	6 (0.8)	5 (1.3)	NA
80 mg	14 (1.8)	9 (2.3)	NA
40 mg	1 (0.1)	1 (0.3)	NA

Source: CRPC2: EX dataset; S-3100-01-1: ADEX dataset; CRPC-MDA-1: ADEXSSM dataset

Overall, dose delays and dose reductions were comparable for enzalutamide- and placebo- treated patients. The enzalutamide-treated patients in the CRPC2 safety population consistently had fewer dose delays and dose reductions compared to the placebo-treated patients. Dose reductions were not common in either study arm.

Reviewer Comment: Dose modifications were collected in two places on the eCRFs and were reported in two different clinical datasets (i.e., the ADAE and EX datasets for

each trial). FDA dose modification analyses were based on data from the exposure datasets provided by the Applicant (see the table above). There were a limited number of differences in dose modifications when comparing the two different sources of dose modification data. The Applicant provided additional data to clarify that these differences were primarily due to the way that dose modifications were collected. For example, for temporary dose interruptions that later became permanent discontinuations for reasons other than AEs, the temporary dose reductions were recorded on the AE CRF, and the permanent dose discontinuation were recorded on the exposure CRF. The limited number of discrepancies identified between the ADAE and EX datasets are not expected to significantly change the incidence of dose modifications in this trial, or to interfere with the overall interpretation of the enzalutamide dose modification data.

7.2.2 Explorations for Dose Response

In the CRPC2 trial, there was no clinically meaningful exposure-response relationship for fatigue, flushing, headache, or hypertension within the limited exposure range of 160 mg per day. There was insufficient exposure data to conduct any definitive analyses to evaluate an exposure-response for seizures in the CRPC2 trial.

See the Clinical Pharmacology review for more information.

7.2.3 Special Animal and/or In Vitro Testing

See the Pharmacology/Toxicology review for more information.

7.2.4 Routine Clinical Testing

In the CRPC2 trial, routine laboratory analyses, vital signs, and physical exams were obtained at screening, during each cycle, and at the end of the clinical trial. To assess cardiac function, a Multi-Gated Acquisition Scan (MUGA) or an echocardiogram were performed at baseline. Scheduled 12-lead ECGs were also periodically assessed and the CRPC2 trial included a QTc substudy. Clinical laboratory evaluations, including liver function tests, were assessed at screening, twice during Cycle 1, prior to initiation of each cycle up to 6 months, every 12 weeks after 6 months, and at the end of study visit.

See Table 6: Study Calendar of the CRPC2 Trial for more detailed information.

7.2.5 Metabolic, Clearance, and Interaction Workup

The mean terminal half-life ($t_{1/2}$) for enzalutamide in patients after a single oral dose is 5.8 days (range 2.8 to 10.2 days). Following a single 160 mg oral dose of enzalutamide in healthy volunteers, the mean terminal $t_{1/2}$ for N-desmethyl enzalutamide (M2, an active metabolite) was approximately 7.8 to 8.6 days. The human mass balance trial

showed that enzalutamide is primarily eliminated by hepatic metabolism. The mean apparent clearance (CL/F) of enzalutamide in patients after a single oral dose is 0.56 L/h (range 0.33 to 1.02 L/h). A dose reduction is not needed in patients with mild or moderate renal impairment (> 30 ml/min) or in patients with mild or moderate hepatic impairment (Child Pugh A or B). The effect of severe renal impairment or severe hepatic impairment on the pharmacokinetics of enzalutamide is not known.

See the Clinical Pharmacology review for more information.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Enzalutamide is an androgen receptor inhibitor hypothesized to block multiple steps in the androgen receptor (AnR) signaling pathway without any agonist effects. The steps in the signaling pathway that are targeted are binding of androgens to AnRs in the cytosol, inhibition of nuclear translocation of activated AnRs, and inhibition of the activated AnR interactions with chromatin. The anti-androgenic effects of enzalutamide have the potential to result in AEs associated with other anti-androgenic drugs indicated for metastatic castrate resistant prostate cancer (mCRPC) such as bicalutamide, nilutamide, and flutamide. These AEs include, but are not limited to anemia, anorexia, asthenia/fatigue, ALT/AST increases, cognitive impairment, constipation, diarrhea, dry skin, depression, dizziness, dyspnea, glucose intolerance, headache, hematuria, hot flashes, hyperlipidemia, hypertension, infection, insomnia, nausea, pain, peripheral edema, pneumonia, and vomiting. The most severe toxicity associated with anti-androgenic drugs is severe hepatic injury and fatal hepatic failure. A majority of the severe hepatotoxicity events have occurred within the first 4 months of treatment with these agents.

Abiraterone acetate inhibits androgen biosynthesis by inhibiting CYP17, resulting in a compensatory increase in adrenal steroids, that often requires concomitant treatment with corticosteroids to manage mineralocorticoid excess. Enzalutamide inhibits the AR signaling pathway downstream from the CYP17 receptor and may not result in these effects or require concomitant corticosteroid treatment. Therefore, enzalutamide and abiraterone acetate (or ketoconazole) likely will have different safety profiles and enzalutamide is not expected to have the mineralocorticoid excess ARs associated with abiraterone. However, other ARs related to the shared anti-androgenic pathway will likely be present in patients treated with enzalutamide.

7.3 Major Safety Results

7.3.1 Deaths

7.3.1.1 Total Deaths

Table 36 shows the reported causes of death in the CRPC2 trial for the original NDA and 60-day safety update submissions.

Table 36: Deaths and Causes of Death in the CRPC2 Trial

	Original NDA Submission (Cutoff Date (b) (6))		60-Day Safety Update (Cutoff Date 31 Jan 2012)	
	CRPC2 (160 mg) (N=800)	CRPC2 (Placebo) (N=399)	CRPC2 (160 mg) (N=800)	CRPC2 (Placebo) (N=399)
	N (%)	N (%)	N (%)	N (%)
Total number of deaths	308 (38.5%)	212 (53.1%)	398 (49.8%)	247 (61.9%)
Disease progression	274 (34.3%)	192 (48.1%)	348 (43.5%)	219 (54.9%)
Other	22 (2.8%)	13 (3.3%)	27 (3.4%)	19 (4.8%)
Unknown	12 (1.5%)	7 (1.8%)	23 (2.9%)	9 (2.3%)
Death Occurring ≤ 30 days after first dose of study drug	2 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
Death occurring ≤ 30 days after last dose of study drug	64 (8.0%)	25 (6.3%)	70 (8.8%)	25 (6.3%)

Source: Original NDA and 60-Day Safety Submission ADSL Datasets

Overall in the CRPC2 trial, 62% of the placebo-treated patients experienced death compared to 50% of the patients treated with enzalutamide. Deaths due to reasons other than disease progression (i.e., “other” and “unknown”) were slightly higher in the enzalutamide arm of the study (6.3% vs. 6.1%, respectively). Sixteen of the deaths attributed to “other” causes and one death attributed to “unknown” causes on the enzalutamide arm were AEs with an outcome of death also reported in the AE datasets (ADAE) and reviewed in Section 7.3.1.2.

The remaining deaths due to “other” or “unknown” reasons occurred during the follow up phase of the CRPC2 trial. A majority of these cases occurred after progression of disease (PD), lack clear temporal associations with enzalutamide, and are thus likely

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

unrelated. Out of the remaining 11 deaths reported as “other” (i.e., Patients: #036-08, #041-04, #053-10, #102-05, #250-12, #257-05, #302-18, #650-08, #659-07, #801-22, #810-02), ten patients discontinued therapy due to PD more than 60 days before death. The remaining patient (#659-07) was an 80-year old man with a medical history significant for deep venous thrombosis (DVTs) who discontinued therapy due to Grade 2 vomiting. He experienced a cerebrovascular accident (CVA) approximately ^{(b) (6)} months after his last dose of enzalutamide. Out of the remaining 22 deaths due to “unknown” causes in enzalutamide-treated patients, 20 of these deaths occurred after discontinuation of therapy due to PD and all of the deaths occurred more than 30 days after the last dose of enzalutamide. The other two deaths occurred in men who discontinued therapy due to AEs [Patient #002-03 (peripheral bacteremia) and #011-02 (worsening of pulmonary disease)] with deaths that occurred over ^{(b) (6)} and ^{(b) (6)} months (respectively) after the last dose of enzalutamide.

7.3.1.2 Adverse Events with an Outcome of Death

In the CRPC2 trial, AEs with an outcome of death were reported in 3.3% of the patients treated with enzalutamide and in 3.8% of the patients treated with placebo. The AEs with an outcome of death reported are listed in Table 37.

Table 37: Adverse Events with an Outcome of Death in the CRPC2 Trial*

Deaths		Enzalutamide (n=800)	Placebo (n=399)
System-Organ-Class (SOC)	Preferred Term	N (%)	N (%)
Total Deaths**		26 (3.3%)	15 (3.8%)
Cardiac disorders		3 (0.4%)	2 (0.5%)
	Acute myocardial infarction	2 (0.3%)	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%)
Gastrointestinal disorders		1 (0.1%)	0 (0.0%)
	Retroperitoneal hemorrhage	1 (0.1%)	0 (0.0%)
General disorders and administration site conditions		8 (1.0%)	6 (1.5%)
	General physical health deterioration	7 (0.9%)	5 (1.3%)
	Death ^a	1 (0.1%)	0 (0.0%)
	Euthanasia	0 (0.0%)	1 (0.3%)
<i>Infections and infestations</i>		8 (1.0%)	1 (0.3%)
	<i>Sepsis***</i>	5 (0.6%)	0 (0.0%)
	Pneumonia	2 (0.3%)	1 (0.3%)
	Infection ^b	1 (0.1%)	0 (0.0%)
Injury, poisoning and procedural		1 (0.1%)	0 (0.0%)

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Deaths		Enzalutamide (n=800)	Placebo (n=399)
System-Organ-Class (SOC)	Preferred Term	N (%)	N (%)
complications			
	Subdural hematoma ^c	1 (0.1%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		3 (0.4%)	1 (0.3%)
	Acute leukemia / Acute monocytic leukemia ^d	2 (0.3%)	0 (0.0%)
	Metastases to meninges or central nervous system	1 (0.1%)	1 (0.3%)
Nervous system disorders		2 (0.3%)	3 (0.8%)
	Cerebral hemorrhage	1 (0.1%)	0 (0.0%)
	Cerebrovascular accident	1 (0.1%)	0 (0.0%)
	Hepatic encephalopathy	0 (0.0%)	2 (0.5%)
	Ischemic stroke	0 (0.0%)	1 (0.3%)
Renal and urinary disorders		1 (0.1%)	0 (0.0%)
	Renal failure	1 (0.1%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders		3 (0.4%)	2 (0.5%)
	Pulmonary embolism	1 (0.1%)	1 (0.3%)
	Pulmonary edema	1 (0.1%)	0 (0.0%)
	Respiratory failure	1 (0.1%)	0 (0.0%)
	Pneumothorax	0 (0.0%)	1 (0.3%)

* Safety cutoff date: 31 Jan 2012

** Three patients on the enzalutamide arm had more than one AE reported for each death [#005-03 (3), #035-04 (2), and #807-06 (2)].

*** Includes deaths attributed to sepsis, septic shock, urosepsis, and Escherichia sepsis.

Narratives for selected AEs with an outcome of death:

a Death (unspecified): Patient #502-08 was a 72-year old man who experienced sudden death at home approximately (b) (6) after initiation of enzalutamide. His relevant past medical history included first degree AV block with normal range QTcF and microcytic anemia. His baseline hemoglobin was 9.2 G/dL with an MCV of 73 fL (normal range 80-100). The Investigator reported that there was no evidence that a gastrointestinal bleed was the cause for the worsening anemia. His last hemoglobin (b) (6) was 8.5 G/dL and a blood transfusion was planned during (b) (6). A cardiovascular cause of death was considered as a possible cause but there was no evidence to support a specific cause of death in this case. No autopsy was performed and the cause of death was not listed on the death certificate.

