# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 203415Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

| Clinical Pharmacology Review | |
|---|---|
| **FDA** | 20-3415 (IND 74,563) |
| **Submission Date:** | 5/22/12 |
| **Brand Name:** | Xtandi™ |
| **Generic Name:** | Enzalutamide |
| **Formulation:** | 40 mg capsules |
| **OCP Reviewer:** | Jeanne Fourie Zirkelbach, PhD |
| **OCP Team Leader:** | Qi Liu, PhD |
| **Pharmacometrics Reviewer:** | Dhananjay D. Marathe, PhD |
| **Pharmacometrics Team Leader:** | Nitin Mehrotra, PhD |
| **OCP Division:** | Division of Clinical Pharmacology V |
| **ORM Division:** | Division of Drug Oncology Products |
| **Sponsor:** | Medivation Inc. |
| **Submission Type; Code:** | NDA 0000/01 |
| **Dosing regimen:** | Once daily oral dose of 160 mg of enzalutamide. |
| **Indication:** | For the treatment of castration-resistant prostate cancer who have received docetaxel (b) (4). |

OCP Briefing was held on August 6, 2012 and was attended by OCP staff, Dr. Amna Ibrahim and Dr. Max Ning and Dr. Katherine Fedenko.

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Reference ID: 3175035

## 1 Executive Summary

Enzalutamide is an androgen receptor inhibitor that targets steps in the androgen receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors, inhibit activated androgen receptor nuclear translocation, and inhibit activated androgen receptor association with DNA. A major metabolite, N-desmethyl enzalutamide (M2), exhibited similar *in vitro* activity to enzalutamide. The proposed indication is for the treatment of patients with metastatic castration-resistant prostate cancer who have received docetaxel (b) (4).

The phase 3 trial (CRPC2) was a randomized, placebo-controlled, double blind trial in patients with metastatic castration-resistant prostate cancer (CRPC) previously treated with docetaxel-based chemotherapy. Patients were randomized 2:1 to receive either enzalutamide (160 mg daily) (N=800) or placebo (N=399). The primary endpoint was overall survival (OS), and the final analysis showed that OS was statistically significantly prolonged on the enzalutamide arm compared to the placebo arm. Based on the results of Phase 3 trial, no exposure-response relationship for the efficacy endpoint of overall survival (OS) could be identified for enzalutamide within a single fixed dose of 160 mg/day. There were no clinically meaningful exposure-response relationships for fatigue, flushing, headache, or hypertension within the limited exposure range for 160mg/day. The effect of enzalutamide 160 mg/day at steady state on the QTc interval was evaluated in 796 patients with castration-resistant prostate cancer. No large difference (i.e., greater than 20 ms) was observed between the mean QT interval change from baseline in patients treated with XTANDI and that in patients treated with placebo, based on the Fridericia correction method.

Following oral administration of enzalutamide at 160 mg in patients with metastatic CRPC, the median time to reach maximum plasma enzalutamide concentrations is 1 hour (range 0.5 to 3 hours). The enzalutamide mean terminal elimination half-fife ($T_{1/2}$), in patients with metastatic CRPC, following a single oral dose is 5.8 days (range 2.8 to 10.2 days). With daily dosing regimen, enzalutamide steady state is achieved by Day 28, and enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in enzalutamide plasma concentrations are low (mean peak-to-trough ratio of 1.25). At steady state, enzalutamide shows approximately dose proportional pharmacokinetics over the daily dose range of 30 to 360 mg. In patients with MCRP cancer, the mean (%CV) predose $C_{min}$ values for enzalutamide and M2 were 11.4 (25.9%) µg/mL and 13.0 (29.9%) µg/mL, respectively.

The single dose pharmacokinetics of the major active metabolite M2 was characterized in healthy volunteers following a single 160 mg oral dose of enzalutamide. The median $T_{max}$ for M2 is 6 days (range 2 to 13 days). The mean terminal half-life for M2 is 8.6 days (%CV: 21%).

The human mass balance trial showed that enzalutamide is primarily eliminated by hepatic metabolism. The extent of enzalutamide absorption was not significantly altered by a high-fat meal. A dose reduction is not needed in patients with mild or moderate renal impairment, or mild or moderate hepatic impairment. The effect of severe renal impairment or severe hepatic impairment on the pharmacokinetics of enzalutamide is not known.

In vitro, enzalutamide is metabolized by CYP2C8 and CYP3A4. In vivo results further 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 by 2.2-fold and 1.3-fold when it was co-administered with gemfibrozil (strong CYP2C8 inhibitor) or itraconazole (strong CYP3A4 inhibitor), respectively. If the co-administration of enzalutamide with a strong CYP2C8 inhibitor cannot be avoided, the daily enzalutamide dose should be reduced to 80 mg. The effects of a CYP2C8 inducer or a CYP3A4 inducer on the PK of enzalutamide are not known, and co-administration of enzalutamide

with CYP2C8 and/or CYP3A4 inducers (e.g. rifampin) should be avoided.

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 $IC_{50}$ 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. Therefore, co-administration of enzalutamide with CYP3A4, 2C9, and 2C19 substrates with a narrow therapeutic index should be avoided. 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.

**Recommendations**
The Office of Clinical Pharmacology (Divisions of Clinical Pharmacology 5 and Pharmacometrics) have reviewed the information contained in NDA 20-3415. This NDA is considered acceptable from a clinical pharmacology perspective.

**Labeling Recommendations**
Please refer to Section 3 - Detailed Labeling Recommendations.

### 1.2 Phase IV Requirements

1. Perform an in vitro screen to determine if N-desmethyl enzalutamide is metabolized by the major human CYP450 isozymes. Based on results from the in vitro screen, clinical drug-drug interaction trials may be needed.
2. 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.
3. 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 protocol must be submitted for review prior to trial initiation.
4. Conduct a drug interaction trial to evaluate the effect of enzalutamide at steady state on the pharmacokinetics of CYP2D6 substrates. The proposed trial protocol must be submitted for review prior to initiation of the trial.
5. Conduct a drug interaction trial to evaluate the effect of enzalutamide at steady state on the pharmacokinetics of CYP1A2 substrates. The proposed trial protocol must be submitted for review prior to initiation of the trial.

### 1.3 Summary of Clinical Pharmacology Findings
Enzalutamide is an androgen receptor inhibitor that targets steps in the androgen receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors, inhibit activated androgen receptor nuclear translocation, and inhibit activated androgen receptor association with DNA. A major metabolite, N-desmethyl enzalutamide (M2), exhibited similar *in vitro* activity to enzalutamide. Enzalutamide also has one major inactive metabolite (M1). The proposed indication is for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have received docetaxel (b) (4). The proposed dosing regimen is 160 mg enzalutamide (four 40 mg liquid-filled capsules) orally, once daily, without regard to food.

The applicant conducted two phase 1 trials and a phase 3 trial in patients with metastatic CRPC, two phase 1 trials in healthy volunteers and a composite pharmacokinetic analysis to characterize the single dose and multiple dose plasma pharmacokinetics of enzalutamide and M2 following oral administration. The extent of enzalutamide absorption was not significantly altered by a high-fat meal compared to the fasted state. Following oral administration of enzalutamide at 160 mg in patients with metastatic CRPC, the median time to reach maximum plasma enzalutamide concentrations is 1 hour (range 0.5 to 3 hours). The enzalutamide mean terminal elimination half-fife ($T_{1/2}$), in patients with metastatic CRPC, following a single oral dose is 5.8 days (range 2.8 to 10.2 days).With daily dosing regimen, steady state is achieved by Day 28, and enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in enzalutamide plasma concentrations are low (mean peak-to-trough ratio of 1.25). At steady state, enzalutamide showed approximately dose proportional pharmacokinetics over the daily dose range of 30 to 360 mg. In patients with MCRP cancer, the mean (%CV) predose $C_{min}$ values for enzalutamide and M2 were 11.4 (25.9%) µg/mL and 13.0 (29.9%) µg/mL, respectively. The apparent total plasma enzalutamide clearance was 0.56 L/hr (%CV: 29.9%).

The single dose pharmacokinetics of the major active metabolite M2 was characterized in healthy volunteers following a single 160 mg oral dose of enzalutamide. The median $T_{max}$ for M2 occurred at 6 days (range 2 to 13 days). The mean terminal half-life for M2 is 8.6 days (%CV: 21%).

After oral administration of 160 mg $^{14}$C-enzalutamide in the mass balance trial, enzalutamide, M1, and M2 accounted for 88% of the $^{14}$C-radioactivity in plasma, representing 30%, 10%, and 49%, respectively, of the total $^{14}$C-$AUC_{0\text{-}inf}$. Approximately 14% of the $^{14}$C-enzalutamide dose was recovered in feces (0.4% as enzalutamide and 1% as M2) and 71% was recovered in urine (with only trace amounts as enzalutamide, and M2). A dose reduction is not needed in patients with mild or moderate renal impairment or mild and moderate hepatic impairment. The effect of severe renal impairment or severe hepatic impairment on the pharmacokinetics of enzalutamide is not known.

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 $IC_{50}$ 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. Therefore, co-administration of enzalutamide with CYP3A4, 2C9, and 2C19 substrates with a narrow therapeutic index should be avoided. 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.

In vitro, enzalutamide is metabolized by CYP2C8 and CYP3A4. In vivo results further suggest that CYP2C8 is primarily responsible for the fornation of the active metabolite - N-desmethyl enzalutamide (M2). The metabolism of M2 was not studied. In vivo trials assessed the effect of a strong CYP2C8 inhibitor (gemfibrozil) and a strong CYP3A4 inhibitor (itraconazole) on enzalutamide and M2 plasma pharmacokinetics. The sum of enzalutamide and M2 $AUC_{inf}$ was increased by 2.2-fold when it was co-administered with gemfibrozil. Therefore, an initial daily dose reduction to 80 mg is needed when enzalutamide is co-administered with a strong CYP2C8 inhibitor. The sum of enzalutamide and M2 $AUC_{inf}$ was increased by 1.3-fold when it was co-administered with itraconazole. The effects of a CYP2C8 inducer or a CYP3A4 inducer on the PK of enzalutamide are not known, and co-administration of enzalutamide with CYP2C8 and/or CYP3A4 inducers (e.g. rifampin) should be avoided.

Based on the efficacy results of Phase 3 trial, no exposure-response relationship for efficacy the endpoint of overall survival (OS) could be identified for enzalutamide within a single fixed dose of 160 mg/day. In addition, there was no clinically meaningful exposure-response relationship for fatigue, flushing, headache, or hypertension within the limited exposure range for 160mg/day. The effect of enzalutamide 160 mg/day at steady state on the QTc interval was evaluated in 796 patients with castration-resistant prostate cancer. No large difference (i.e., greater than 20 ms) was observed between the mean QT interval change from baseline in patients treated with XTANDI and that in patients treated with placebo, based on the Fridericia correction method.