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

b Infection: Patient #315-16 was a 74-year old man who was permanently discontinued from therapy approximately (b) (6) months after initiation of enzalutamide due to “lumbar bone pain due to prostate cancer”. Approximately (b) (6) after discontinuation, he experienced spinal cord compression [T12 (MRI verified)]. Surgical decompression was performed and (b) (6) later the event was considered resolved. The Investigator assessed the event of “spinal cord compression” as unrelated to the study drug. Approximately one month after discontinuing study drug, the patient experienced “general health status alteration” and “infectious syndrome (without fever)” requiring hospitalization. The oral amoxicillin/clavulanic acid he was taking at home for a urinary tract infection was replaced with an intravenous formulation. The “general health status alteration” was considered resolved approximately (b) (6) later. However, he subsequently suffered a fever (38°C) and was treated with parenteral levofloxacin. The patient’s level of consciousness deteriorated and he died due to “infectious syndrome” (probably sepsis). The Investigator assessed the events of “general health status alteration” and “infectious syndrome” as not related to study drug.

c Subdural hematoma: Patient #029-01 was an 85-year old man who experienced hypoglycemia and pneumonia and discontinued therapy on Study Day (b) (6) due to Grade 3 fatigue. On Study Day (b) (6) he experienced hypoglycemia and pneumonia. He had a past medical history significant for diabetes and was receiving concomitant glimepiride / rosiglitazone (Avandaryl). His Day (b) (6) platelet count was 315 x103/uL and Day (b) (6) was 178 x103 uL. During his hospitalization, he developed left hemiparesis. A repeat CT scan on Day (b) (6) revealed worsening bilateral subdural hematomas and a new 3 mm right to left midline shift. Platelet values remained above 100 x103 /uL. Prothrombin time (PT) and partial thromboplastin time (PTT) were slightly elevated on admission, at 13.5 sec (9.5 – 10.9) and 34.3 sec (23.7 - 31.1), respectively, and his INR was 1.31. There was no clear history of fall, trauma, or other events to account for his fatal subdural hematoma AE.

d Acute leukemia / Acute monocytic leukemia (2): (1) Patient #005-03 was a 59-year old man who experienced acute monocytic leukemia on Day (b) (6) of therapy. He was previously treated with radiotherapy. On Day (b) (6), enzalutamide was permanently discontinued due to “acute monocytic leukemia”. His hematology results included leukocytosis (319 K/uL) with 35.4% monocytes, thrombocytopenia (35 K/mm³), and anemia (hemoglobin of 8.8 g/dL). His peripheral smear and bone marrow biopsy were diagnostic of acute monocytic leukemia (AML M5) with blast crisis. He was treated with hydroxyurea, rasburicase, allopurinol, aggressive hydration, oxygen, and was transfused fresh frozen plasma, cryoprecipitate, platelets, and packed red blood cells. After leukapheresis, his white blood cells (WBC) were 100 X 10⁹/L. On Study Day (b) (6), he experienced renal failure [serum creatinine= 2.42 mg/dl (reference range 0.50-1.20)] and a pulmonary embolism. His WBC count was 120 K/uL at 8AM and rose to 172 K/uL by noon that day. During his second leukapheresis procedure, he became unresponsive with “pulseless electrical activity” and could not be revived despite CPR, intubation, and epinephrine and atropine administration. The cause of death was reported as “acute monocytic leukemia.” The Investigator and Applicant assessed the

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

event as unrelated to enzalutamide. The Applicant added that there was possible dysplasia at baseline due the rapid progression of AML shortly after initiation of enzalutamide.

(2) Patient #112-01 was an 81-year old man who experienced “possible acute leukemia” on Study Day (b) (6). At the time of the event, he was experiencing malaise, diaphoresis, dizziness, leg weakness, nausea, vomiting, headache, chest pain, dyspnea, cough, and expectoration. Upon admission, he had a stool positive for blood with a low hemoglobin, hematocrit, and platelet level. He was initially diagnosed with an upper gastrointestinal bleed with possible reduced marrow production due to metastatic bone marrow disease. His white blood cell count (WBC) on admission was cells $28 \times 10^9/L$ (reference range 4.0 - 11.0). Promyelocytes and metamyelocytes were noted on the differential. He received four units of packed cells, declined an upper endoscopy, and was discharged. He was readmitted on Day (b) (6) and had a WBC of $75 \times 10^9/L$ and platelet count of $24 \times 10^9/L$. He was also noted to have promyelocytes (5% of white cells), metamyelocytes (17% of white cells), and blasts (47% of white cells). No further work-up ensued given the patient’s wishes for palliative care and on Study Day (b) (6) he died. The causes of death listed on the death certificate were digestive hemorrhage, bone marrow invasion, bone/lung metastases, and prostate neoplasia. After the Applicant’s request to reassess this death, the Investigator added “possible acute leukemia” as the cause of death given the marked blast transformation and high WBC counts. The Investigator and Applicant attribution for this death were unrelated to enzalutamide.

Reviewer Comment: The two deaths attributed to AML in this trial (one after radiation exposure) are insufficient to establish a safety signal or a clear association to enzalutamide. No other AEs for AML were identified in the enzalutamide clinical trials. Given that this drug does not have a direct cytotoxic mechanism of action (e.g., alkylating agents and anthracycline), and AML has not been a safety issue for other anti-androgenic agents, these findings are unexpected. FDA will continue to monitor for AML and other related events in the ongoing controlled clinical trials, future periodic safety update reports, and spontaneous AE reports to determine if a safety signal for AML becomes apparent with increased enzalutamide exposure.

In the CRPC2 trial, the most common deaths related to AEs reported were “general health deterioration” and were comparable across study arms. On the enzalutamide arm (compared to placebo), there was a small increase in fatal AEs related to infection driven primarily by sepsis. Deaths due to cardiac disorders were comparable for enzalutamide-treated patients (0.4%) and placebo-treated (0.5%) patients. Deaths potentially related to thromboembolic events (i.e., cerebrovascular accident, ischemic stroke, pulmonary embolism, myocardial infarction) occurred at a low incidence and were less common in enzalutamide-treated patients (enzalutamide= 0.5%; placebo= 0.8%). There were no hepatotoxicity- or seizure- related AEs that resulted in death reported in enzalutamide-treated patients.

7.3.1.3 Deaths within 30 Days of Drug Initiation and Drug Discontinuation

The number of deaths that occurred within the first 30 days of study therapy were comparable across the study arms (both 0.3%). One enzalutamide-treated patient (#300-31) with a death attributed to disease progression within the first 30 days of treatment had no evidence of acute drug-related toxicity. The other death on the enzalutamide arm (#005-03) was also reported as a death due to AEs (i.e., AML/renal failure/pulmonary embolism; see Section 7.3.1.2).

The number of total deaths that occurred within 30 days of the last dose of treatment was slightly increased in the enzalutamide-treated patients (8.0%) compared to the placebo treated patients (6.3%), but this difference appears to be driven primarily by deaths due to disease progression [6.6% (out of 8.0%); 4.8% (out of 6.3%), respectively].

The AEs with a fatal outcome that occurred during study drug administration or within 30 days of study drug discontinuation were comparable for the enzalutamide and placebo arms in the CRPC2 trial (i.e., both 2.5%). Table 38 shows the types of AEs with an outcome of death that occurred within 30 days of study drug discontinuation in the CRPC2 trial. These AEs were also included in the review of Section 7.3.1.2.

Table 38: Deaths Due to an Adverse Event Within 30 Days of Study Drug*

Deaths	Enzalutamide (n = 800)	Placebo (n = 399)
	N (%) (Patient #s)	N (%) (Patient #s)
All	20 (2.5%)	10 (2.5%)
General Physical Health Deterioration	4 (0.5%) #112-09 #300-38 #302-13 #315-13	4 (1.0%) #112-19 #300-11 #303-07 #315-05
Sepsis	5 (0.6%) #108-04 #252-01 #803-03 #809-03 #807-06	0 (0.0%)
Acute Leukemia	2 (0.3%) #005-03 #112-01	0 (0.0%)
Pneumonia	2 (0.3%) #009-09 #811-02	1 (0.3%) #354-02
Myocardial Infarction	1 (0.1%) #023-02	1 (0.3%) #011-01
Cerebrovascular Accident	1 (0.1%)	1 (0.3%)

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Deaths	Enzalutamide (n = 800)	Placebo (n = 399)
	N (%) (Patient #s)	N (%) (Patient #s)
	#029-05	#103-04
Cardiac failure	1 (0.1%) #251-01	0 (0.0%)
Cerebral Hemorrhage/Pancytopenia	1 (0.1%) #300-09	0 (0.0%)
Death	1 (0.1%) #502-08	0 (0.0%)
Pulmonary Edema	1 (0.1%) #301-03	0 (0.0%)
Subdural hematoma/Pneumonia	1 (0.1%) #029-01	0 (0.0%)
Cardiogenic Shock	0 (0.0%)	1 (0.3%) #951-03
Hepatic Encephalopathy	0 (0.0%)	1 (0.3%) #257-01
Pulmonary Embolism	0 (0.0%)	1 (0.3%) #654-06

* Safety cutoff date: 31 Jan 2012

There were no AEs leading to death reported in any of the open-label studies in the pooled analysis for up to 30 days after discontinuation of therapy. Therefore, all deaths that were included in these analyses were reported in the randomized controlled (CRCP2) trial.

7.3.2 Nonfatal Serious Adverse Events (SAE)

The nonfatal SAEs reported in more than 1.0% of the enzalutamide-treated patients and that were more common in placebo-treated patients are shown in Table 39.

Table 39: Nonfatal SAEs in ≥ 1.0 % and > Placebo*

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

	CRPC2 (160 mg) (N=800)	CRPC2 (Placebo) (N=399)	Safety Analysis Population (Pooled) (150-160 mg) (N=925)
	N (%)	N (%)	N (%)
Total # of Patients with ≥ 1 SAE	279 (34.9)	149 (37.3)	311 (33.6)
Spinal cord compression	50 (6.3)	15 (3.8)	53 (5.7)
Hematuria	14 (1.8)	5 (1.3)	15 (1.6)
Bone pain	13 (1.6)	4 (1.0)	14 (1.5)
Pathological Fracture	13 (1.6)	2 (0.5)	13 (1.4)
Metastatic pain	13 (1.6)	3 (0.8)	14 (1.5)
General physical health deterioration	12 (1.5)	4 (1.0)	14 (1.5)
Pneumonia	12 (1.5)	5 (1.3)	13 (1.4)

* Safety cutoff date: 31 Jan 2012

Overall, serious adverse events (SAEs) were more common in the placebo arm compared to enzalutamide-treated patients. The largest increase in SAEs ($> 1.0\%$) occurred in spinal cord compression and pathological fracture. A full discussion of fracture and spinal cord compression findings can be found in Section 7.3.5.

Reviewer Comment: Despite an improvement in the secondary endpoint for time-to-skeletal related events (SRE), more SAEs for pathologic fracture and spinal cord compression were reported on the enzalutamide arm of the study. .

7.3.3 Treatment Discontinuations due to Adverse Events

Table 40 shows the AEs that lead to permanent discontinuation more frequently on the enzalutamide arm and in more than one patient (i.e., $> 0.1\%$ and $>$ placebo) in the CRPC2 trial.

Table 40: Permanent Discontinuation due to Adverse Events (CRPC2 trial)

	CRPC2 (160 mg) (N=800)	CRPC2 (Placebo) (N=399)
	N (%)	N (%)
Total	61 (7.6%)	39 (9.8%)
Seizure*	6 (0.8%)	0 (0.0%)
Fatigue	5 (0.6%)	2 (0.5%)
Thrombocytopenia	2 (0.2%)	0 (0.0%)
Colonic obstruction	2 (0.2%)	0 (0.0%)
Diarrhea	2 (0.2%)	0 (0.0%)
Rash	2 (0.2%)	0 (0.0%)

Source: Original NDA ADAE Dataset (Safety cutoff date- 25 SEP 2011)

* For the seven seizure events in the CRPC2 trial, six patients were permanently discontinued. One seizure occurred (b) (6) after the patient had already discontinued therapy (#358-05).

Overall, treatment discontinuation due to AEs was more common for placebo-treated patients than for enzalutamide-treated patients (10% vs. 8%). With the exception of seizures, AEs that lead to permanent discontinuation of treatment were comparable across study arms.

7.3.4 Significant Adverse Reactions

AE rates were compared between the two treatment groups in the CRPC2 trial using the MedDRA Preferred Terms (PT), Higher Level Terms (HLTs), and Higher Level Group Terms (HLGTs) to determine clinically relevant ARs. AEs which occurred more frequently on the enzalutamide arm, with an absolute increase in incidence of 2% or greater, or were considered possibly related enzalutamide treatment are discussed in Section 7.4.1. Other clinically relevant AEs with a 3-fold or greater increase on the enzalutamide arm compared to placebo were also considered ARs and possibly associated with enzalutamide. These AEs included deaths due to infections, falls and fall-related injuries, and hallucinations.

Because the treatment duration for the enzalutamide arm was 2.5 fold longer than that of the placebo arm (i.e., 36 weeks versus 13 weeks), the Applicant performed an analysis to standardize the AE rates by treatment exposure time (i.e., AEs per 100 patient-years). ARs that remained increased with the time adjusted analysis included hot flushes, headache, hypertension, falls, non-pathologic fracture (and all fractures), memory impairment, and pruritis/dry skin. In general, this methodology attenuated the differences between the treatment arms for other ARs. This approach is not typically used in oncology drug or biologic review to determine ARs. Therefore, the FDA safety reviewer considered these exploratory analyses and did not use the standardized data to ultimately determine the ARs for labeling.

7.3.5 Review of Specific Primary Safety Concerns

7.3.5.1 Seizures

Proposed mechanism for enzalutamide-induced seizures

Seizures were identified as a potential dose-dependent enzalutamide AR in nonclinical studies in mice and dogs, and subsequently in the phase 1 dose escalation study (S-3100-1-01) in humans. The proposed mechanism of action is due to an off-target effect mediated through inhibition of the gamma aminobutyric acid (GABA) gated chloride (Cl⁻) channel. In nonclinical trials conducted in mice, enzalutamide and the active metabolite (M2) both cross the blood brain barrier. Based on nonclinical studies, the magnitude of GABA Cl⁻ channel inhibition may be dependent on the concentration of enzalutamide or other antiandrogen in the brain. One nonclinical study in the published literature compared the concentrations of anti-androgenic drugs (including enzalutamide) and determined that the extent these drugs cross the blood brain barrier varies across the anti-androgenic drug class. In this nonclinical study, the ability of electroencephalograms (EEGs) to predict and diagnose anti-androgenic drug-related

seizures was not definitive. In some animals, EEG recordings were not predictive of seizure risk, while abnormal EEG patterns were observed in other animals in the absence of seizures.¹⁵

Seizure management strategy in enzalutamide clinical trials

In the CRPC2 trial (Version 3), the Applicant managed the risk of seizure and seizure ARs that occurred as follows:

- Exclusion Criteria, Past Medical History: “History of seizure, including any febrile seizure, loss of consciousness, or transient ischemic attack within 12 months of enrollment (Day 1 visit), or any condition that may pre-dispose to seizure (e.g., prior stroke, brain arteriovenous malformation, head trauma with loss of consciousness requiring hospitalization).”
- Exclusion Criteria, Concomitant Medications: “Have used or plan to use from 30 days prior to enrollment (Day 1 visit) through the end of the study the following medications known to lower the seizure threshold or prolong the QT interval: 1) aminophylline/theophylline; 2) atypical antipsychotics (e.g., clozapine, olanzapine, risperidone, ziprasidone); 3) bupropion; 4) class IA and III antiarrhythmics (e.g., amiodarone, bretylium, disopyramide, ibutilide, procainamide, quinidine, sotalol); 5) dolasetron; 6) droperidol; 7) gatifloxacin/moxifloxacin; 8) insulin; 9) lithium; 10) macrolide antibiotics (e.g., erythromycin, clarithromycin); 11) pethidine; 12) phenothiazine antipsychotics (e.g., chlorpromazine, mesoridazine, thioridazine); 13) pimozide; 14) tricyclic and tetracyclic antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine); 15) venlafaxine.”
- Permanent Discontinuation: Any seizure AR reported resulted in permanent discontinuation of patients from study medication.
- Expedited SAE Reporting of Seizure and Seizure-related AEs: Seizure or loss of consciousness AEs were required to be reported as SAEs and required sponsor notification within 24 hours of the event’s occurrence.

Applicant-identified Seizures

In the CRPC2 study (safety cutoff date 31 Jan 2012), the Applicant reported six seizures on the enzalutamide arm (0.6%) compared to no seizures (0%) on the placebo arm. Two additional seizure-like events [Patient #300-83 (vasovagal syndrome); Patient #812-01 (TIA with abnormal EEG)] were also reported as “AEs of strong concern for seizure activity”. Three additional seizures were reported in S-3100-1-01 at doses of 360 mg, 480 mg, and 600 mg (one at each dose level). No seizures were reported at the 150-160 mg dose in the open-label studies included in the safety analysis population. Table 41 shows the seizures reported in enzalutamide trials in the overall safety analysis population.

15 Foster WR, Bruce DC, Hong, S, et. al. Drug Safety is a Barrier to the Discovery and Development of New Androgen Receptor Antagonists. The Prostate. 2011 (71) 480-488

Table 41: Summary of Seizure Cases in Enzalutamide Trials

Pat. ID# / Patient Age	Dose (mg/day) / Study Day	Relevant Medical History	Seizure Type / Witnessed	Verbatim Term	Pot. Contrib. Factors / Concomitant Meds	Treatment	Notes / Outcome
160 mg/day							
CRPC2-300-39 / 77 years	160 / Day (b) (6)	None	Complex Partial / Yes	Confusion associated with complex partial status epilepticus	None	Phenytoin, clonazepam, levetiracetam Improved with clonazepam and phenytoin treatment	Loss of consciousness No incontinence Abnormal EEG with later improvement Normal lumbar puncture Investigator attribution probably related Resolved / No recurrence
CRPC2-812-01 / 82 years	160 / Day (b) (6)	Active alcoholism	Convulsive / No	Seizure	Alcohol Brain atrophy Haloperidol (started 7 days prior to seizure),	Discontinued haloperidol	Urinary incontinence Witnessed during post-ictal state No brain metastases on CT/MRI Investigator attribution probably related Resolved / No recurrence

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Pat. ID# / Patient Age	Dose (mg/day) / Study Day	Relevant Medical History	Seizure Type / Witnessed	Verbatim Term	Pot. Contrib. Factors / Concomitant Meds	Treatment	Notes / Outcome
CRPC2-025-03 / 68 years	160 / Day (b) (6)	None	Convulsive , Complex Partial / Yes	Seizures- new onset generalized seizures and partial complex seizures	Hypovolemia	Levetiracetam	Loss of consciousness Tonic-clonic activity EEG with epileptiform activity Investigator attribution probably related Recurrence after IV hydration for hypotension

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Pat. ID# / Patient Age	Dose (mg/day) / Study Day	Relevant Medical History	Seizure Type / Witnessed	Verbatim Term	Pot. Contrib. Factors / Concomitant Meds	Treatment	Notes / Outcome
*CRPC2-300-83 / 62 years	160 / Day (b) (6)	None	Complex Partial / Yes	Vasovagal syndrome (Seizure was initial verbatim AE term with probably related attribution; later deleted by sub-Investigator)	Vasovagal syndrome	Levetiracetam	Loss of consciousness Remained seated Fecal incontinence EEG with epileptiform activity No brain metastases (CT and MRI) Neurologist consultant “(EEG) shows clearly signs of seizure” Cardiologist consultant “compatible with vasovagal syncope and requested confirmatory tests not reported
CRCP2-014-02 / 64 years	160 / Day (b) (6)	None	Partial / Yes	Focal seizures associated with brain metastases	Brain metastases (with possible hemorrhage/edema), low sodium level, cyclobenzaprine	Surgery Dexamethasone Levetiracetam	No loss of consciousness No EEG reported; Resolved / No recurrence

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Pat. ID# / Patient Age	Dose (mg/day) / Study Day	Relevant Medical History	Seizure Type / Witnessed	Verbatim Term	Pot. Contrib. Factors / Concomitant Meds	Treatment	Notes / Outcome
CRCP2-358-05 / 70 years	160 / Day (b) (6)	None	Partial / Yes	Focal Seizure	Brain metastases (cerebellar, pachymeningitis)	None	Convulsive symptoms No EEG reported Resolved / No recurrence
CRCP2-300-21 / 74 years	160 / Day (b) (6)	None	Convulsive / Yes	Lidocaine-induced convulsion	Inadvertent IV lidocaine administered Propafenone Tramadol (prn)	None	Resolved / No recurrence
> 160 mg/day							
S3100-6671 / 64 years	480 mg / Day (b) (6)	None	Convulsive / Yes	Seizure	Brain atrophy	None	No brain metastases or lesions (CT only) Investigator attribution is possibly related
S3100-1676 / 71 years	360 mg / Day (b) (6)	None	Convulsive / Yes	Seizure	Dehydration with subsequent IV fluids 1 day prior to seizure (i.e., electrolyte shifts) Mirtazepine Methylphenidate (Both started (b) (6) days before seizure)	Levetiracetam	“Grand mal” seizure (tonic-clonic) No brain metastases or lesions (CT and MRI scans) Investigator attribution is possibly related

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Pat. ID# / Patient Age	Dose (mg/day) / Study Day	Relevant Medical History	Seizure Type / Witnessed	Verbatim Term	Pot. Contrib. Factors / Concomitant Meds	Treatment	Notes / Outcome
S3100-1726 / 62 years	600 mg / Day (b) (6)	Transient ischemic attack (TIA) Myoclonic jerks attributed to olanzapine	Convulsive / Yes	Seizure	Olanzapine	None	No brain metastases or lesions on CT Low grade fever (100.7°) / normal WBC, urinalysis, chest X-ray, lumbar puncture Investigator attribution is possibly related

*CRPC2-300-83: The Applicant reported this AE as a “Adverse Event of Strong Concern for Seizure Activity Following Sponsor Review”. FDA review of this patient concludes that seizure is at least as likely a cause for this AE as a vasovagal syndrome. This is primarily based on the neurologist consultant’s conclusions and the lack of confirmation of the vasovagal syndrome as requested by the cardiologist consultant.