Signatures:

| | |
|---|---|
| Reviewer: Jeanne Fourie Zirkelbach, PhD | Team Leader: Qi Liu, PhD |
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| Reviewer: Dhananjay Marathe, PhD | Team Leader: Nitin Mehrotra, PhD |
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CP TL - Q Liu , PM TL - N Mehrotra
DDD - B Booth DD - A Rahman

## 2 QUESTION BASED REVIEW

### 2.1 GENERAL ATTRIBUTES

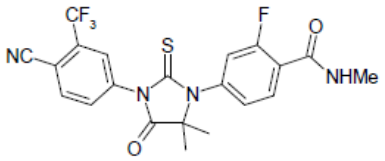
#### 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The immediate-release, liquid filled soft gelatin capsules for oral administration each contain 40 mg of enzalutamide (MDV3100).

**Physical-chemical properties**

- **Structural formula:**

**Figure 1. Structural Formula of Enzalutamide**




- **Established names:** Enzalutamide (MDV3100)
- **Molecular Weight:** 464.44 g/mol
- **Molecular Formula:** $C_{21}H_{16}F_4N_4O_2S$
- **Calculated Partition coefficient (log P (water)):** 2.98
- **Chirality:** Enzalutamide has no chiral centers.
- **Dissociation Constant (pKa (Acidic)):** No pKa between pH 3-11
- **Chemical Name:** 4-{3-[4-Cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-N-methylbenzamide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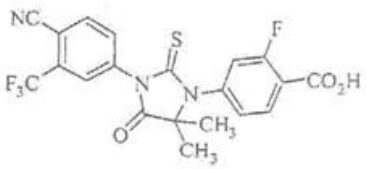
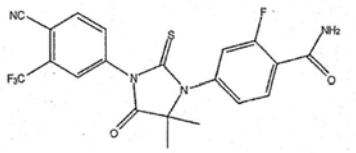
- **Solubility:** Enzalutamide is practically insoluble in water, with a kinetic solubility of 2.0 x $10^{-3}$ mg/ml. Enzalutamide is soluble in methanol and freely soluble in acetonitrile and methyl 2-pyrrolidinone.

**Figure 2. Structure of Major Inactive Metabolite: MDPC0001 (M1)**



Molecular Weight: 451.39 g/mol (free base)
Molecular Formula: $C_{20}H_{13}F_4N_3O_3S$

**Figure 3. Structure of Major Active Metabolite: MDPC0002 (N-desmethyl enzalutamide, M2)**



Molecular Weight: 450.41 g/mol
Molecular Formula: $C_{20}H_{13}F_4N_4O_2S$

### 2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Enzalutamide and its active metabolite M2 competitively inhibit androgen-induced receptor activation (binding of androgens to androgen receptors (ARs)) in the cytosol. Enzalutamide and M2 also inhibit nuclear translocation of activated ARs. Enzalutamide treatment decreases the growth of prostate cancer cells and can induce cancer cell death and tumor regression. The proposed indication is for the treatment of patients with metastatic castration-resistant prostate cancer who have received docetaxel (b) (4).

### 2.1.3 What are the proposed dosage(s) and route(s) of administration?

The applicant's proposed dosing regimen is 160 mg (four 40 mg capsules) enzalutamide orally, once daily, without regard to food.

## 2.2 GENERAL CLINICAL PHARMACOLOGY

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Table 1 below summarizes the design features of the clinical trials that were used to support the Clinical Pharmacology and Biopharmaceutics Section of the NDA.

Table 1. Clinical trials that were used to support the Clinical Pharmacology and Biopharmaceutics.

| Study | Population | Description | Subjects | Formulation, Dose, Food Intake, and Drug Product Batch Number | PK Data (Duration of Treatment) |
|---|---|---|---|---|---|
| 9785-CL-0001 | Healthy volunteers | Phase 1 mass balance and biotransformation study | 6 Males | Liquid-filled capsule.<br>160 mg (4 × 40 mg capsules) and 1 capsule containing 100 µCi of $^{14}$C-MDV3100.<br>Food intake: Dosing under fasted conditions (no caloric intake for at least 10 h pre and 4 h post).<br>Batch number: 1082869 (Study #BX1003909). | Single-dose PK with intensive sampling of whole blood, plasma, urine, and feces for 77 days postdose. Measure MDV3100, M1, and M2 in plasma and urine. Identify metabolites in plasma, urine, and feces. |
| MDV3100-05* | Healthy volunteers | Phase 1 food-effects study | 60 Males under fed (n = 30) or fasted (n = 30) conditions | Liquid-filled capsule.<br>160 mg (4 × 40 mg capsules).<br>Food intake: Dosing under fasted conditions (no caloric intake for at least 10 h pre and 4 h post) or fed conditions (high-fat, high-calorie meal).<br>Batch number: 1021828. | Single-dose PK with intensive sampling for 42 days postdose. Measure MDV3100, M1, and M2 in plasma. Fasted and fed conditions as parallel comparison. |
| S-3100-1-01 | Castration-resistant prostate cancer patients (post-chemo and chemo-naive) | Phase 1 dose-escalation | 140 Males | Liquid-filled capsule.<br>Dose-escalation: 30, 60, 150, 240, 360, 480 (as 240 mg BID), and 600 (as 300 mg BID) mg/day.<br>Food intake: For the single dose, drug was taken in the clinic with breakfast (patient could provide his own breakfast). For the multiple-dose period, food intake was uncontrolled.<br>Batch numbers: 0706030, 0708037, 0805020, 0810065, 964932, 1021828, 1082869, 1120714. | Single-dose PK for first dose with intensive sampling for 6 days in 3–6 patients at each dose level. During multiple-dose and long-term dosing periods (i.e., daily administration until treatment discontinuation): $C_{min}$ samples taken ~once/month for at least 6 months, and sufficient sampling on Day 84 (i.e., at 3 months) to estimate steady-state $C_{max}$ and $AUC_\tau$. Measure MDV3100 in plasma. |
| CPRC2 | Castration-resistant prostate cancer patients (post-chemo) | Phase 3 efficacy study | 1199 Males (randomized 2:1 active-to-placebo) | Liquid-filled capsule.<br>160 mg/day (4 × 40 mg capsules).<br>Food intake: Uncontrolled.<br>Batch numbers: 964932, 1021828, 1082869, 1120714. | Daily administration until treatment discontinuation. Predose $C_{min}$ PK samples were collected from all patients at Weeks 1, 2, 5, 9, 13, and 25, and every 12 weeks thereafter. Measure MDV3100, M1, and M2 in plasma. |

* Details and results of the food-effects study are presented in Section 2.7.1.2.5.2. This study included a pilot bioequivalence crossover comparison of the liquid-filled capsule versus a small-batch tablet formulation under fed or fasted conditions. The results for the tablet formulation are not presented.

$AUC_\tau$, area under the curve for one 24-hour dosing interval at steady state; BID, twice per day; $C_{max}$, maximum plasma concentration; $C_{min}$, minimum plasma concentration; mg, milligrams; PK, pharmacokinetics; µCi, microcurie

Three additional trials were submitted during the review cycle on June 29, 2012 (Table 2).

Table 2. Additional Clinical trials to support the Clinical Pharmacology submitted on June 29, 2012.

| Study | Design |
|---|---|
| 9785-CL-0006 | Phase 1 randomized, open-label, 3-arm, parallel-design drug-drug interaction study in 41 healthy male subjects to determine the effect of multiple-dose gemfibrozil (a potent CYP2C8 inhibitor) or itraconazole (a potent CYP3A4 inhibitor) on the PK, safety, and tolerability of a single oral 160 mg dose of enzalutamide. |
| 9785-CL-0007 | Phase 1, open-label, single-sequence crossover drug-drug interaction study in 14 castration-resistant prostate cancer (CRPC) patients to determine the effect of multiple-dose enzalutamide (160 mg/day) on the PK of a single oral dose of pioglitazone (CYP2C8 substrate), S-warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), and midazolam (CYP3A4 substrate). |
| 9785-CL-0009 | Phase 1, open-label, 2-arm study in subjects with baseline mild (n = 8) or moderate (n = 8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 17 matched control subjects with normal hepatic function to determine the effect of hepatic impairment on the PK, safety and tolerability of a single oral 160 mg dose of enzalutamide. |

**Applicant's Population Pharmacokinetic (PK) and Population Pharmacokinetic-Pharmacodynamic (PK-PD) Reports:**

Population PK and population PK-PD Analysis (9785-PK-0001):

Data from Study S-3100-1-01 that enrolled 140 patients with castration-resistant prostate cancer (CRPC)



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were used to develop a population PK model of enzalutamide pharmacokinetics and population PK-PD models for the effect on prostate-specific antigen (PSA) concentration (a biomarker for prostate cancer progression) and spontaneously reported fatigue (the most frequently reported adverse event).

Exposure-response analysis (ICON 214016):
Data from study CRPC2 were used to perform an exposure-response analyses for efficacy (overall survival, radiographic progression-free survival, time to PSA progression, and PSA response) and safety (adverse events of clinical interest). Exposure variables were the average steady-state $C_{min}$ of enzalutamide alone, active metabolite M2 alone, and the sum of enzalutamide + M2 as exposure variables.

Population PK and population PK-PD Analysis (ICON 2147014):
A population PK analysis was performed with data from 3 studies: MDV3100-05 (healthy volunteers), S-3100-1-01 (patients), and CRPC2 (patients). The PK dataset included single dose and multiple dose data covering a dose range of 30 to 600 mg/day. The analysis included 985 individual volunteers (59 healthy volunteers and 926 patients). The objective of the analysis was to assess cofactors that contribute to inter-individual variability in enzalutamide PK and the need for dose adjustment based on body weight, age and creatinine clearance values to support labeling claims.

Statistical analysis of time-dependent increases in M1 plasma concentrations in castration-resistant prostate cancer patients in study CRPC2 (M1 Analysis Report v1):
The purpose of the present analyses was to identify patient characteristics that may be predictive of the time-dependent increase in M1 plasma concentrations that were observed during the course of the CRPC2 trial.

PK-PD Analysis (CRPC2 ERT Cardiac Safety Report):
An independent exposure-QTc response analysis was done by the QT-IRT using data from trial CRPC2.

### 2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

A randomized, double-blind, placebo-controlled, phase 3 trial (CRPC2, AFFIRM) served to demonstrate the efficacy and safety of enzalutamide in patients with castration-resistant prostate cancer. The primary efficacy endpoint of CRPC2 was overall survival, defined as time from randomization to death from any cause. Meeting minutes regarding the design elements of this clinical trial indicate that FDA did communicate to the applicant that overall survival was the most appropriate primary endpoint for this trial.

### 2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the clinical pharmacology related studies analyzed plasma and urine samples for the active parent compound (enzalutamide), and its two major human metabolites M1( inactive carboxylic acid derivative) and M2 (active N-desmethyl enzalutamide). Based on in vitro data, M2 demonstrates key primary pharmacodynamics of similar potency to enzalutamide (see Pharmacology/Toxicology Review).

Preclinical trials PRO3100NC59, PRO3100NC65 and PRO3100NC73 evaluated the binding affinity of enzalutamide and its metabolites M1 and M2 to the AR, and the ability of enzalutamide, M1 and M2 to inhibit the binding of testosterone to the AR. Based on the Pharmacology/Toxicology reviewer's

analysis, these studies indicate that M2 has similar AR binding affinity and inhibitory activity compared to enzalutamide. M1 showed no AR binding affinity or inhibitory activity.

The pre-clinical trial PRO3100NC70, PRO3100NC43 and PRO3100NC57 evaluated the ability of enzalutamide, M1 and M2 to inhibit AR nuclear translocation. Based on the Pharmacology/Toxicology reviewer's analysis, these studies indicate that M2 has a similar $IC_{50}$ for inhibition of AR nuclear translocation as enzalutamide. The $IC_{50}$ value for the inhibition of AR nuclear translocation by M1 was significantly greater than that of enzalutamide.

Results from the mass-balance trial (9785-CL-0001) indicate that the primary radioactive components in circulating human plasma are enzalutamide, M1 and M2. The mean enzalutamide, M1 and M2 to $^{14}C$-radioactivity $AUC_{0\text{-inf}}$ ratios in plasma were 0.30, 0.10 and 0.49, respectively.

**2.2.4 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?**

Based on the efficacy results of the Phase 3 trial, no exposure-response relationship for the efficacy endpoint of overall survival (OS) could be identified for enzalutamide within a single fixed dose of 160 mg/day. There was no significant difference in survival among the four quartiles and all the exposure quartiles were uniformly beneficial relative to placebo in overall survival (see Pharmacometrics Review).

**2.2.5 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?**

Based on the safety results of the Phase 3 trial, there was no clinically meaningful exposure-response relationship for adverse events (AE) of clinical interest (fatigue, flushing, headache, hypertension) within the limited exposure range of a single dose (160mg/day). For seizures, the incidence rate and the number of patients in the exposure categories were very low, which precluded having a meaningful analysis of association between exposure and seizure incidence rates (see Pharmacometrics Review).

**2.2.6 Does this drug prolong the QT or QTc interval?**

The effect of enzalutamide 160 mg/day at steady state on the QTc interval was evaluated in 796 patients with castration-resistant prostate cancer. No large difference (i.e., greater than 20 ms) was observed between the mean QT interval change from baseline in patients treated with XTANDI and that in patients treated with placebo, based on the Fridericia correction method. However, small increases in the mean QTc interval (i.e., less than 10 ms) due to enzalutamide cannot be excluded due to limitations of the study design (See QT/IRT review for details).

**2.2.7 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?**

In Phase 3 pivotal study, there was no exposure-response relationship for overall survival (OS) with 160 mg/day dose, and all the exposure quartiles were uniformly beneficial relative to placebo in OS. There was no clinically meaningful exposure-response relationship for fatigue, flushing, headache, or hypertension within the limited exposure range of a single dose (160mg/day) in phase 3. Moreover, the proposed dose of 160 mg/day rather than the maximum tolerated dose of 240 mg/day was adequately justified by the applicant based on the PSA inhibition response (proportion of patients with 50% reduction in PSA from baseline) and safety findings in the Phase 1 dose escalation study. In phase 1, there was a dose/concentration dependant increase in proportion of patients showing a 50% decrease from baseline in PSA for doses from 30mg/day to 150 mg/day and this effect saturated at higher doses. The maximum tolerated dose (MTD) was determined to be 240 mg/day, based on occurrence of dose-limiting toxicities (seizure, rash, confusion) and fatigue adverse events that led to dose reduction. A dose-

dependent increase in fatigue adverse events occurred, with incidences of 2.9%, 7.5% and 20.0% at 240 mg, 360 mg and 480 mg daily dosing respectively. Overall, with the comparable PSA inhibition response for doses ≥ 150 mg/day, and increasing safety issues at higher doses (≥ 240 mg/day), a dose of 160 mg/day selected for the Phase 3 AFFIRM study seems reasonable (see Pharmacometrics Review).

With daily dosing, enzalutamide steady state was reached by Day 28. With daily oral administration, enzalutamide accumulation was observed at steady state with an 8.3-fold higher exposure (AUC) relative to a single dose. The proposed daily dosing regimen, rather than a regimen that includes a higher loading dose to achieve steady state more rapidly was justified based on safety considerations that include dose reductions needed at doses of 240 mg and higher, as well as seizures resulting in study drug discontinuation at doses of 360 mg and higher.

In the phase 1 dose escalation trial (S3100-1-01) the twice daily (BID) dosing regimen was implemented at doses higher than 360 mg. This was due to the 30 to 40 mg capsule strength, which would have resulted in patients having to take 12-15 capsules of drug in a once/day dosing regimen (40 mg capsule strength). The applicant justified the BID regimen at higher doses based on concerns raised by the study investigators on the feasibility and patient compliance with a once/day dosing regimen in which patients had to take 12-15 capsules.

**Pharmacokinetic characteristics of the drug and its major metabolites**

### 2.2.8 What are the single dose and multiple dose pharmacokinetic (PK) parameters?

Trials describing the PK of enzalutamide in patients with castration-resistant prostate cancer:

- Study S-3100-1-01 was a dose-escalation trial that characterized the single dose and multiple dose PK of enzalutamide in patients with castration-resistant prostate cancer. Two patient populations were enrolled: chemotherapy-naïve patients (n = 65) and post-chemotherapy patients (n = 75). In the 30 mg, 60 mg, 150 mg, 240 mg and 360 mg dosing cohorts, patients received enzalutamide orally once daily. In the 480 and 600 mg dosing cohorts, patients received enzalutamide orally twice a day (480 mg as 240 mg BID, and 600 mg as 300 mg BID). Full PK profiles for enzalutamide were collected from 3 or 6 patients per dose level during the Single-Dose Period (over an approximate 6-day period) and from all patients during the Multiple-Dose Period (with a full PK profile on Day 84 over a 24-hour dosing interval). In addition, predose $C_{min}$ samples were collected from all patients throughout the study. Initially in this trial, the liquid formulation was provided as a hard gelatin 30 mg capsule. During the trial, the liquid formulation was filled into soft gelatin capsules containing 40 mg enzalutamide. The difference in capsule dose strength is strictly a function of the capsule fill volume, and there were no changes in the composition of the liquid formulation.

- Study CRPC2 was a Phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral enzalutamide in 1199 patients with castration-resistant prostate cancer. Predose $C_{min}$ samples were collected from all patients at Weeks 1, 2, 5, 9, 13, and 25, and every 12 weeks thereafter to assess plasma concentrations of enzalutamide, M1, and M2.

- Study 9785-CL-0007 was a phase 1, open-label, single-sequence crossover drug-drug interaction study in 14 castration-resistant prostate cancer (CRPC) patients to determine the effect of multiple-dose enzalutamide(160 mg/day) on the PK of a single oral dose of CYP2C8, 2C9, 2C19 and 3A4 substrates. In this trial, the multiple dose PK parameters of enzalutamide, M1 and M2 were obtained.

Trials describing the single dose PK of enzalutamide in healthy volunteers:

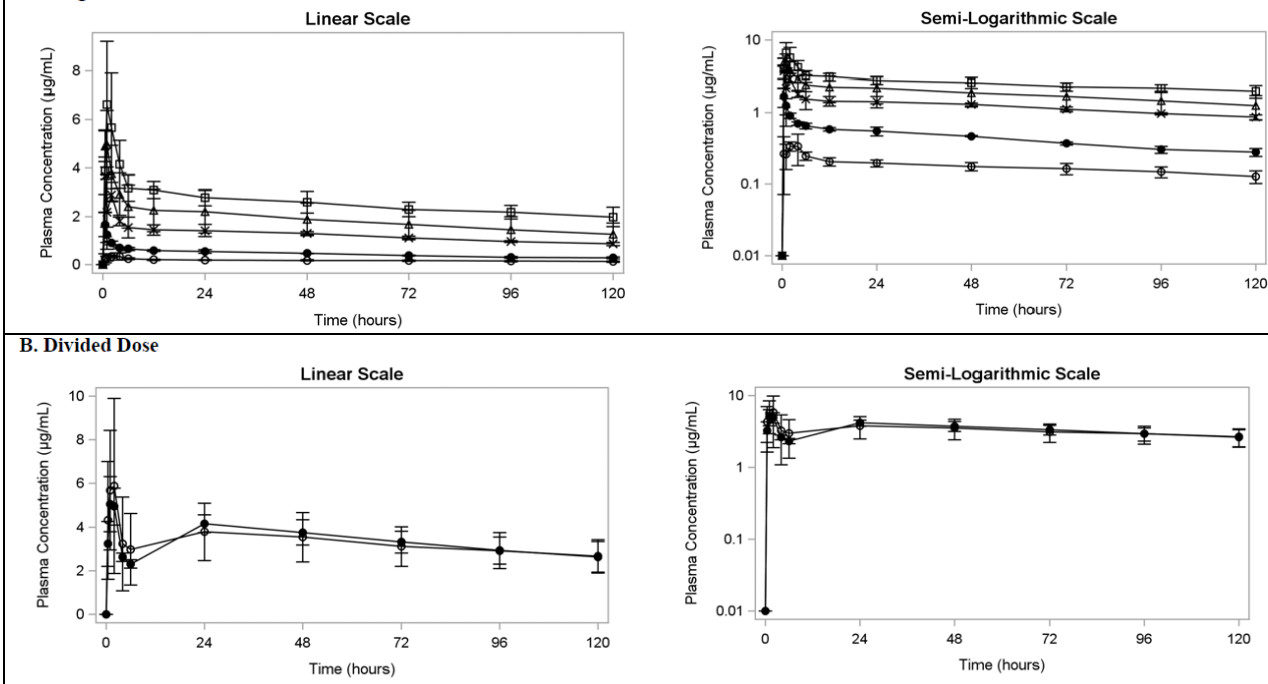
- Study 9785-CL-0001 was conducted in 6 healthy male volunteers and evaluated the PK, metabolism, and excretion of enzalutamide and its metabolites (including M1 and M2). On Day 1, volunteers received a single oral dose of 160 mg enzalutamide (4 × 40 mg capsules) plus an additional liquid-filled capsule containing a tracer dose of $^{14}$C-labeled enzalutamide (100 μCi) under fasted conditions (at least 10 h pre to 4 h post dosing). Whole blood, plasma, urine, and feces were collected through Day 77 post dose.

- Study MDV3100-05 was a Phase 1, open-label, randomized, single-dose, parallel design food-effects study in healthy male volunteers. On Day 1, 60 volunteers were randomized to receive a single oral dose of 160 mg enzalutamide (4 × 40 mg capsules) under fasted or fed conditions (n = 30 volunteers per treatment arm). PK parameters for enzalutamide and its major metabolites (M1 and M2) were calculated from the plasma concentration-time data and a non-compartmental analysis.

- The PK profiles of the M1 and M2 major metabolites were characterized in healthy volunteers in trial MDV3100-05 and 9785-CL-0001.

**Single dose**
Table 3 summarizes the single dose pharmacokinetic parameters of enzalutamide over the 30 to 600 mg/day dose range, as determined using noncompartmental analysis. For dose levels up to 360 mg/day, patients received one dose of enzalutamide orally with breakfast. Dose levels higher than 360 mg/day were divided equally into a morning dose to be taken with breakfast and an evening dose to be taken with dinner, with doses 12 hours apart (see Section 2.2.7 for justification). For the 480 mg/day dose group (240 mg BID) and the 600 mg/day dose group (300 mg BID), the $C_{max}$ were considered for a 240 mg dose and for a 300 mg dose respectively.