FDA-identified Seizures

In the CRPC2 trial, FDA analysis determined there were seven seizures (0.9%) on the enzalutamide arm compared to no seizures (0%) on the placebo arm. For all of the cases in the safety database, the median onset of seizure was on Study Day (b) (6) (range: 26-603), with six out of ten of the seizures occurring within the first 60 days of therapy. All of the patients in the CRPC2 trial who experienced seizures were afebrile. All of the patients were taking enzalutamide at the time of the reported seizure AR, with the exception of Patient #358-05, who experienced a seizure (b) (6) days after discontinuation of enzalutamide due to disease progression, which included meningeal metastases, amblyopia, and gait disturbances. All of the patients who experienced seizures were permanently discontinued from enzalutamide. Six out of seven of the patients experiencing seizures had factors (e.g., medications, brain metastases) that may have reduced the seizure threshold or contributed to the seizure event. These factors included medications that may reduce the seizure threshold and/or disease factors such as brain metastases. None of the enzalutamide-treated patients experienced a seizure-related death. All of the patients who experienced seizures had additional information related to survival that confirmed that they were alive at least 120 days after the seizure except Patient #025-03; who was also alive at least (b) (6) days after the seizure event based on the last available follow-up.

Reviewer Comment: Based on an approximate 7-fold increase in the incidence of seizures at enzalutamide doses greater than 160 mg (3.5%; 3/85 patients) in the Phase 1-2 study and the nonclinical findings, it appears that seizure ARs may be dose-related.

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Patients experiencing seizure were permanently discontinued from therapy and all seizures resolved. There is no clinical trial experience re-administering enzalutamide to patients who experienced seizures.

Patients with predisposing factors for seizure were excluded from the trial; these include a history of seizure, underlying brain injury with loss of consciousness, transient ischemic attack, cerebral vascular accident, brain metastases, brain arteriovenous malformation or patients receiving concomitant medications that may lower the seizure threshold. However, there were 11 patients who had prior or probable cerebrovascular events, five patients with a history of head trauma, and one patient each with a history of intracranial hemorrhage (#904-03) and prior seizure (#312-09). None of these patients experienced a seizure while receiving enzalutamide in the CRPC2 trial.

Adequate human exposure data in patients that experienced a seizure was not available to further evaluate a relationship to drug exposure. See the nonclinical and clinical pharmacology reviews for more information.

Possible seizures in enzalutamide-treated patients

The Applicant reviewed the safety database for other potential seizure cases using the AE terms for syncope, presyncope, loss of consciousness, depressed level of consciousness, encephalopathy, and transient ischemic attack (TIA); and evaluated AEs and AE narratives for potential seizure cases for patients who experienced urinary or fecal incontinence, tonic-clonic activity (e.g., stiffening, jerking activity, tremulousness, shaking), abnormal EEGs, and who had treatment emergent initiation of anti-seizure medications.

From the CRPC2 trial, the Applicant's analysis identified 18 (2.3%) additional enzalutamide-treated patients and 8 (2.0%) placebo-treated patients with potential seizure AEs. The additional AEs evaluated included syncope (both arms 0.8%), presyncope (0.6% vs. 0%), loss of consciousness and depressed level of consciousness (0% vs. 0.3% each), encephalopathy (both arms 0.5%), and transient ischemic attack (0.4% vs. 0.3%) (enzalutamide compared to placebo, respectively). Each of these cases was reviewed and no additional seizure ARs were identified. FDA review also expanded this search for possible seizures to include the verbatim AE terms reported in the pooled safety data for "simple", "partial", "complex", "generalized", "blackout", "ictal", "coma", and "epil" and did not identify any additional seizure ARs.

Reviewer Comment: Narratives were available for 15 out of 18 of the possible seizure AEs identified. The three cases that did not include narratives (#659-09, #054-08, #300-70) were reported as nonserious AEs and do not appear to be seizures based on the tabular case details provided by the Applicant. FDA review identified one additional patient who reported an SAE (#657-01) with "generalized limb shaking without loss of consciousness" (PT coded term = tremor). This was not considered a seizure AR because he had a CT and an EEG that were unremarkable and the consultant neurologist at the clinical site did not believe the event was consistent with a seizure.

One presyncope AE in CRPC-MDA-1 (#004-54), two TIA AEs in the S-3100-1-01 trial (#3355, #3356), and one TIA AE (#004-06) in the CRPC-MDA-1 trial were also reported. With the

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

exception of Patient #004-06, the presyncope and TIA AEs reported all had alternative attributions and included no evidence to suggest a drug-induced seizure. Patient #004-06 was reported as a (“TIA with abnormal EEG”) and is a possible seizure, but is significantly confounded by advanced coronary artery disease, hypotension, cardiac catheterization performed (b)(6) prior to the AE, and initiation of new anti-hypertensive medications after the catheterization. He was treated with levetiracetam, but the neurologist consultant (at the clinical site) for this case concluded that the AE was “not typical of a seizure”.

Concomitant medications

FDA review of the concomitant anti-seizure medications used in the CRPC2 trial did not identify any additional seizure ARs or a significant increase in the use of anti-seizure medications for patients treated with enzalutamide compared to patients treated with placebo in this trial. None of the reported indications included treatment of seizures or seizure-like disorders for cases not identified in Table 41. One patient (#106-05) was treated with concomitant phenobarbital for seizure prophylaxis. Patient #106-05 was a 69-year old man who had a reported SAE for “pontine lesion” and an unreported unwitnessed syncope AE on Study Day (b)(6). His past medical history was significant for occasional headaches, but he had no previous history of syncope or brain metastases. An MRI of the brain revealed a single left pontopeduncular lesion with surrounding edema in the posterior aspect of the corona radiata. The Investigator reported that the most likely diagnosis was an aggressive pontine gliomatous lesion. After the SAE and syncope event, enzalutamide was continued until his death from PD at Day (b)(6). He did not experience any additional syncope or seizure events. There was no additional evidence to suggest that this was a drug-related seizure.

In the CRPC2 trial, approximately 13% of the enzalutamide-treated patients compared to 11% of the placebo-treated patients were on concomitant medications that include indications to treat epilepsy or seizure-related disorders. The indications for these concomitant medications were reported in 11% (out of 13%) of the enzalutamide-treated patients and 9% (out of 11%) of the placebo treated patients. The most common indications were insomnia/sleep disorders (4% for both arms), anxiety (4% vs. 3%), pain (2% vs. 1%), and neuropathies (2% vs. 1%); all common disorders in this patient population.

In the CRPC2 trial, approximately 7% (n=58) of the enzalutamide-treated patients were treated with one or more concomitant medications that may lower the seizure threshold while on the CRPC2 trial. These medications included amiodarone, amitriptyline, bupropion, chlorpromazine, droperidol, erythromycin, insulin, gatifloxacin, mirtazepine, moxifloxacin, olanzapine, risperidone, sotalol, theophylline, and venlafaxine. None of these patients experienced a seizure during the CRPC2 trial.

Reviewer Comment: Because patients at increased risk of seizure were excluded from the randomized clinical trial, it is unclear if patients with predisposing conditions or who are taking medications that may reduce the seizure threshold are at a higher risk of seizure. Additional postmarketing studies may be warranted to better characterize this AR.

7.3.5.2 Falls and Fall-Related Injuries

Based on the 60-day safety update (January 31, 2012 database cutoff date) for the CRPC2 trial, falls or injuries related to falls [i.e., AE coded terms for post-traumatic pain, rib fracture, wrist fracture, joint injury, muscular weakness (concurrent with fall)] were reported in 4.6% (n= 37) of the patients treated with enzalutamide compared with 1.3% (n= 5) of the placebo-treated patients. Two patients (0.3%) on the enzalutamide arm experienced Grade 3 falls compared to no patients on the placebo arm. One enzalutamide-treated patient in the CRPC2 trial reported a fall SAE (#002-05). In the CRPC2 trial, one patient (0.1%) had therapy temporarily discontinued due to falls (#CRPC2-356-10) compared to no placebo-treated patients.

In the CRPC2, the fall AEs observed were primarily accidental [73% (n= 27)] and included slips, trips, or falls on specific surfaces. Two additional cases were related to weakness (#006-02, #801-21), one due to “awkwardness” (#302-13); seven cases did not include a fall etiology. None of the fall AEs reported were associated with neurologic symptoms such as dizziness or pre-syncope. One case included concomitant mental status changes (#017-07). The median onset of the falls was 161 days (range 8 - 564 days) after initiation of enzalutamide therapy; no trends related to onset time of these AEs are apparent from these cases. Four patients (#002-05, #017-07, #302-13, and #650-10) experienced recurrent fall AEs and one patient (#043-04) reported “intermittent falls” after being continued on enzalutamide therapy. These cases were significantly confounded by disease-related factors [i.e., advanced bone disease (n=4), pathological fracture (n=4), and spinal cord compression (n=4)] and past medical history [gait disturbance (n=2), prior falls (n=1), vertigo (n=1), orthostatic hypotension (n=1), and peripheral neuropathy (n=2)]. Investigator attribution for these recurrent AEs was “not related” for four of the five recurrent/intermittent fall AEs and possible for the other fall AE.

In the pooled safety population, all of the fall AEs occurred in patients who received a 150-160 mg dose of enzalutamide (or placebo). An additional five fall AEs were reported in the open-label trials; two were Grade 3 or 4 [MDA1-004-19 (Grade 3); 9785-CL-0111B-E00201 (Grade 4)] and also reported as SAEs, with the latter case leading to permanent discontinuation of enzalutamide.

Table 42 shows the incidence rates for falls by age categories and ECOG performance status (PS) for patients treated in the CRPC2 trial and in the pooled safety analysis population.

Table 42: Fall and Fall-related Injuries by Age and Performance Status

	CRPC2 (160 mg) (N=800)	CRPC2 (Placebo) (N=399)	Safety Analysis Population (Pooled) (150-160 mg) (N=925*)
Age (Years)	N (%**)	N (%**)	N (%**)
< 65	9 (3.8%)	2 (1.5%)	9 (3.3%)
≥ 65	33 (5.8%)	3 (1.1%)	38 (5.8%)
< 75	28 (4.7%)	3 (1.0%)	31 (4.5%)
≥ 75	14 (6.0%)	2 (1.9%)	16 (6.8%)
ECOG PS			
0 or 1	36 (4.9%)	5 (1.4%)	40 (4.7%)
2	6 (8.6%)	0 (0%)	7 (9.6%)

* Safety cutoff date: 31 Jan 2012

** Percentages based on number of patients enrolled in study for each age category.

The number of falls for placebo-treated patients was generally comparable ($\pm 1\%$) for patients < 65, ≥ 65 , and ≥ 75 years of age. For all of the age categories, the incidence of falls on the enzalutamide arm was greater than the incidence on the placebo arm. For both the CRPC2 and pooled safety populations, there was a small increase in the incidence of falls for enzalutamide-treated patients ≥ 65 years of age compared to < 65 years of age (+ 2.0% - 2.5%), patients ≥ 75 years of age compared to < 75 years of age (+ 1.3% - 2.3%). There was also a small increase in fall AEs for enzalutamide-treated patients with ECOG PS of 2 compared to 0 / 1 (+ 3.7% – 4.9%).

Reviewer Comment: The number of fall AEs in the CRPC2 trial do not permit formal statistical analysis and the magnitude of this small increase based on the limited number of cases are not adequate to establish that there is a higher risk for falls in elderly patients compared to younger patients, or for patients with a poorer performance status, when treated with enzalutamide. In the CRPC2 trial, five additional falls were reported in enzalutamide-treated patients after the January 31, 2012 cutoff date (#035-01, #315-02, #500-23, #606-11, and #656-0). These fall AEs were not included in the CRPC2 calculations or labeling.