The mean plasma enzalutamide concentration time profiles, following a single (A) (or divided (B)) dose, are shown in Figure 4.




Upper panel (A): -o- 30 mg (n = 3), -•- 60 mg (n = 3), -×- 150 mg (n = 3), △240 mg (n = 3), and -□- 360 mg (n = 6) as single dose.
Lower Panel (B): -o- 480 mg (n = 6) and -•- 600 mg (n = 3) as a divided dose (240 and 300 mg BID, respectively), with approximately 12 hours between the 2 doses.
NOTE: Error bars denote SD values.

Figure 4. The mean plasma enzalutamide concentration time profiles following a single (A) or divided (B) dose (Trial S-3100-1-01).

The summary statistics of plasma enzalutamide pharmacokinetic parameters, following administration of a single oral (or divided) dose of enzalutamide, in patients with castration-resistant prostate cancer are shown in Table 3 and Table 4. Following a single oral dose of enzalutamide, the median $T_{max}$ was 1 hour (range 0.42 to 4.00 hours). The terminal elimination half-life, CL/F and V/F values were constant over the dose range studied. Summary statistics of the plasma enzalutamide pharmacokinetic parameters for the single (or divided) dose with all dose groups combined are shown in Table 4. The median terminal half-life for enzalutamide was 5.8 days (range 2.8 to 10.2 days). The apparent total plasma clearance (total clearance/oral bioavailability [CL/F] was 0.56 L/hr (%CV arithmetic mean: 29.9). The mean apparent volume of distribution (V/F) of enzalutamide was 110 L (%CV arithmetic mean: 29.0%).

Table 3. Summary statistics of plasma enzalutamide pharmacokinetic parameters for the single-dose period (Trial S-3100-1-01).

| Parameter (units) | 30 mg | 60 mg | 150/160 mg | 240 mg | 360 mg | 480 mg[a] | 600 mg[a] |
|---|---|---|---|---|---|---|---|
| n | 3 | 3 | 3 | 3 | 6[b] | 6[c] | 3 |
| $C_{max}$ (µg/mL) | 0.44 ± 0.07 | 1.69 ± 0.48 | 3.36 ± 0.78 | 5.25 ± 0.92 | 7.07 ± 2.52 | 6.78 ± 3.49 | 5.23 ± 0.99 |
| $t_{max}$ (h) | 1.98 (0.42–4.00) | 0.50 (0.48–1.00) | 0.53 (0.50–1.98) | 1.00 (0.57–1.00) | 1.03 (0.53–2.20) | 1.54 (0.53–2.08) | 1.03 (1.03–2.00) |
| $AUC_{24h}$ (µg·h/mL) | 5.46 ± 0.66 | 15.64 ± 0.54 | 38.87 ± 8.40 | 62.10 ± 23.91 | 80.45 ± 14.85 | ND | ND |
| $AUC_{120h}$ (µg·h/mL) | 21.3 ± 2.9 | 53.1 ± 2.2 | 145.8 ± 14.4 | 220.0 ± 79.6 | 321.9 ± 39.7 | 382.0 ± 132.6 | 394.5 ± 55.6 |
| $AUC_{0-inf}$ (µg·h/mL) | 53.9 ± 21.3 | 93.8 ± 16.6 | 333.9 ± 50.0 | 474.1 ± 137.8 | 715.3 ± 121.8 | 1010.1 ± 378.1 | 895.9 ± 269.9 |
| %AUC | 43.3 ± 15.8 | 28.6 ± 10.1 | 40.6 ± 11.3 | 39.9 ± 10.3 | 43.8 ± 8.2 | 41.0 ± 14.2 | 39.5 ± 10.0 |
| $t_{1/2}$ (h) | 164.9 ± 69.8 | 100.5 ± 30.9 | 143.7 ± 34.8 | 138.9 ± 22.6 | 149.1 ± 26.1 | 144.0 ± 68.4 | 130.4 ± 37.7 |
| CL/F (L/h) | 0.613 ± 0.219 | 0.655 ± 0.129 | 0.456 ± 0.064 | 0.541 ± 0.182 | 0.516 ± 0.094 | 0.537 ± 0.232 | 0.722 ± 0.260 |
| V/F (L) | 132.8 ± 20.0 | 91.3 ± 14.4 | 92.4 ± 11.8 | 111.9 ± 56.0 | 109.4 ± 18.1 | 100.7 ± 29.7 | 126.7 ± 10.9 |

[a] 480 and 600 mg were given as a divided dose (240 and 300 mg BID, respectively), with approximately 12 hours between the 2 doses.
[b] n = 5 for $AUC_{0-inf}$, AUC%, t1/2, CL/F, and V/F.
[c] n = 4 for $AUC_{0-inf}$, AUC%, t1/2, CL/F, and V/F.
NOTE: Reported values are the arithmetic mean ± SD; for Tmax, the median (range) is reported.
ND, not determined.
$AUC_{24h}$: Area under the enzalutamide plasma concentration versus time curve (AUC) from time 0 to 24 hours after dosing on Day 1 of the Single-Dose Period; calculated by the linear trapezoidal rule.
$AUC_{120h}$: AUC from time 0 to 120 hours after dosing on Day 1 of the Single-Dose Period; calculated by the linear trapezoidal rule.
$AUC_{0-inf}$: AUC from time 0 to infinity (after a single or first dose), calculated as $AUC_{0-t} + (C_{last}/\lambda z)$, where $C_{last}$ is the last observed quantifiable concentration.
NOTE: No patients were enrolled at the 160 mg oral dose.

Table 4. Summary statistics of plasma enzalutamide pharmacokinetic parameters for the single-dose period with all dose groups combined (Trial S-3100-1-01).

| | Summary Statistic | | | | | | |
|---|---|---|---|---|---|---|---|
| Parameter (units) | n | Arithmetic Mean | SD | CV% | Median | Min | Max |
| $t_{max}$ (h) | 33 | ND | ND | ND | 1.00 | 0.42 | 4.00 |
| $t_{1/2}$ (h) | 30 | 139.6 | 39.0 | 27.9% | 133.8 | 66.4 | 245.4 |
| CL/F (L/h) | 30 | 0.564 | 0.169 | 29.9% | 0.510 | 0.327 | 1.020 |
| V/F (L) | 30 | 109.5 | 31.7 | 29.0% | 99.2 | 70.2 | 176.5 |

CL/F; apparent total plasma clearance; ND, not determined; t1/2, apparent terminal elimination half-life; Tmax, time to maximum observed plasma concentration; V/F; apparent volume of distribution.

The single dose PK profiles of the enzalutamide major metabolites (M1 and M2) were characterized in healthy volunteers in trial MDV3100-05 and 9785-CL-0001 (Table 5 and Table 6). Following a single 160 mg oral dose of enzalutamide, the median $T_{max}$ for the major metabolites, M1 and M2, occur at 4 to 6 days and 6 days, respectively. The mean terminal half-life for M1 was approximately 8.9 to 9.3 days, and the mean terminal half-life for M2 was approximately 7.8 to 8.6 days. The intersubject variability in $C_{max}$ and $AUC_{0-inf}$ was moderate (%CV ≤ 58%) for M1 and low (%CV ≤ 29%) for M2.

Table 5. Single dose M1 metabolite PK summary statistics in healthy volunteers.

| Enzalutamide dose (mg), regimen | Trial | N | PK Interval | Cmax (µg/mL) | Tmax (h) | AUCinf (µg•h/mL) | t1/2 (h) | Metabolite /Parent Ratio[a] Cmax | Metabolite /Parent Ratio[a] AUCinf |
|---|---|---|---|---|---|---|---|---|---|
| 160 (fed high fat) | MDV3100-05 | 30 | Days 1-42 | 0.210 ± 0.080 (38%) | 144.0 (48.0–312) | 83.6 ± 19.9 (24%) | 214 ± 57 (27%) | 0.059 ± 0.022 (38%) | 0.30 ± 0.07 (23%) |
| 160 (fasted) | MDV3100-05 | 30 | Days 1-42 | 0.230 ± 0.133 (58%) | 96.0 (24.0–312) | 92.4 ± 22.1 (24%) | 216 ± 49 (23%) | 0.044 ± 0.023 (53%) | 0.31 ± 0.11 (35%) |
| 160 (fasted) | 9785-CL-0001 | 6 | Days 1-77 | 0.186 ± 0.0777 (42%) | 96.0 (96.0–240) | 78.4 ± 14.4 (18%) | 223 ± 69.1 (31%) | 0.042[b] | 0.34 ± 0.08 (23%) |

[a] Based on µg/mL concentrations for M1 and enzalutamide.
[b] Based on mean steady-state values for M1 and enzalutamide.
NOTE: Values reported as mean ± SD (%CV), except Tmax, which is reported median (range).
AUCinf, area under the curve for single dose from t = 0 to infinity; Cmax, observed maximum plasma concentration; %CV, percent coefficient of variation; t1/2, elimination half-life; Tmax, time of maximum plasma concentration.

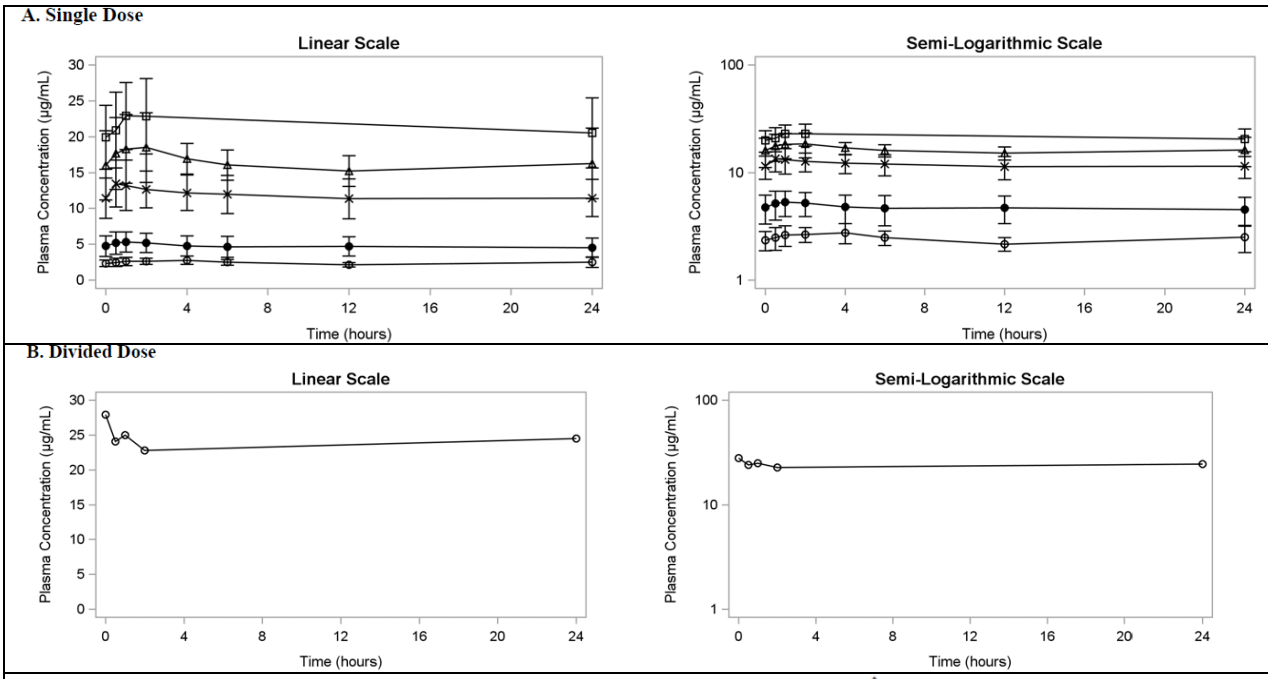
Table 6. Single dose M2 metabolite PK summary statistics in healthy volunteers.

| Enzalutamide dose (mg), regimen | Trial | N | PK Interval | Cmax (µg/mL) | Tmax (h) | AUCinf (µg•h/mL) | t1/2 (h) | Metabolite /Parent Ratio[a] Cmax | Metabolite /Parent Ratio[a] AUCinf |
|---|---|---|---|---|---|---|---|---|---|
| 160 (fed high fat) | MDV3100-05 | 30 | Days 1-42 | 0.824 ± 0.168 (20%) | 144.0 (48.0–312.0) | 425 ± 119 (28%) | 197 ± 50 (25%) | 0.23 ± 0.05 (23%) | 1.53 ± 0.38 (25%) |
| 160 (fasted) | MDV3100-05 | 30 | Days 1-42 | 0.791 ± 0.226 (29%) | 144.0 (48.1–312.0) | 389 ± 90 (23%) | 206 ± 43 (21%) | 0.15 ± 0.04 (27%) | 1.44 ± 0.50 (34%) |
| 160 (fasted) | 9785-CL-0001 | 6 | Days 1-77 | 0.891 ± 0.128 (14%) | 132.0 (72.0–240.0) | 395 ± 97.8 (25%) | 186 ± 38.4 (21%) | 0.20[b] | 1.75 ± 0.59 (34%) |

[a] Based on µg/mL concentrations for M2 and enzalutamide.
[b] Based on mean steady-state values for M2 and enzalutamide.
NOTE: Values reported as mean ± SD (%CV), except Tmax, which is reported as median (range). AUCinf, area under the curve for single dose from t = 0 to infinity; Cmax, observed maximum plasma concentration; t1/2, elimination half-life; Tmax, time of maximum plasma concentration.

**Multiple doses**

The multiple dose (Day 84) plasma concentration-time profiles of enzalutamide from trial S-3100-1-01 are summarized in Figure 5. For dose levels form 30 mg to 360 mg, patients received one dose of enzalutamide orally each day with breakfast for 84 days. Dose levels higher than 360 mg/day were divided equally into a morning dose to be taken with breakfast and an evening dose to be taken with dinner, with doses 12 hours apart.




Upper panel (A): -o- 30 mg (n = 3), -•- 60 mg (n = 20), -×- 150 mg (n = 24), △ 240 mg (n = 29), and -□- 360 mg (n = 16) during Day 84 after once daily dosing.
Lower Panel (B): -o- 480 mg (n = 1) during Day 84 after twice daily dosing (240 mg BID), with approximately 12 hours between the 2 doses.
NOTE: Error bars denote SD values.

Figure 5. The mean plasma enzalutamide concentration time profiles following multiple dosing as a once daily (A) or divided daily (B) dose (Trial S-3100-1-01).

The summary statistics of plasma enzalutamide pharmacokinetic parameters following multiple dose administration as a once daily oral dose (30, 60, 150, 240, 360 and 480 mg), or divided daily dose (240 mg bid) of enzalutamide in patients with castration-resistant prostate cancer are shown in Table 7 and Table 8. The enzalutamide median $T_{max}$ ranged from 1.00 to 2.07 hours. The mean apparent total plasma clearance (Dose/$AUC_{0-\tau}$ [CL/F]) was 0.614 L/hr (%CV arithmetic mean: 33%) (Table 8). The peak-to-trough ratio (PTR) ($C_{max}/C_{24h}$) averaged 1.25 (range 1.00 to 1.72). The mean accumulation index was 8.33 (range 4.17 to 13.56) (Table 8).

Table 7. Summary statistics of plasma enzalutamide multiple dose PK parameters (Trial S-3100-1-01).

| Parameter | 30 mg | 60 mg | 150 mg | 240 mg | 360 mg | 480 mg |
|---|---|---|---|---|---|---|
| **n** | **3** | **21[b]** | **23[c]** | **29[d]** | **16[e]** | **1** |
| $C_{max}$ (µg/mL) | 2.80 ± 0.55 | 5.68 ± 1.46 | 14.46 ± 3.29 | 19.52 ± 5.04 | 25.08 ± 5.19 | 27.90 |
| $t_{max}$ (h) | 2.07 (1.00–3.92) | 1.07 (0.50–23.67) | 1.00 (0.00–25.80) | 1.08 (0.00–26.17) | 1.57 (0.48–24.08) | 0.00[f] |
| $AUC_{0-\tau}$ (µg·h/mL) | 60.9 ± 11.8 | 115.2 ± 34.4 | 299.6 ± 67.5 | 409.6 ± 111.6 | 501.8 ± 119.2 | 463.1 |
| CL/F (L/h) | 0.507 ± 0.111 | 0.580 ± 0.245 | 0.530 ± 0.149 | 0.628 ± 0.179 | 0.755 ± 0.176 | 1.037 |
| PTR | 1.14 ± 0.12 | 1.28 ± 0.19 | 1.30 ± 0.18 | 1.21 ± 0.13 | 1.25 ± 0.20 | 1.14 |
| Accumulation Index[g] | 11.19 ± 2.18 | 7.64 ± 2.14 | 10.38[a] | 4.17[a] | 6.13 ± 0.59 | ND |
| Accumulation Ratio[h] | 12.65 ± 2.40 | 9.49 ± 3.93 | 11.09 ± 0.65 | 4.90[a] | 7.03 ± 0.09 | ND |

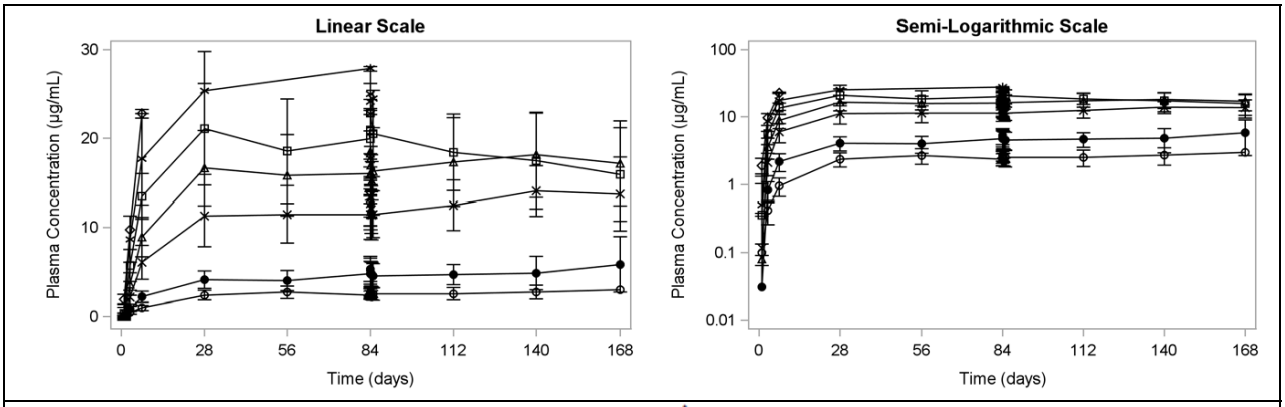
[a] Individual value reported.
[b] n = 20 for $AUC_{0-\tau}$, CL/F, and PTR, n = 3 for Accumulation Ratio and Accumulation Index.
[c] n = 22 for $AUC_{0-\tau}$, CL/F, and PTR, n = 2 for Accumulation Ratio, n = 1 for Accumulation Index.
[d] n = 1 for Accumulation Ratio and Accumulation Index.
[e] n = 14 for $AUC_{0-\tau}$, CL/F, and PTR, n = 2 for Accumulation Ratio and Accumulation Index.
[f] Tmax was observed in the predose sample.
[g] Accumulation Index = Ratio of 24-hour AUC on Day 84 to Day 1; calculated as $AUC_{0-\tau}/AUC_{24h}$.
[h] Accumulation Ratio = Ratio of $C_{24h}$ from Day 84 to Day 1.
PTR: The peak-to-trough ratio ($C_{max}/C_{24h}$)
NOTE: Reported values are the arithmetic mean ± SD, for Tmax, the median (range) is reported.
ND, not determined; PTR, peak-to-trough ratio.
AUC0-τ: AUC from time 0 to 24 hours after dosing on Day 84 of the Multiple-Dose Period; calculated by the linear trapezoidal rule.
Cmax: Maximum observed plasma concentration of enzalutamide during the first 24 hours after dosing on Day 1 of the Single-Dose Period, or Day 84 of the Multiple-Dose Period.
NOTE: No patients were enrolled at the 160 mg oral dose.

Table 8. Summary of plasma enzalutamide PK parameters for the multiple-dose period, all dose groups combined ((Trial S-3100-1-01).

| | Summary Statistic | | | | | | |
|---|---|---|---|---|---|---|---|
| **Parameter (units)** | **n** | **Arithmetic Mean** | **SD** | **CV%** | **Median** | **Min** | **Max** |
| CL/F (L/h) | 89 | 0.614 | 0.202 | 33% | 0.586 | 0.318 | 1.48 |
| PTR | 89 | 1.25 | 0.17 | 14% | 1.23 | 1.00 | 1.72 |
| Accumulation Index[a] | 10 | 8.33 | 2.91 | 35% | 8.00 | 4.17 | 13.56 |
| Accumulation Ratio[b] | 11 | 9.78 | 3.32 | 34% | 9.88 | 4.90 | 14.12 |

[a] Accumulation Index = Ratio of 24-hour AUC on Day 84 to Day 1; calculated as AUC0-τ/AUC24h.
[b] Accumulation Ratio = Ratio of C24h from Day 84 to Day 1.
NOTE: Parameters are defined in Table 9.7.3-1.
CL/F; apparent total plasma clearance; PTR, peak-to-trough ratio; SD, standard deviation.

The multiple dose mean plasma enzalutamide $C_{min}$ concentration-time plots are shown in Figure 6. Plots of the mean $C_{min}$ vs. time during multiple dosing show that steady state was achieved by Day 28. Beyond Day 28 (steady state) the mean $C_{min}$ values remained constant.




-o- 30 mg (n = 3), -•- 60 mg (n = 24), -×- 150 mg (n = 24), △ 240 mg (n = 29), and -□- 360 mg (n = 28), ✱ 480 mg (n = 15), ◇ 600 mg (n=3). Doses of 480 mg and 600 mg were given as 240 and 300 mg/day BID, respectively.
NOTE: Error bars denote SD values.