Based on the January 31, 2012 safety cutoff dates, 1.8% (n=14) of the CRPC2 enzalutamide-treated patients who experienced falls also experienced temporally-related injuries (during or reported within 10 days of fall) compared to 0.5% (n=2) of the placebo-treated patients. The injuries in the enzalutamide- treated patients included eight non-pathologic fractures [1.0%; rib (n=4), hip, wrist, facial bone/upper limb, patella (all n=1)], four joint injuries [0.5%; unspecified (n=3); torn rotator cuff], and three hematomas (0.3%) compared to one hematoma/eye injury (0.3%) in a placebo-treated patient . There were also six (0.8%) enzalutamide-treated patients who reported post-traumatic pain (Grade 1 or 2) after experiencing fall AEs compared to one placebo-treated patient (0.3%).

7.3.5.3 Spinal Cord Compression and Cauda Equina Syndrome

In the CRPC2 trial, spinal cord compression and cauda equina syndrome occurred in 7.5% (n=60) of the enzalutamide-treated patients compared to 4.8% (n=19) of the placebo-treated patients. The median time of onset for the ARs was 109 days (range: 8 to 532 days) on the enzalutamide arm and 82 days (range: 14 to 202 days) on the placebo arm after initiation of therapy. The median age of the patients who experienced spinal cord compression and cauda equina syndrome was 68 years (range: 41 – 82) on the enzalutamide arm and 62 (range: 56 - 86) on the placebo arm. A majority of the cases on both arms occurred while the patients were on therapy [i.e., enzalutamide: 5.6% (out of 7.5%); placebo: 4.3% (out of 4.8%)].

A majority of the ARs were Grade 3 or 4 on both arms and there was an increase in Grade 3 or 4 events on the enzalutamide arm [6.6% (out of 7.5%)] compared to the placebo arm [3.8% (out of 4.8%)]. Seven patients (0.9%) temporarily withdrew and one patient permanently discontinued enzalutamide due to these AEs. No patients permanently discontinued and one patient temporarily withdrew placebo. These AEs were reported as resolved or resolved with sequelae in a majority of the cases on both study arms [enzalutamide: 4.9% (out of 7.5%); placebo: 3.3% (out of 4.8%)]. Investigator attribution to drug therapy was unlikely or unrelated in all of the reported cases. The spinal cord compression and cauda equina syndrome that occurred in the CRPC2 trial are shown in Table 43.

Table 43: Spinal Cord Compression and Cauda Equine Syndrome (CRPC2 Trial)

	CRPC2 (160 mg) (N=800)		CRPC2 (Placebo) (N=399)	
	All Grades*	Grades 3/4*	All Grades*	Grades 3/4*
	N (%)	N (%)	N (%)	N (%)
Patients with ≥ 1 spinal cord compression or cauda equina syndrome**	60 (7.5%)	53 (6.6%)	19 (4.8%)	15 (3.8%)
Spinal cord compression	53 (6.6%)	48 (6.0%)	18 (4.5%)	15 (3.8%)
Cauda equina syndrome	7 (0.9%)	5 (0.6%)	1 (0.3%)	0 (0.0%)

* Safety cutoff date: 31 Jan 2012

In the CRPC2 trial, Investigators were instructed to report all skeletal-related events on the skeletal-related event (SRE) CRF. These included spinal cord compression and pathologic bone fracture. The study protocol required SREs to be reported only if they met the criteria for an SAE. The SRE CRF did not collect the severity of the SRE events. Based on the SRE dataset, 8.3% (n=66) of the patients treated with enzalutamide and 7.3% (n=29) of the patients treated on the placebo arm experienced a treatment-emergent spinal cord compression.

Reviewer Comment: There was a small increase in spinal cord compression in patients treated with enzalutamide compared to placebo. Disease progression and a longer duration of follow up are potential confounding factors. However, a majority of these AEs occurred while

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

patients were on therapy, the AEs were Grade 3 or 4 in severity, and resulted in a significant number of SAEs.

7.3.5.4 Nonpathologic Fractures

Based on the AE data for the CRPC2 trial (safety cutoff date: 31 Jan 2012), 4.0% (n=32) of the enzalutamide-treated patients experienced nonpathologic fractures compared to 0.8% (n=3) of the placebo-treated patients. The median time of onset for the nonpathologic fractures was 159 days (range: 2 to 574 days) after initiation of therapy. The median age of the patients who experienced nonpathologic fractures was 73 years (range: 57 - 88). Significant past medical history for these patients included three patients with osteopenia and four patients with osteoporosis; all on the enzalutamide arm. Overall on the CRPC2 trial, 5.9% (n=47) of the patients on the enzalutamide arm and 5.0% of the patients on the placebo arm had a past medical history significant for osteopenia or osteoporosis.

FDA review compared the nonpathologic AEs reported in the AE datasets (ADAE) to the skeletal-related events (SRE) reported in the SRE endpoint datasets (TESRE) to remove nonpathologic AEs possibly confounded by disease-related SREs. For this analysis, the incidence of non-pathologic fractures for enzalutamide-treated patients decreased. However, a 3-fold increase over placebo-treated patients [2.5% (n=20) vs. 0.8% (n=3), respectively] was maintained.

Grade 3/4 nonpathologic fractures occurred in 1.4% (n=11) of the patients treated with enzalutamide (all Grade 3) compared to 0.3% (n=1) of the placebo-treated patients (Grade 4). There were 13 nonpathologic fracture SAEs reported in 10 patients (1.3%) on the enzalutamide arm compared to one SAE (0.3%) reported on the placebo arm. On the enzalutamide arm, two patients (#043-04, #606-01) permanently and one patient (#110-07) temporarily discontinued therapy due to nonpathologic fractures. There were no temporary or permanent discontinuations from therapy due to nonpathologic fractures reported on the placebo arm. The nonpathologic fractures resolved/recovered in a majority of the patients who experienced these AEs, but were reported as not recovered/not resolved in 1.9% (n=15) of the enzalutamide-treated patients and 0.5% (n=2) of the placebo patients. Investigator attribution was unlikely or unrelated in all but two cases on the enzalutamide arm [i.e., #043-04 (dental fracture, possible); #904-03 (spinal compression, probable)]. The types of nonpathologic fractures reported in the CRPC2 trial are shown in Table 44.

Table 44: Nonpathologic Fractures (CRPC2 Trial)

	CRPC2 (160 mg) (N=800)		CRPC2 (Placebo) (N=399)	
	All Grades*	Grades 3/4*	All Grades*	Grades 3/4*
	N (%)	N (%)	N (%)	N (%)
Patients with > 1 nonpathologic fracture**	32 (4.0%)	11 (1.4%)	3 (0.8%)	1 (0.3%)
Upper limb	10 (1.3%)	2 (0.3%)	1 (0.3%)	0 (0.0%)
Lower limb	9 (1.1%)	6 (0.8%)	0 (0.0%)	0 (0.0%)

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

	CRPC2 (160 mg) (N=800)		CRPC2 (Placebo) (N=399)	
	All Grades*	Grades 3/4*	All Grades*	Grades 3/4*
	N (%)	N (%)	N (%)	N (%)
Spinal	8 (1.0%)	3 (0.4%)	1 (0.3%)	1 (0.3%)
Thoracic cage	6 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Skull fractures and facial bone	1 (0.1%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Fractures Unspecified	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Dental fracture	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Pelvic fractures	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

* Safety cutoff date: 31 Jan 2012

** More than one type of fracture reported in some patients

Reviewer Comment: To the degree possible, the FDA safety review focused on nonpathologic fractures in this trial. Based on the fall and fall-related injuries data, approximately 1% of the fractures on the enzalutamide arm are likely fall-related. Even after adjusting for these falls, the incidence of nonpathologic fracture remains higher on the enzalutamide treatment arm using either AE or SRE data. In addition, the Applicant's analysis adjusting nonpathologic fracture ARs for time (per 100 patient-years) [5.9 (n=40) vs. 1.7 (n=3)] and the analysis of all fractures (pathologic or non-pathologic) [7.5% (n=60) vs. 4.0% (n=16)] both show increases in patients treated with enzalutamide compared to placebo.

Of the 32 patients who experienced nonpathologic fractures in the CRPC2 trial, 12 patients (1.5% out of 4.0%) on enzalutamide and all three patients (0.8% out of 0.8%) on placebo were treated with bone agents prior to the nonpathologic fracture. All of the placebo-treated patients and nine of the enzalutamide-treated patients received bisphosphonates concomitantly with study therapies. Bisphosphonates were initiated after the start of study therapies (a.k.a., treatment emergent) for two patients on the enzalutamide arm (#044-01, #065-01).

On the CRPC2 trial, patients were treated with bisphosphonates or denosumab (i.e., 3 on enzalutamide; 1 on placebo) before, during, or after receiving study therapy in 56% (n=451) of patients on the enzalutamide arm compared to 53% (n= 211) of the patients on the placebo arm. Out of these patients, 51% (n= 406) and 48% (n=190) received bone targeted agents concomitantly with enzalutamide or placebo, respectively. Out of the patients who received concomitant bone agents, 8% (n=67) and 5% (n= 20) were treatment emergent on the enzalutamide and placebo arms, respectively.

Reviewer Comment: Limited conclusions can be drawn from the small number of nonpathologic fracture AEs that were reported in the CRPC2 trial. Overall in the trial, there was a small increase in the number of patients who received bisphosphonates on the enzalutamide arm compared to the placebo arm. This difference favors the enzalutamide arm, but is not expected to change the interpretation of these safety findings significantly. Compared to the overall study population, a smaller percentage of the patients who experienced nonpathologic fractures were using bisphosphonates (51% vs. 38%, respectively). The overall study population also appears to have underutilized bone preserving therapies (i.e., 92% had bone disease; 55% received them). When evaluating the patients in the United States alone,

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

59% (enzalutamide: 107/181; placebo: 63/107) of the patients on both arms received bisphosphonates or denosumab before, during, or after study therapies. Assuming complete reporting of concomitant medications, this finding suggests that bone preserving drugs were also underutilized in the United States. These findings emphasize the importance of maintaining optimal bone health and initiating bone preserving therapies when indicated, particularly in patients receiving enzalutamide with or after other hormone therapies.

7.3.5.5 Infection

In the CRPC2 trial, 1.0% of the patients treated with enzalutamide experienced deaths related to infections or sepsis compared to 0.3% of the placebo-treated patients. Infection-related SAEs were reported in approximately 6% of the patients on both treatment arms.

7.3.5.6 Hallucinations

In the CRPC2 trial, 1.5% of the patients treated with enzalutamide experienced Grade 1 or 2 hallucinations and delusions not attributed to opioid medications compared to 0.5% of the placebo-treated patients. A majority (1.1% out of 1.5%; n=9) of the hallucinations experienced by patients treated with enzalutamide were visual; with one tactile hallucination and two that were unspecified. None of the non-opioid attributed hallucination AEs were Grade 3 or 4, reported as SAEs, or lead to permanent discontinuation of therapy. Two cases were reported as possibly related to enzalutamide by the Investigator. The visual hallucinations resolved in a majority of the patients, but were ongoing/unresolved in five enzalutamide-treated patients. The median onset time for the hallucinations was 90 days (range: 6 - 423 days) after initiation of study treatment and did not appear to be time-dependent. Potential confounding factors in nine of these cases included other concomitant medications such as opioids and corticosteroids. Regarding concomitant opioid therapy, two cases were censored from this analysis due to the Investigators attributing the visual hallucinations to opioid or pain medications (Patient #139-05 and #650-16).

7.3.5.7 Patients Treated with Concomitant Steroids

Patients enrolled in the CRPC2 trial were permitted to take up to 10 mg per day of prednisone, or an equivalent dose of corticosteroids, or a higher dose if deemed medically necessary. The number of patients taking systemic corticosteroids in the CRPC2 trial was balanced across the treatment arms and included 47.8% (382/800) of the enzalutamide-treated patients compared to 45.6% (182/399) of the placebo-treated patients.