Figure 6. Mean plasma enzalutamide $C_{min}$ concentrations vs. time plots during multiple dosing (Trial S-3100-1-01).

Based on the descriptive summary of steady state enzalutamide (SS)-$C_{min}$ values, the %CV (standard deviation/mean) was ≤ 59% for within-patient variability and ≤ 29% for between-patient variability (Table 9).

Table 9. Descriptive statistics of plasma enzalutamide steady-state $C_{min}$ ((Trial S-3100-1-01).

| Dose Group | No. of Observations | SS-$C_{min}$ (µg/mL) | SS-$C_{min}$ Range (µg/mL) [min–max] | DN-SS-$C_{min}$ (µg/mL/g) | Within Patient %CV | Between Patient %CV |
|---|---|---|---|---|---|---|
| 30 mg | n = 19 (3) | 2.53 ± 0.63 | 1.81–3.01 | 84.2 ± 21.1 | 4%–9% | 25% |
| 60 mg | n = 124 (26) | 4.48 ± 1.31 | 1.55–8.06 | 74.7 ± 21.9 | 5%–49% | 29% |
| 150/160 mg | n = 128 (27) | 11.72 ± 2.78 | 5.21–16.42 | 78.1 ± 18.5 | 3%–33% | 24% |
| 240 mg | n = 167 (48) | 15.94 ± 4.30 | 7.97–31.85 | 66.4 ± 17.9 | 1%–42% | 27% |
| 360 mg | n = 105 (33) | 20.41 ± 5.44 | 11.20–36.70 | 56.7 ± 15.1 | 3%–59% | 27% |
| 480 mg | n = 7 (5) | 24.53 ± 3.00 | 20.00–28.23 | 51.1 ± 6.3 | 14% | 12% |

NOTE: Reported values are the arithmetic mean ± SD.
NOTE: The numbers in parentheses correspond to the number of patients.
µg/mL, micrograms per milliliter; %CV, coefficient of variation; DN-SS-Cmin, dose-normalized SS-Cmin; SS-Cmin, Steady-state Cmin.

The steady state predose $C_{min}$ values for enzalutamide, M1 and M2 following dosing at 160 mg/day were determined in cancer patients in the phase 3 trial (CRPC2). The mean (%CV) steady-state (13 week) predose $C_{min}$ values at the 160 mg daily dose for enzalutamide, M1 and M2 were 11.4 (25.9), 8.44 (80.2) and 13.0 (29.9) µg/mL, respectively (Table 10).

Table 10. Summary statistics for steady-state plasma $C_{min}$ values for enzalutamide (MDV3100), M1

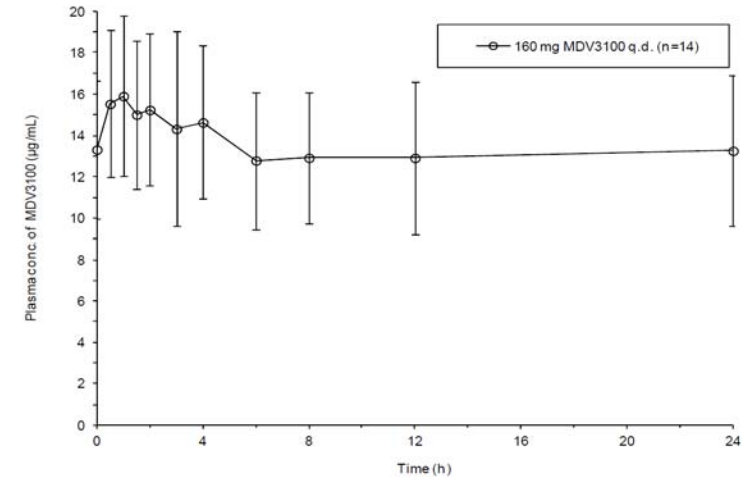
and M2 at week 13 with dosing at 160 mg/day (CRPC2).

| Statistic[a] | MDV3100 | M1 | M2 |
|---|---|---|---|
| Number of Observations[b] | 679 [c] | 680 | 680 |
| Mean (µg/mL) | 11.4 | 8.44 | 13.0 |
| SD (µg/mL) | 2.95 | 6.77 | 3.78 |
| %CV | 25.9 | 80.2 | 29.2 |
| 95% CI Lower Mean (µg/mL) | 11.2 | 7.93 | 12.7 |
| 95% CI Upper Mean (µg/mL) | 11.6 | 8.95 | 13.2 |
| Min (µg/mL) | 0.248 | 0.0372 | 0.205 |
| Median (µg/mL) | 11.3 | 6.57 | 12.6 |
| Max (µg/mL) | 23.5 | 74.8 | 32.4 |

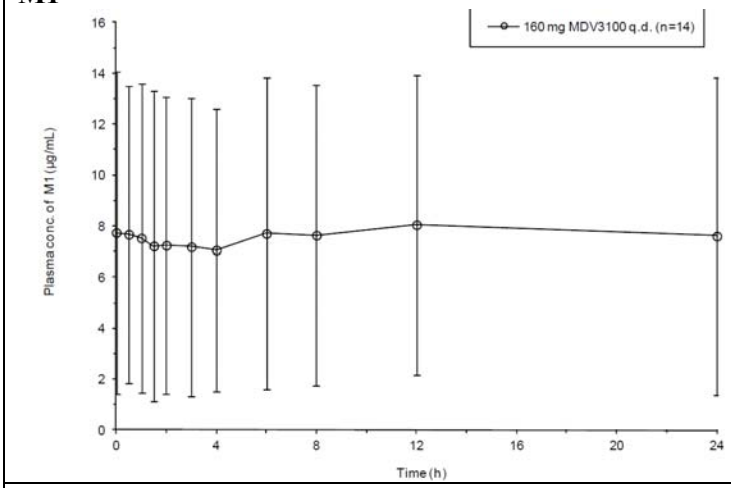
a Data are reported for patients randomized to the enzalutamide treatment.
b At Week 13, 680 patients had plasma concentration results for enzalutamide (MDV3100), M1, and M2.
c There was 1 BLQ value for MDV3100, which was excluded from the summary statistics, bringing the number of observations for MDV3100 to 679.
BLQ, Below the limit of quantification; CI, Confidence interval; %CV, percent coefficient of variation; SD, standard deviation; µg/mL, micrograms per milliliter.

The multiple dose pharmacokinetic profiles for enzalutamide, M1 and M2 were determined in trial 9785-CL-0007 following 49 days of dosing at 160 mg daily in patients with metastatic CRPC (Figure 7). The multiple dose PK parameters of enzalutamide, M1 and M2 are summarized in Table 11. Enzalutamide PK parameters were similar to those reported in Trial S-3100-1-01 and CRPC2. Forty-nine days after once daily dosing of enzalutamide $T_{max}$ of M1 ranged from 0.00 h to 24.03 h after dosing. Fluctuations in the plasma concentrations were small (mean $C_{min}$: 6.32 µg/mL; mean $C_{max}$: 8.87 µg/mL). Inter-subject variability, expressed as CV%, on the M1 pharmacokinetic parameters $AUC_{tau}$, $C_{min}$ and $C_{max}$ was high, ranging from 73.5% to 82.2%. After 49 days of once daily dosing of enzalutamide, the $T_{max}$ of M2 was wide and ranged from 0.00 h to 24.03 h after dosing. Median $T_{max}$ was 4.02 h. Fluctuations in the plasma concentrations were small (mean $C_{min}$: 10.6 µg/mL; mean $C_{max}$: 12.7 µg/mL). Inter-subject variability, expressed as CV%, on the M2 pharmacokinetic parameters $AUC_{tau}$, $C_{min}$ and $C_{max}$ was low (range: 29.7% to 30.9%).

**Enzalutamide (MDV3100)**




**M1**




**M2**

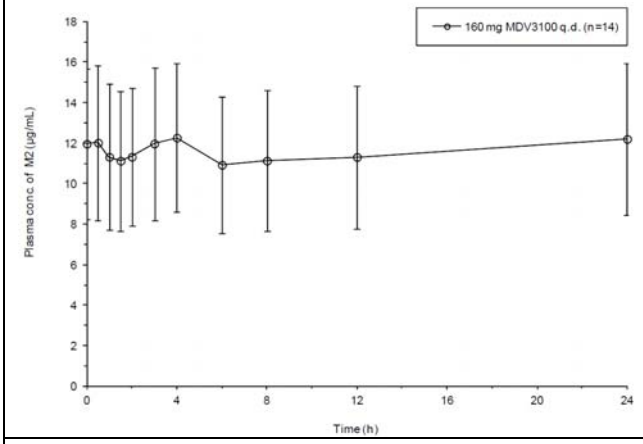



Figure 7. Mean (± SD) plasma enzalutamide, M1 and M2 concentration time profiles after 49 days 160 mg enzalutamide once daily dosing in patients with metastatic castrate-resistant prostate cancer (trial 9785-CL-0007).

Table 11. Summary statistics of the multiple dose plasma enzalutamide, M1 and M2 PK parameters after

160 mg enzalutamide QD for 49 days in patients with metastatic castrate-resistant prostate cancer (9785-CL-0007).

**Enzalutamide:**

| Parameter | $AUC_{tau}$ (h*µg/mL) | $C_{0h}$ (µg/mL) | $C_{min}$ (µg/mL) | $C_{max}$ (µg/mL) | $t_{max}$ (h) | CL/F (L/h) | PTR |
|---|---|---|---|---|---|---|---|
| N | 14 | 14 | 14 | 14 | 14 | 14 | 14 |
| Mean | 321.5 | 13.32 | 12.00 | 16.59 | NA | 0.520 | 1.266 |
| SD (CV%) | 85.39 (26.6) | 3.341 (25.1) | 3.512 (29.3) | 3.812 (23.0) | NA | 0.0942 (18.1) | 0.1271 (10.0) |
| Min - Max | 240-593 | 9.86-23.4 | 6.92-22.4 | 11.8-28.0 | 0.52-3.02 | 0.27-0.67 | 1.09-1.51 |
| Median | 295.6 | 12.70 | 11.45 | 15.55 | 1.02 | 0.541 | 1.240 |

**M1:**

| Parameter | $AUC_{tau}$ (h*µg/mL) | $C_{0h}$ (µg/mL) | $C_{min}$ (µg/mL) | $C_{max}$ (µg/mL) | $t_{max}$ (h) | MPR (MWC) |
|---|---|---|---|---|---|---|
| n | 13 | 14 | 14 | 14 | 14 | 13 |
| Mean | 193.3 | 7.739 | 6.315 | 8.867 | NA | 0.621 |
| SD (CV%) | 144.01 (74.5) | 6.3111 (81.5) | 5.1909 (82.2) | 6.5201 (73.5) | NA | 0.4931 (79.4) |
| Min - Max | 63.6-466 | 2.47-20.4 | 1.97-17.3 | 2.88-21.5 | 0.00-24.03 | 0.20-2.00 |
| Median | 145.6 | 5.135 | 4.030 | 6.925 | 3.517 | 0.471 |

**M2:**

| Parameter | $AUC_{tau}$ (h*µg/mL) | $C_{0h}$ (µg/mL) | $C_{min}$ (µg/mL) | $C_{max}$ (µg/mL) | $t_{max}$ (h) | MPR (MWC) |
|---|---|---|---|---|---|---|
| n | 14 | 14 | 14 | 14 | 14 | 14 |
| Mean | 278.3 | 11.97 | 10.57 | 12.68 | NA | 0.913 |
| SD (CV%) | 85.47 (30.7) | 3.716 (31.0) | 3.271 (30.9) | 3.773 (29.7) | NA | 0.2812 (30.8) |
| Min - Max | 182-442 | 7.80-18.8 | 6.99-16.5 | 8.65-19.6 | 0.00-24.03 | 0.56-1.66 |
| Median | 263.2 | 11.15 | 10.23 | 12.10 | 4.02 | 0.886 |

CV: coefficient of variation; Min – Max: Minimum and maximum recorded values; MPR(MWC): ratio of the metabolite - parent AUC values corrected for the difference in molecular weight; NA: not applicable; qd: once daily.