The incidence and types of ARs reported in patients taking concomitant corticosteroids in the CRPC2 trial were comparable to the ARs in the overall CRPC2 safety population. No new safety signals were detected in these patients and there were no significant increases of $\geq 4\%$ in the incidence of any Grade 3 or 4 AEs.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 46 shows the treatment emergent ARs that occurred in the CRPC2 study and the pooled 150-160 mg safety analysis population with an increase in incidence of 2% or greater on the enzalutamide arm compared to the placebo arm.

Table 45: Adverse Reactions with an Increase of $\geq 2\%$ vs. Placebo*

MedDRA System-Organ-Class (SOC) Term	MedDRA Preferred Term (PT)	CRPC2 (160 mg) (N=800)				CRPC2 (Placebo) (N=399)				Safety Analysis Population (Pooled) (150-160 mg) (N=925)*			
		All Grades		Grades 3/4		All Grades		Grades 3/4		All Grades		Grades 3/4	
		N	%	N	%	N	%	N	%	N	%	N	%
General disorders and administration site conditions	Asthenic conditions ^a	408	51.0	72	9.0	178	44.6	37	9.3	479	51.8	81	8.8
	Edema peripheral	123	15.4	8	1.0	53	13.3	3	0.8	147	15.9	8	0.9
Musculoskeletal and connective tissue disorders	Back pain	211	26.4	42	5.3	97	24.3	16	4.0	232	25.1	50	5.4
	Arthralgia	164	20.5	20	2.5	69	17.3	7	1.8	191	20.6	25	2.7
	Musculoskeletal pain	120	15.0	10	1.3	46	11.5	1	0.3	132	14.3	11	1.2
	Muscular weakness	78	9.8	12	1.5	27	6.8	7	1.8	84	9.1	13	1.4
	Musculoskeletal stiffness	21	2.6	2	0.3	1	0.3	0	0.0	23	2.5	2	0.2
Gastrointestinal disorders	Diarrhea	174	21.8	9	1.1	70	17.5	1	0.3	189	20.4	9	1.0
Vascular disorders	Hot flush	162	20.3	0	0.0	41	10.3	0	0.0	180	19.5	0	0.0
	Hypertension	51	6.4	17	2.1	11	2.8	5	1.3	58	6.3	22	2.4
Nervous system disorders	Headache	97	12.1	7	0.9	22	5.5	0	0.0	106	11.5	8	0.9
	Dizziness ^b	76	9.5	4	0.5	30	7.5	2	0.5	90	9.8	6	0.6
	Spinal cord compression and cauda equina syndrome	60	7.5	53	6.6	19	4.8	15	3.8	64	6.9	56	6.1
	Paraesthesia	53	6.6	0	0.0	18	4.5	0	0.0	56	6.1	0	0.0
	Mental impairment disorders ^c	34	4.3	2	0.3	7	1.8	0	0.0	45	4.9	2	0.2
	Hypoaesthesia	32	4.0	2	0.3	7	1.8	0	0.0	37	4.0	0	0.0
	Epistaxis	26	3.3	1	0.1	5	1.3	1	0.3	28	3.0	1	0.1

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Infections and infestations	Upper respiratory tract infections ^d	87	10.9	0	0.0	26	6.5	1	0.3	98	10.6	0	0.0
	Lower respiratory tract and lung infections ^e	66	8.3	17	2.1	18	4.5	4	1.0	70	7.6	18	1.9
Psychiatric disorders	Insomnia	70	8.8	0	0.0	24	6.0	2	0.5	79	8.5	0	0.0
	Anxiety	52	6.5	2	0.3	16	4.0	0	0.0	55	5.9	2	0.2
Renal and urinary disorders	Hematuria	55	6.9	14	1.8	18	4.5	4	1.0	61	6.6	17	1.8
	Pollakiuria	38	4.8	0	0.0	10	2.5	0	0.0	50	5.4	0	0.0
Injury, poisoning and procedural complications	Fall	37	4.6	2	0.3	5	1.3	0	0.0	42	4.5	4	0.4
	Nonpathologic fractures	32	4.0	11	1.4	3	0.8	1	0.3	39	4.2	13	1.4
Skin and subcutaneous tissue disorders	Pruritus	30	3.8	0	0.0	5	1.3	0	0.0	32	3.5	0	0.0
	Dry skin	28	3.5	0	0.0	5	1.3	0	0.0	33	3.6	0	0.0

* Safety Cutoff Date: 31 Jan, 2012

a MedDRA HLT term: Includes asthenia and fatigue

b Includes MedDRA PT terms dizziness and vertigo

c MedDRA HLGT term: Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention

d MedDRA HLT term: Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, laryngitis

e MedDRA HLT term: Includes pneumonia, lower respiratory tract infection, bronchitis, lung infection

Based on the 60-day safety update (safety cutoff date: 31 Jan 2012), nearly all of the patients on both arms in the CRPC2 trial experienced at least one AE (i.e., 98.3% for enzalutamide; 97.5% for placebo). The most common ARs ($\geq 5\%$ and $> 2\%$ compared to placebo) reported in patients receiving enzalutamide in the randomized clinical trial were asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, dizziness, spinal cord compression and cauda equina syndrome, muscular weakness, insomnia, lower respiratory infection, hematuria, paresthesia, anxiety, and hypertension. Grade 3 and 4 ARs were reported among 47% of enzalutamide- treated patients and 53% of placebo-treated patients. The most common Grade 3 and 4 ARs ($>2\%$ and $>$ placebo) reported in patients receiving enzalutamide were spinal cord compression and cauda equina syndrome, back pain, arthralgia, hypertension, and lower respiratory tract infections.

7.4.2 Laboratory Findings

Table 46 below shows the treatment-emergent laboratory findings from the CRPC2 clinical trial.

Table 46: Treatment Emergent Laboratory Findings*

	Enzalutamide N = 797		Placebo N = 395	
	All Grades N (%)	Grades 3/4 N (%)	All Grades N (%)	Grades 3/4 N (%)
Hematology				
<i>Neutropenia</i>	121 (15%)	9 (1%)	25 (6%)	0
Lymphopenia	294 (37%)	71 (9%)	157 (40%)	47 (12%)

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

	Enzalutamide N = 797		Placebo N = 395	
	All Grades N (%)	Grades 3/4 N (%)	All Grades N (%)	Grades 3/4 N (%)
Low Hemoglobin	633 (79%)	36 (5%)	321 (81%)	21 (5%)
Thrombocytopenia	64 (8%)	4 (0.5%)	28 (7%) ¹	4 (1%) ¹
Chemistry				
AST	186 (23%)	3 (0.4%)	146 (37%)	4 (1%)
ALT	81 (10%)	2 (0.3%)	72 (18%)	2 (0.5%)
Bilirubin	23 (3%)	2 (0.3%)	7 (2%)	1 (0.3%)
Creatinine	77 (10%)	0	49 (12%)	1 (0.3%)
Hyperglycemia	720 (90%)	18 (2%)	342 (86%)	10 (3%)
Hyperkalemia	28 (4%)	2 (0.3%)	19 (5%)	3 (0.8%)
Hypokalemia	29 (4%)	6 (0.8%)	22 (6%)	4 (1%)
Hypermagnesemia	68 (9%)	0	44 (11%)	1 (0.3%)
Hypercalcemia	25 (3%)	1 (0.1%)	12 (3%)	0
Hypocalcemia	76 (10%)	13 (2%)	46 (12%)	15 (4%)
Hypophosphatemia	96 (12%)	23 (3%)	37 (9%)	10 (3%)
AST	186 (23%)	3 (0.4%)	146 (37%)	4 (1%)

* Safety cutoff date: 31 Jan 2012

¹N = 395

With the exception of neutropenia and hyperglycemia, the hematology and chemistry laboratory tests analyzed were comparable across the enzalutamide and placebo arms in the CRPC2 trial.

There was an increase in all Grade (15% versus 6%) and Grades 3 / 4 (1% versus 0%) neutropenia on the enzalutamide arm of the study compared to the placebo arm. For the nine patients (1%) on the enzalutamide treatment arm who experienced Grade 3 or 4 neutropenia, there were no deaths due to AEs or infection-related causes. One patient (#300-09) died within 30 days of the neutropenia event due to thrombocytopenia and cerebrovascular hemorrhage attributed to disease progression and "massive medullary invasion by the prostate tumor cells". Seven of the nine Grade 3 / 4 neutropenia AEs resolved based on the final neutrophil count while on enzalutamide therapy. The other two patients [#300-09; #311-05] died of disease progression prior to neutropenia resolution. Three patients (#025-09, #201-02, #355-03) experienced transient infection-related AEs (i.e., oral fungal, urinary tract infection, and nasopharyngitis; respectively) during the neutropenic events. There were no clear risk factors identified that predisposed enzalutamide- treated patients to an increased risk of neutropenia. None of the patients who experienced Grade 3 or 4 neutropenia had Grade 2 or greater neutropenia at study baseline; two patients (#300-09 and #355-03) had baseline neutrophil levels less than 2.0 GI/L; three patients had a past medical history significant for pancytopenia (#300-09; #355-03; #011-02).

In the CRPC2 trial, there was an increase in Grades 1-4 hyperglycemia (90% versus 86%), with no increase in Grades 3 and 4 hyperglycemia (2% versus 3%), on the enzalutamide arm compared to the placebo arm. There were also more treatment emergent hyperglycemia AEs reported on the placebo arm (2.3% versus 0.6%), and Grade 3 hyperglycemia AEs reported on the placebo arm were higher (0.8% versus 0.1%; no Grade 4 AEs reported). However,

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

only one patient (enzalutamide arm, #814-03) reported a worsening of diabetes AE in the CRPC2 trial.

There were no patients meeting Hy's Law criteria. One patient in each treatment group had ALT or AST ≥ 3 times the upper limit of normal with a concurrent total bilirubin (Tbili) ≥ 2 times the upper limit of normal. The patient (#453-01) on the enzalutamide arm was admitted to the hospital on Study Day (b) (6) days after discontinuing enzalutamide for "aggravation of general clinical condition." During his hospitalization, an abdominal ultrasound showed ubiquitous lesions throughout the hepatic parenchyma consistent with hepatic metastases. Over the next (b) (6) days his condition worsened with increasing bilirubin levels. On Study Day (b) (6) the patient died from PD. The primary cause of death on his death certificate was adenocarcinoma of the prostate with hepatic metastases and hepatic insufficiency.

Reviewer Comment: Other anti-androgenic drugs approved for mCRPC have been associated with severe and fatal hepatic toxicity with marked increases in liver enzymes. On the CRPC2 trial, no patients appear to have experienced severe drug-related hepatotoxicity based on AE reporting and laboratory monitoring. FDA will continue to monitor for severe liver toxicities related to enzalutamide in the ongoing clinical trials and postmarketing reports.

Hypercholesterolemia has also been associated with other anti-androgenic drugs, but was not measured in the CRPC2 trial, so it is unclear if enzalutamide has negative effects on serum lipid levels.

7.4.3 Vital Signs

Vital signs were obtained at screening and during each follow up visit. Table 47 shows the findings related to blood pressure, pulse rate, and temperature.

Table 47: Vital Signs in CRPC2 Study*

Vital Signs	Enzalutamide N (%)	Placebo N (%)
Patients with baseline and post-baseline vital signs	800 (100%)	399 (100%)
Systolic Blood Pressure (mmHg)		
> 180 and > 40 increase	26 (3.3%)	8 (2.0%)
< 90 and > 30 decrease	12 (1.5%)	5 (1.3%)
Diastolic Blood Pressure (mmHg)		
> 105 and > 30 increase	5 (0.6%)	3 (0.8%)
< 50 and > 20 decrease	9 (1.1%)	3 (0.8%)
Any of the above SBP or DBP Abnormalities		
Any of the above SBP or DBP abnormalities	46 (5.8%)	18 (4.5%)
Pulse Rate (BPM)		
< 50 and > 20 decrease	13 (1.6%)	1 (0.3%)
> 120 and > 30 increase	4 (0.5%)	5 (1.3%)
Any of the above pulse rate abnormalities	17 (2.1%)	6 (1.5%)
Temperature (°C)		
> 38° C and > 1° C increase	9 (1.1%)	8 (2.0%)

* Safety cutoff date: 31 Jan 2012).

Reviewer Comment: There are no differences in the incidence of vital sign abnormalities of > 1.5% when comparing study arms. Weight was not collected after the screening visit, therefore an analysis of weight changes while being treated with enzalutamide was not conducted.

7.4.4 Electrocardiograms (ECGs)

The Applicant conducted a thorough QT/QTc substudy in the CRPC2 trial. Triplicate ECGs (i.e., three separate recordings at 15 minute intervals) were obtained on Days 1, 8, 29, and 57 prior to drug administration. Single ECGs were also collected at Screening, Days 85, 113, 141, 169, every 12 weeks thereafter while patients received therapy, and at the safety follow up visit. The ECGs were evaluated by an independent core ECG laboratory (b) (4) by a limited number of readers. A total of 796 subjects treated with enzalutamide had safety assessments available for analysis.

The submitted ECG data was reviewed by the FDA’s Interdisciplinary Review Team (IRT) for QT studies. The IRT team review concludes that there was no significant QTc prolongation for enzalutamide at the 160 mg PO QD dose. The QTc change from baseline and placebo was 6.5 ms (90%CI: 4.8, 8.3) at Week 13 of treatment. The QTc interval change appears to be concentration dependent. There were no large differences (i.e., greater than 20 ms) observed

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

between the mean QT interval change from baseline in patients treated with enzalutamide or compared to patients treated with placebo, based on the Fridericia correction method.

Thirteen patients in the CRPC2 trial had a post-baseline QTcF of > 500 ms or an increase of > 60 ms compared to the QTcF reported at baseline. Nine patients (1.1%) treated with enzalutamide compared to one patient treated with placebo (0.3%) experienced a post-baseline QTcF of > 500 ms. Five of the enzalutamide-treated patients (#011-02, #037-03, #043-01, #054-04, and #110-13), and none treated with placebo, had with a QTcF of > 500 ms and an increase of > 60 ms from baseline. The median onset of QTc prolongation of > 500 ms was 29 days (range: 1 - 262 days). For three events (#011-02, #043-01, #302-39) the isolated QTcF value > 500 ms were observed prior to Study Day 8. Patient #315-09 reported QTcF values of > 500 ms on Study Days 59, 115, and 262. Five patients (#011-02, #037-03, #043-01, #054-04, and #302-39) had subsequent QTcF values on study that were lower.

A majority of the cases of QTc prolongation that occurred in enzalutamide-treated patients have potential confounding factors that suggest the events were not drug related. Of the nine enzalutamide-treated patients with a QTcF > 500 ms, four cases were confounded by patient-related factors. Two patients (#057-01, #650-17) had pre-existing QTcF prolongation on the screening ECGs. Patient #054-04's QTc prolongation was associated with hypokalemia (2.3 mEq/L). Patient #110-13 was taking concomitant solifenacin and metoclopramide, two medications associated with QTc prolongation. Of the eight enzalutamide-treated patients with a post-baseline QTcF > 60 ms compared to baseline, five cases are likely related to the patients underlying cardiovascular disease or other concomitant medications. Regarding past medical histories: Patient #011-02 had coronary artery disease with a prior CABG, CHF, hypertension, and diabetes; Patient #043-01 had a complete AV block; Patient #047-01 had hypertension and bradycardia; and Patient #303-18 had atrial fibrillation, effort dyspnea, and was also taking metoclopramide. Patient #817-03 had a history of hypertension, hyperlipidemia, and intermittent dizziness, and was taking solifenacin, haloperidol, and prochlorperazine. Therefore, four of the five cases of QTc > 500 and > 60 msec increase from baseline are significantly confounded.

None of the patients with QTcF prolongation reported Torsades de Pointes or ventricular arrhythmia AEs. Out of the 13 patients, three experienced cardiac AEs. Two of the AEs were related to heart failure and were serious, but both men (#011-02, #057-01) had confounding heart disease at baseline (i.e., CHF/CABG, atrial fibrillation/sick sinus syndrome/pacemaker, respectively). Patient #331-09, a 75-year old man, experienced a nonserious Grade 2 "prefibrillatory state" arrhythmia. All of these AE resolved and the Investigator attribution for all three AEs was reported as "unlikely related" or "unrelated".

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

Reviewer Comment: The ECG results from the substudy in this trial did not show evidence of clinically significant increases in the QTcF interval in enzalutamide-treated patients. Cardiac AEs (6.6% vs. 7.8%, respectively), cardiac arrhythmias (HLGT term, 4.4% vs. 4.5%, respectively), and Torsades de Pointes (1.4% vs. 1.5%, respectively) were all less common on the enzalutamide arm of the CRPC2 trial compared to the placebo arm. Deaths attributed to cardiac AEs were also less common on the placebo arm (0.4% vs. 0.5%). FDA will continue to monitor future controlled clinical trials and postmarketing safety reports for potential cardiac safety signals.

See the Interdisciplinary Review Team (IRT) review filed under this NDA for more information.

7.4.5 Immunogenicity

Not Applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There were 33 patients treated with enzalutamide at doses of < 150 mg once a day (QD) and 85 patients treated at dose of 240 mg to 600 mg PO QD. At higher doses of enzalutamide, the incidence of asthenic conditions and seizures, both leading to permanent discontinuation of treatment in some patients, were increased. When the < 150 mg, 150-160mg, and > 160 mg doses of enzalutamide were compared from the trials included in the pooled safety database, no dose dependent differences in Grade 3 or 4 AEs were identified other than these conditions. There was an increase in Grade 1 and 2 dysgeusia [3.0%, 5.5%, and 16.5%, respectively (vs. 3.5% for placebo)] and small increases (~ 3-4%) in Grade 1 and 2 nausea, muscular weakness, hypertension, and depression at the higher doses.

Reviewer Comment: With the exception of seizures, the clinical significance of the other modest increases in AEs at higher doses is not known. Definitive conclusions can not be made due to the small number of patients assessed at enzalutamide doses other than 150-160 mg and the nature of cross study comparisons using pooled open label trials.

7.5.2 Time Dependency for Adverse Events

There were no new safety signals detected based on time dependency. In the original NDA submission, the Applicant submitted an analysis of the most common AEs within the first 60 days of treatment with study products compared to treatment through Day 180. The AEs reported within the first 60 days of treatment with an increase of 2% or greater compared to placebo were headache, insomnia, hot flush, and hypertension. Headache, insomnia, and hot flush also had a two-fold decrease in incidence when comparing between Days 1–60 and Days 61–180 of therapy. Grade 3/4 fatigue was also more common within 60 days of initiating

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

enzalutamide (3.0%) compared to Days 61–180 (1.8%). Grade 3/4 anemia, back pain, and spinal cord compression were more common between days 61–180 of enzalutamide exposure.

Given the long half life of enzalutamide, FDA was concerned that AEs may be slow to resolve and requested additional information from the Applicant related to AE resolution. The Applicant provided a response to the FDA information request [July 11, 2012 (STN 0008)] that included an analysis of the time to resolution of AEs that lead to dose interruptions and/or dose reductions. Table 48 shows the findings from the Applicant’s analysis.

Table 48: Time to Resolution of Treatment Emergent AEs Leading to Dose Modification

(copied from Applicant’s submission)

	MDV3100 160 mg	Placebo	Total
Time(Days) to Resolution of Adverse Event Leading to Dose Interruption			
n	148	93	241
Mean (SD)	19.0 (33.33)	14.0 (15.88)	17.1 (27.98)
Median	9.0	7.0	8.0
Min, Max	1.0, 250.0	1.0, 77.0	1.0, 250.0
Time(Days) to Resolution of Adverse Event Leading to Dose Reduction			
n	9	5	14
Mean (SD)	36.3 (49.91)	14.0 (19.22)	28.4 (42.07)
Median	21.0	5.0	18.0
Min, Max	3.0, 165.0	2.0, 48.0	2.0, 165.0
Time(Days) to Resolution of Adverse Event Leading to Any Dose Modification[1]			
n	157	98	255
Mean (SD)	19.9 (34.51)	14.0 (15.95)	17.7 (28.93)
Median	9.0	7.0	8.0
Min, Max	1.0, 250.0	1.0, 77.0	1.0, 250.0

n - number of events

[1] Dose modification include dose interruption and dose reduction

Source: irina.walsh MDV3100\AFFIRM\FDA_Requests\programs\t_dosemod_ae.sas 11JUL12:10:02 Output File: t_dosemod_ae.rtf

The median time to resolution of AEs that lead to dose interruption was 9 days on the enzalutamide arm and 7 days on the placebo arm; and was 21 days for AEs leading to dose reduction compared to 5 days, respectively.

Reviewer Comment: Limited conclusions can be drawn from the AE resolutions leading to dose reductions given the small number of cases. The time to resolution (9 day median) for dose interruptions suggests that enzalutamide should be held for one week or more for severe toxicities before restarting the drug at a reduced dose when therapy is still indicated. The time to resolution of dose reductions (median 21 days) also suggests that dose titration of enzalutamide to manage ARs should be done over several weeks.

7.5.3 Drug-Demographic Interactions

7.5.3.1 Comparison of Adverse Reactions in Older Patients

No overall differences in drug exposure or safety were identified when older and younger patients were compared in the CRPC2 trial. Exploratory analysis for age categories identified comparable AR incidences and severities for most of the enzalutamide ARs.

In the CRPC2 trial, the median age of patients on both arms was 69 years of age. Approximately 70% (n=568) of the patients were 65 years of age or older and 25% (n=199) were 75 years or older. Of the 909 patients treated in the 150-160 mg safety analysis population, 71% (n= 641) and 26% (n= 233) were 65 years or older or 75 years or older, respectively.

There were no safety concerns related to enzalutamide exposure in elderly patients. Based on the original NDA data, the duration of drug exposure was longer in patients who were 65 years of age or older compared to patients less than 65 years of age (median: CRPC2= 38 vs. 33 weeks; ISS = 36 vs. 29 weeks) and longer in patients 75 years of age or older compared to patients less than 75 years of age (median: CRPC2= 45 vs. 36 weeks; ISS = 40 vs. 32 weeks).

For the most common ARs reported in enzalutamide-treated patients, patients who were 65 years of age or older had comparable AR incidence rates and AR severities to patients less than 65 years of age. There were no Grade 1-4 ARs with an incidence rate that increased by more than 5% or any Grade 3 or 4 ARs with an increase of more than 2%. When comparing the incidence of common ARs for patients 75 years or older to patients less than 75 years of age, most of the ARs were also comparable with no increase of more than 10% for Grade 1-4 ARs and no increase in Grade 3 / 4 ARs of more than 5%. The comparison of ARs of interest for age category comparisons are shown in Table 49.