### 2.2.9 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The single dose plasma enzalutamide, pharmacokinetic parameters were determined in patients after a single 150 mg oral dose of enzalutamide in trial S-3100-01-1, and in healthy volunteers after a single 160 mg oral dose in trial MDV3100-05 (fasted and fed conditions) and trial 9785-CL-0001 (fasted condition). Overall, the elimination half-life (T1/2) is shorter, CL/F is higher and V/F is smaller in healthy male volunteers vs. patients enrolled in trial S-3100-01-1 (Table 12).

| Table 12. Single dose enzalutamide PK summary statistics in patients and healthy volunteers. | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Enzalutamide dose (mg), regimen** | **Population Studied** | **Trial** | **N** | **PK Interval** | **Cmax (µg/mL)** | **Tmax (h)** | **AUCinf (µg•h/mL)** | **t1/2 (h)** | **CL/F (L/h)** | **V/F (L)** |
| 150 (with a meal) | Metastatic CRPC | S-3100-1-01 | 3 | Days 1-6 | 3.36 ± 0.78 (23%) | 0.53 (0.50–1.98) | 334 ± 50 (15%) | 143.7 ± 34.8 (24%) | 0.456 ± 0.064 (14%) | 92.4 ± 11.8 (13%) |
| 160 (fed high fat) | Healthy Male Volunteers | MDV3100-05 | 30 | Days 1-42 | 3.74 ± 1.15 (31%) | 2.00 (0.50–6.00) | 285 ± 73 (26%) | 87.4 ± 24.7 (28%) | 0.599 ± 0.160 (27%) | 71.9 ± 16.6 (23%) |
| 160 (fasted) | Healthy Male Volunteers | MDV3100-05 | 30 | Days 1-42 | 5.25 ± 1.06 (20%) | 1.02 (0.75–3.07) | 292 ± 88 (30%) | 94.3 ± 30.0 (32%) | 0.600 ± 0.193 (32%) | 76.4 ± 21.9 (29%) |
| 160 (fasted) | Healthy Male Volunteers | 9785-CL-0001 | 6 | Days 1-77 | 4.46 ± 0.871 (20%) | 1.75 (1.00–3.00) | 237 ± 49.5 (21%) | 69.8 ± 8.38 (12%) | 0.705 ± 0.174 (25%) | 71.5 ± 20.8 (29%) |
| NOTE: Values reported as mean ± SD (%CV), except Tmax, which is reported median (range).<br>$AUC_{inf}$, area under the curve for single dose from t = 0 to infinity;<br>CL/F, apparent oral clearance, where F is fraction of the dose that reaches the systemic circulation (oral bioavailability); V/F, apparent volume of distribution. | | | | | | | | | | |

### 2.2.10 What are the characteristics of drug absorption?

Following oral administration of enzalutamide, the median $T_{max}$ is approximately 1 hour (range 0.42 to 4.00 hours). The drug product is administered as a liquid-filled capsule of enzalutamide fully dissolved in (b) (4). This formulation circumvents the typical dissolution issues associated with Biopharmaceutics Classification System (BCS) Class 2 compounds, and allows for rapid dissolution of the capsule and release of solubilized enzalutamide into the gut lumen.

The food effect trial (MDV3100-05) indicated that a high fat meal reduces the rate of enzalutamide absorption ($T_{max}$ and $C_{max}$), but the extent of absorption (AUC) is not changed (Section 2.5.4).

The mass-balance trial (9785-CL-0001) showed that following administration of a single oral dose of 160 mg $^{14}$C-enzalutamide, administered as oral capsules, a mean of 84.6% of the administered dose was recovered, with 71.0% of $^{14}$C-radioactivity excreted in urine. The remainder of the radioactivity was excreted via feces (13.6% of dose), with a trace amount of unchanged parent enzalutamide (0.39% of dose).

In vitro studies indicate that enzalutamide and M2 are not substrates of human p-glycoprotein (P-gp) (9785-ME-0026).

### 2.2.11 What are the characteristics of drug distribution?

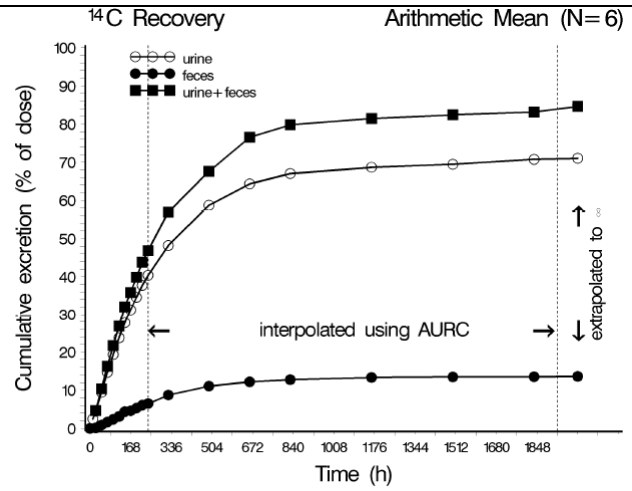
The mean apparent volume of distribution (V/F) of enzalutamide in patients after a single oral dose is 110 L (29% CV) (S-3100-1-01).

*In vitro* Plasma Protein Binding Assays:
The in vitro plasma protein binding of enzalutamide (trial PRO3100NC32) and metabolites M1 and M2 (trial 9785-ME-0018) were determined in human plasma by equilibrium dialysis. The concentration range of enzalutamide used was 0.1 – 54 μM (0.05 to 25 μg/mL). The concentration range of M1 and M2 used was 0.5 to 25 μg/mL. The concentration ranges evaluated in these studies appear appropriate, as the mean steady state $C_{max}$ for the 150 mg/day dosing regimen is 14.46 μg/mL (31.1 μM) (S-3100-1-01). The average ± relative standard deviation (RSD) overall percent binding of enzalutamide to human plasma protein was 97.56 ± 0.24 (Study PRO3100NC32), and binding was concentration independent over the dose range studied. The average overall percent binding of M1 and M2 to plasma proteins were 98.1 and 95.3, respectively, and the binding was concentration independent over the dose range studied (9785-ME-0018). In vitro results showed that albumin is the main enzalutamide binding protein in human plasma (97%) (9785-ME-0008).

Blood to Plasma Ratio: Distribution to red blood cells was investigated in the human $^{14}$C-enzalutamide mass balance and biotransformation study (9785-CL-0001) in healthy male volunteers (N=6) following administration of a single oral dose of 160 mg $^{14}$C-enzalutamide, administered as oral capsules. The overall whole blood-to-plasma ratio ($C_b/C_p$; based on the area under the 14C-radioactivity curve) was 0.55.

Transporter proteins:
In vitro, enzalutamide and M2 are inhibitors, but not substrates, of human P-glycoprotein (P-gp); whereas M1 is neither an inhibitor nor substrate of P-gp (study 9785-ME-0026) (Section 2.4.5).

**2.2.12 Does the mass balance study suggest renal or hepatic as the major route of elimination?**
Enzalutamide is primarily eliminated by hepatic metabolism. In the mass balance trial (9785-CL-0001), a single 160 mg enzalutamide (combined with a tracer dose (100 μCi) of $^{14}$C-enzalutamide) was administered to six healthy adult male volunteers as four 40 mg capsules following an overnight fast. Over the 0 to 77-Day collection period, the mean total recovery of $^{14}$C-radioactivity in urine and feces was 84.6% of the administered dose. The major route of excretion of $^{14}$C-radioactivity was via urine (arithmetic mean=71.0%). Metabolite M1 was the main component in urine (62.7% of dose). A trace amount of unchanged parent enzalutamide was excreted in urine (0.0% of dose). Metabolite M2 was not detected in urine. Approximately 13.6% of the $^{14}$C-enzalutamide dose was recovered in feces (0.39% as enzalutamide and 0.98% as M2) (Figure 8).




NB: Interpolation and extrapolation were based on the area under the excretion rate time curve (AURC).

Figure 8. Mean cumulative $^{14}$C-radioactivity recovery-time profile in urine and feces following administration of a single oral dose of 160 mg $^{14}$C-enzalutamide to healthy male volunteers (trial 9785-CL-0001) (N=6).

**2.2.12 What are the characteristics of drug metabolism?**

*In vitro* screens show that CYP2C8 and CYP3A4/5 are the major human cytochrome P450 isozymes responsible for the metabolism of enzalutamide to M6. Incubation of enzalutamide with microsomes produced metabolites M2 and M6. M2 forms when M6 degrades to M2 in a reaction that may or may not require metabolic enzymes. The metabolism of M2 was not studied.

*In vitro* metabolic profile and identification of metabolites (Study 9785-ME-0001 and 9785-ME-0025):
Study 9785-ME-0001 characterized the in vitro metabolite profile of $^{14}$C-enzalutamide in human recominant CYPs (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5). Enzalutamide was metabolized by CYP2C8, CYP3A4, and CYP3A5. The mean recovery of the parent molecule after the 2-hour incubation with CYP3A4, CYP3A5, and CYP2C8 were 67.0%, 74.4%, and 81.8%, respectively. The main metabolite in the reaction mixtures eluted at approximately the same retention time as M6, suggesting that CYP2C8, CYP3A4, and CYP3A5 catalyze the formation of M6, which is a precursor to M2 (active metabolite). M1 was not detected, and M2 was detected at trace concentrations.

Study 9785-ME-0025 with human liver microsomes, human plasma, and phosphate buffer (100 mM; pH 7.4) was conducted to identify the enzymatic and non-enzymatic routes of metabolism of enzalutamide and potential pathways for subsequent metabolite degradation. Incubation of enzalutamide (10 $\mu$ M) with microsomes produced metabolites M2 (active) and M6; whereas, no metabolites were observed in enzalutamide incubations with human plasma or phosphate buffer. Incubation of M6 (10 $\mu$ M) with microsomes, human plasma, or phosphate buffer resulted in M2 formation. The results suggest that enzalutamide is metabolized to M2 and M6 in the presence of human microsomes, and M6 degrades to the active metabolite M2 in a reaction that may or may not require metabolic enzymes.