Table 49: Exploratory Safety Analysis by Age Groups

	Enzalutamide (n=800)							
	Age < 65 (n=232)		Age ≥ 65 (n=568)		Age < 75 (n=601)		Age ≥ 75 (n=199)	
	Grades 1-4	Grades 3/4	Grades 1-4	Grades 3/4	Grades 1-4	Grades 3/4	Grades 1-4	Grades 3/4
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Any Adverse Event	225 (97.0%)	102 (44.0%)	562 (98.9%)	280 (49.3%)	588 (97.8%)	275 (45.8%)	199 (100%)	107 (53.8%)
ARs with an increase in older patients of > 5% for Grade 1-4, > 2% for Grade 3/4, or of interest in older patients								
Fatigue	79 (34.1%)	13 (5.6%)	196 (34.5%)	38 (6.7%)	195 (32.4%)	32 (5.3%)	80 (40.2%)	19 (9.5%)
Peripheral Edema	28 (12.1%)	1 (0.4%)	95 (16.7%)	7 (1.2%)	78 (13.0%)	2 (0.3%)	45 (22.6%)	6 (3.0%)
Hematuria	19 (8.2%)	2 (0.9%)	36 (6.3%)	12 (2.1%)	42 (7.0%)	7 (1.2%)	13 (6.5%)	7 (3.5%)

Clinical Review of NDA 203415 for XTANDI (enzalutamide)

Proposed for Treatment of Castration-Resistant Prostate Cancer after Prior Docetaxel Chemotherapy

	Enzalutamide (n=800)							
	Age < 65 (n=232)		Age ≥ 65 (n=568)		Age < 75 (n=601)		Age ≥ 75 (n=199)	
	Grades 1-4	Grades 3/4	Grades 1-4	Grades 3/4	Grades 1-4	Grades 3/4	Grades 1-4	Grades 3/4
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Dizziness/ Vertigo	16 (6.9%)	0 (0.0%)	60 (10.6%)	4 (0.7%)	58 (9.7%)	1 (0.2%)	18 (9.0%)	3 (1.5%)
Hypertension	13 (5.6%)	2 (0.9%)	38 (6.7%)	15 (2.6%)	37 (6.2%)	10 (1.7%)	14 (7.0%)	7 (3.5%)
ARs with an increase in younger patients								
Hot Flush	60 (25.9%)	0 (0.0%)	102 (18.0%)	0 (0.0%)	131 (21.8%)	0 (0.0%)	31 (15.6%)	0 (0.0%)

The overall incidence of Grades 1-4 ARs were all close to 100% and were comparable across the age categories for these analyses. There was a small increase in overall Grade 3 and 4 ARs when comparing older and younger patients, but the overall incidence rate of Grade 3 / 4 ARs in older patients treated with enzalutamide remained less than patients who were treated with placebo. In patients 65 years of age or older treated with enzalutamide, the increase in Grade 3 / 4 ARs was from 44% to 49% compared to patients < 65 years of age. In patients treated with enzalutamide that were 75 or older, there was an increase from 46% to 54% in Grade 3 / 4 ARs compared to patients 75 years of age or less. However, for patients 65 years of age or older, the incidence of Grade 3 or 4 ARs in the enzalutamide-treated patients remained less than the incidence of Grade 3 or 4 ARs in the placebo arm (49% vs. 54%, respectively). Similarly, for patients 75 years of age or older, the incidence of Grade 3 or 4 ARs in the enzalutamide-treated patients remained less than the incidence of Grade 3 or 4 ARs in the placebo arm (54% vs. 55%, respectively). The largest increases in Grade 3 or 4 ARs were Grade 3 / 4 fatigue (i.e., 5% to 10%) and peripheral edema (0.3% to 3%) when comparing patients 75 years of age or older to patients < 75 years. For Grade 3 / 4 fatigue, the incidence rate on the placebo arm was 8% for patients 75 or older, which is comparable to the incidence rate (10%) of the enzalutamide-treated patients who were 75 years of age or older. For peripheral edema and hematuria, the small number of cases of Grade 3 or 4 ARs (n= 6 and n=7 respectively) and small increases limit the conclusions and clinical relevance of this exploratory finding. Hot flush ARs were more common in younger patients, but there were no Grade 3 or 4 ARs reported in any patients.

Reviewer Comment: The clinical significance of the small increases in the incidence of total and select Grade 3 and 4 ARs appears to be insignificant since the overall incidence remains less than or comparable to the incidence on the placebo arm. The small increases in the selected ARs may also be related to underlying patient comorbidities that increase during aging since there was a corresponding increase in these incidence rates with age on the placebo arm.

Also see Section 7.5.3 of this review for an analysis of falls and nonpathologic fracture age considerations and analyses.

7.5.4 Drug-Drug Interactions

In vitro, enzalutamide is metabolized by CYP2C8 and CYP3A4. In vivo results suggest that CYP2C8 is primarily responsible for the formation of the active metabolite - N-desmethyl enzalutamide (M2). In vivo, the sum of enzalutamide and M2 exposure was increased when it was co-administered with gemfibrozil (strong CYP2C8 inhibitor) or itraconazole (strong CYP3A4 inhibitor).

In vitro, enzalutamide, M1 and M2 caused direct inhibition of multiple CYP enzymes including CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. Enzalutamide also caused time-dependent inhibition of CYP1A2. Among these enzymes, the IC50 of CYP2C8 was the lowest. However, enzalutamide at steady state did not cause a clinically relevant change in the AUC of pioglitazone (CYP2C8 substrate) in vivo. In vitro, enzalutamide caused induction of CYP3A4. In vivo, enzalutamide can be classified as a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. In vitro, enzalutamide, M1 and M2 are not substrates for human P-glycoprotein (P-gp). In vitro, enzalutamide and M2 are inhibitors of P-gp, while M1 is not an inhibitor of P-gp.

Reviewer Comment: The Clinical Pharmacology reviewer recommends the following regarding enzalutamide administration:

- *If co-administration with a strong CYP2C8 or a strong CYP3A4 inhibitor cannot be avoided, the daily enzalutamide dose should be reduced to 80 mg or 120 mg, respectively.*
- *The effects of a CYP2C8 inducer or a CYP3A4 inducer on the PK of enzalutamide are not known, and co-administration with CYP2C8 and/or CYP3A4 inducers (e.g., rifampin) should be avoided.*
- *Co-administration with CYP3A4, 2C9, and 2C19 substrates with a narrow therapeutic index should be avoided.*

See the Clinical Pharmacology review for more information.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Enzalutamide is not genotoxic. Long-term animal studies have not been conducted to evaluate carcinogenic potential. Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not clastogenic in either the *in vitro* cytogenetic assay with mouse lymphoma cells or the *in vivo* mouse micronucleus assay.

See the nonclinical pharmacology toxicology review for more information.

7.6.2 Human Reproduction and Pregnancy Data

Dedicated developmental or reproductive studies were not conducted with enzalutamide. The major findings in general toxicology studies in rats and dogs included atrophy of the prostate

and epididymis and decreased weight of reproductive organs. These findings are consistent with the anti-androgenic mechanism of action for enzalutamide. Although unlikely to be used in women (outside the context of clinical trials), enzalutamide is thus contraindicated in pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Based on increased incidence of seizures that were observed at doses higher than 160 mg (3.5%; 3/85 patients), patients may be at increased risk of seizures following an overdose. One overdose was reported in the clinical trial database. This was a patient in study S-3100-1-01 who was assigned a dose of 240 mg per day, but received 640 mg per day for 8 days. During this period, AEs for Grade 2 fatigue and asthenia were reported and were self limiting. Enzalutamide was studied in an early phase dose-escalation study (S-3100-1-01) of castration-resistant prostate cancer patients in daily doses ranging from 30 mg to 600 mg. Five dose-limiting toxicities were observed in four patients at doses exceeding 160 mg per day. These included three seizures [1 each at 360 mg, 480 mg, and 600 mg doses (600 mg case was with confusion)] and rash (1 at 600 mg). The Applicant determined the maximum tolerated dose was determined was 240 mg PO QD. The 160 mg PO QD dose was selected for future development based on the comparable anti-tumor activity, the dose-dependent increase in fatigue that led to dose reductions at the higher doses studied, and the increased risk of seizures at doses > 240 mg.

There is no reason to believe that enzalutamide has any potential for drug abuse in the intended or other populations.

There is no evidence of withdrawal or rebound phenomena associated with discontinuation of enzalutamide in the CRPC2 trial. The Applicant provided data that shows a lower incidence of Grades 1-4 AEs for enzalutamide-treated patients compared to the placebo arm (29.0% vs. 34.3%) and a comparable incidence for Grades 3 and 4 AEs (14.8% vs. 14.6%, respectively) and SAEs (10.8% vs. 11.3%, respectively) after discontinuation of drug therapy to the end of the safety reporting period.

8 Postmarket Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

See footnotes on pages where references were inserted.

9.2 Labeling Recommendations

At the time of completion of this clinical review, labeling is ongoing. Please see the final product label that reflects recommended changes.

9.3 Advisory Committee Meeting

This NDA was not presented to advisory committee because the benefit risk profile demonstrated for MDV3100 is clearly favorable for its use in the intended patient population. There were no controversial issues identified prior to or during the review that would necessitate an advisory committee meeting.

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

/s/

YANGMIN NING
08/19/2012

WILLIAM F PIERCE
08/19/2012

VIRGINIA E MAHER
08/19/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203415 Applicant: Medivation Inc. Stamp Date: May 22, 2012

**Drug Name: Enzalutamide NDA/BLA Type: Type 1- New
(Xtandi, proposed but not finalized) Molecular Entity**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	Not indicated with the key study in support of the proposed indication
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Section 2.5 Clinical Overview (2.5.6)
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study S-3100-1-01 "A Phase 1, Open-label, Dose-Escalation Safety and Pharmacokinetic Study of MDV3100 in Patients with Castration-Resistant Prostate Cancer" Sample Size: 140 Arms: Single Location in submission: 5.3.5.2. S-3100-1-01	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			Two recently approved products, abiraterone acetate and

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p>Pivotal Study #1: “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”</p> <p>Proposed Indication: “for the treatment of patients with castration-resistant prostate cancer who have received docetaxel (b) (4)”</p> <p>Pivotal Study #2: none</p>				cabazitaxel, were also studied in patients with metastatic CRPC who have previously received docetaxel-based therapy, and were associated with an improvement in overall survival in the patient population.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	Twenty four percent of the patients were from the United States. In addition, the study patients represent a well-characterized population.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			5.3.5.1: Appendix 16.2.8.7, Cardiac Safety Report (CRPC2 trial); CRPC2 ERT Datasets
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			A summary of the human exposure from all enzalutamide clinical trials or confirmation that the safety information provided in the NDA is complete is required. An FDA Information Request (IR) was sent on 6/11/2012. In a 6/14/2012 response to the FDA IR, the Applicant agreed to submit this

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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					information to the NDA on or before 6/28/2012.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			- CRPC2, s-3100-1-01, Clinical Study Report (CSR) (14.3.3) - CRPC-MDA-1 CSR (12.3.2) - 9785-CL-0111, 9785-CL-0321, 9785-CL-0222, and 9785-CL-0007 (eCTD 5.3.5)
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	The U.S. was the highest enrolling country in the CRPC2 trial (24.0%) with 288 patients.
DATASETS					

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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	Content Parameter	Yes	No	NA	Comment
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____ Yes ____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Drs. Ning and Pierce

 Reviewing Medical Officer

June 14, 2012

_____ Date

Dr. Maher

 Clinical Team Leader

Please date if you agree

_____ Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

WILLIAM F PIERCE
06/15/2012

YANGMIN NING
06/18/2012

VIRGINIA E MAHER
06/18/2012