Metabolic Profile from the mass-balance trial (9785-CL-0001):
The proposed metabolic profile is shown in Figure 9. Enzalutamide, M1, and M2 accounted for 88% of the $^{14}$C-radioactivity in plasma, representing 30%, 10%, and 49%, respectively, of the total $^{14}$C-AUC$_{0\text{-inf}}$. Metabolites M6 and M7 were trace components in plasma; each accounting for ≤ 2% of the radioactivity in the 6- and 24-hour postdose plasma samples and not detected at any other time point.

In urine, the most abundant $^{14}$C-component was M1 (62.7% of dose). In urine, M7 accounted for 9.45% of the radioactive dose. Minor components in urine were M5, M9, and M10, which accounted for 0.98%, 0.69%, and 0.67% of the dose, respectively. In addition, trace amounts of enzalutamide, M2, M6, and an unknown $^{14}$C component were observed in urine and each accounted for ≤ 0.42% of the dose.

In feces, the most abundant $^{14}$C-components were M1 and M10, which accounted for 3.34% and 4.26% of the radioactive dose, respectively. Less abundant $^{14}$C-components in feces were enzalutamide, M2, and M7, which accounted for 0.39%, 0.98%, and 1.12% of the radioactive dose, respectively.

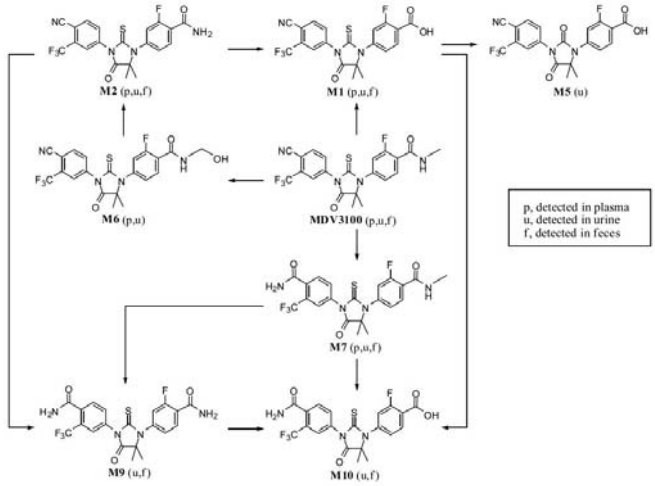



Figure 9. Proposed metabolic pathways of enzalutamide in humans *in vivo* (Study 9785-ME-0020).

### 2.2.14 What are the characteristics of drug excretion?

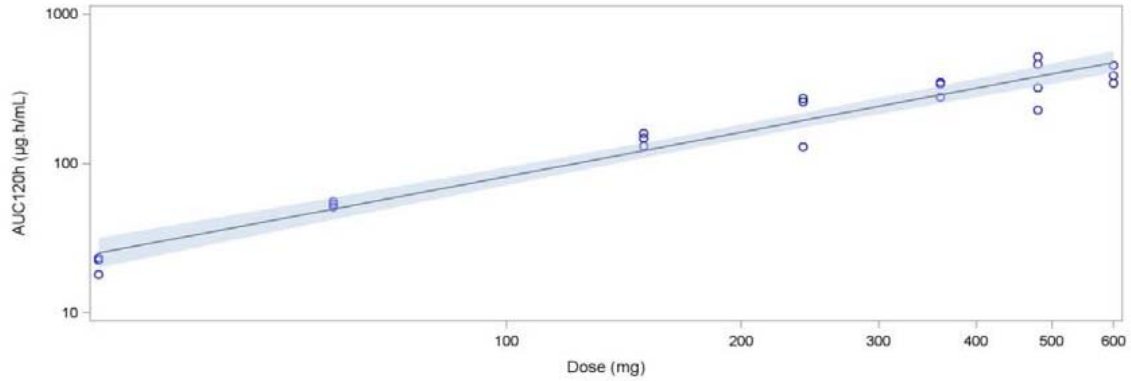
**Elimination**
Within 77 days post-dose, the mean percent of $^{14}$C-enzalutamide related material recovered in urine and feces were 71.0 and 13.6%, respectively (trial 9785-CL-0001).
**Clearance**
The applicant's estimated non compartmental model parameters obtained in trial S-3100-1-01 were used to calculate the enzalutamide apparent clearance. The mean apparent clearance (CL/F) of enzalutamide after a single oral dose in patients is 0.56 L/h (%CV = 29.9%, range 0.33 to 1.02 L/h). The mean apparent clearance of enzalutamide after a single oral dose appeared constant over the dose range of 30 mg to 600 mg/day (Section 2.2.8).
**Half-life**
The enzalutamide mean terminal elimination half-fife ($T_{1/2}$) following a single oral dose in patients is 5.8 days (range 2.8 to 10.2 days) (S-3100-1-01) (Section 2.2.8). Following a single 160 mg oral dose of enzalutamide in healthy volunteers (MDV3100-05), the mean $T_{1/2}$ values for the inactive major metabolite (M1) and the major active metabolite (M2) were 9 days (%CV: 23%), and 8.6 days (%CV: 21%), respectively.

### 2.2.15 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

Single Dose:
The Day 1 single dose noncompartmental model predicted $AUC_{24h}$, $AUC_{120h}$ and $C_{max}$ obtained from trial

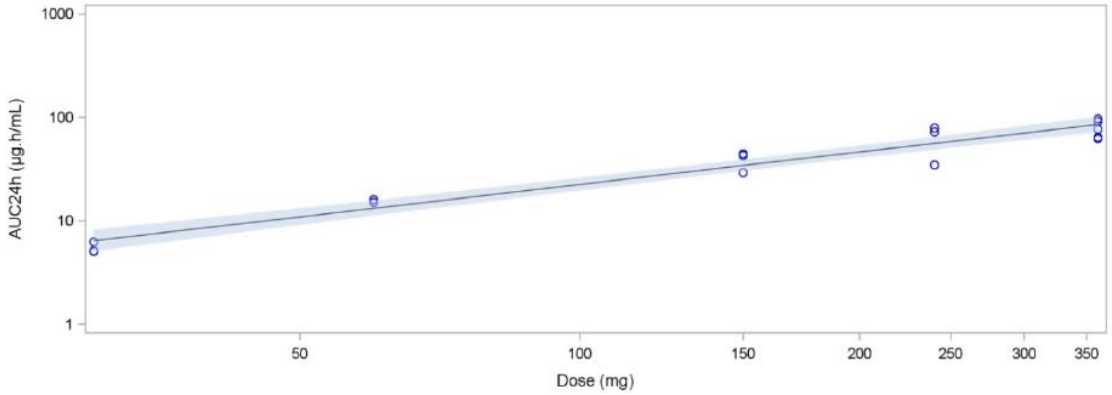
S-3100-1-01 were used by the applicant to asses the dose proportionality of enzalutamide in plasma at 30, 60, 150, 240, 360, 480 (240 mg BID) and 600 (300 mg BID) mg/day. Over the dose range of 30 to 600 mg/day, the slope (90% CI) of the line of the log $AUC_{120h}$ vs. log dose plot was 0.981 (0.891, 1.072). Over the dose range of 30 to 360 mg/day, the slope (90% CI) of the line of the log $AUC_{24h}$ vs. log dose plot was 1.042 (0.933, 1.151). Over the dose range of 30 to 360 mg/day, the slope (90% CI) of the line of the log $C_{max}$ vs. log dose plot was 1.035 (0.873, 1.198). These results from the analyses with $AUC_{120h}$, $AUC_{24h}$ and $C_{max}$ suggest dose-proportional pharmacokinetics of the daily dose range of 30 to 600 mg enzalutamide (Figure 10). The mean apparent clearance of enzalutamide after a single oral dose appeared constant over the dose range of 30 mg to 600 mg. This is consistent with the approximately linear enzalutamide pharmacokinetics observed over the same dose range.

Panel A



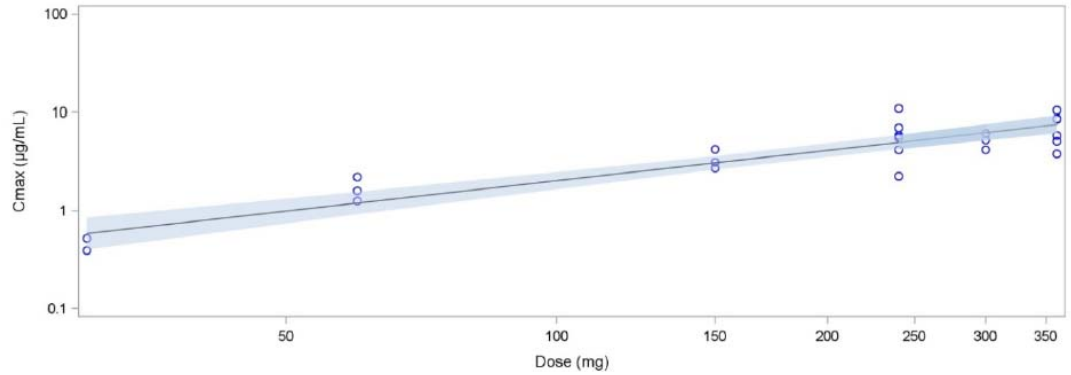

Ln(y)= 0.981*Ln(x) +b

Panel B




Ln(y)= 1.042*Ln(x) +b

Panel C



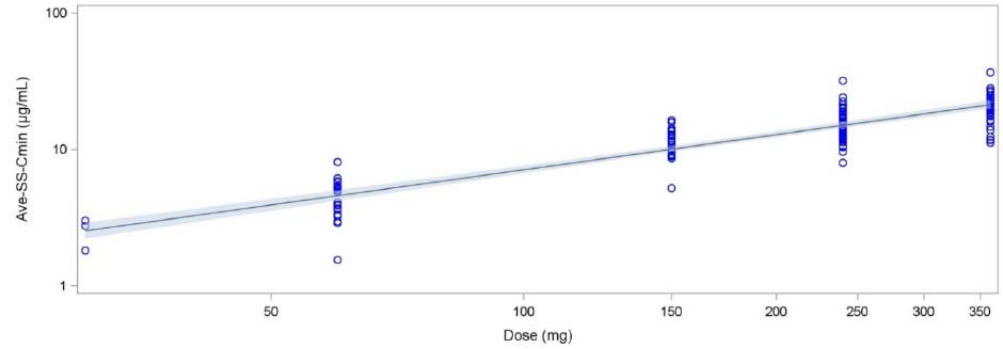

Ln(y)= 1.035 *Ln(x) +b

Figure 10. Transformed fit: Log $AUC_{120h}$ vs. Log of dose over the 30 to 600 mg/day dose range in patients. Panel B: Transformed fit: Log $C_{24h}$ vs. Log of dose over the 30 to 360 mg/day dose range in patients. Panel C: Transformed fit: Log $C_{max}$ vs. Log of dose over the single 30 to 360 mg/day oral dose range in patients. The shaded area represents the 90% confidence interval of the slope. (Study S-3100-1-01).

Multiple Dose:

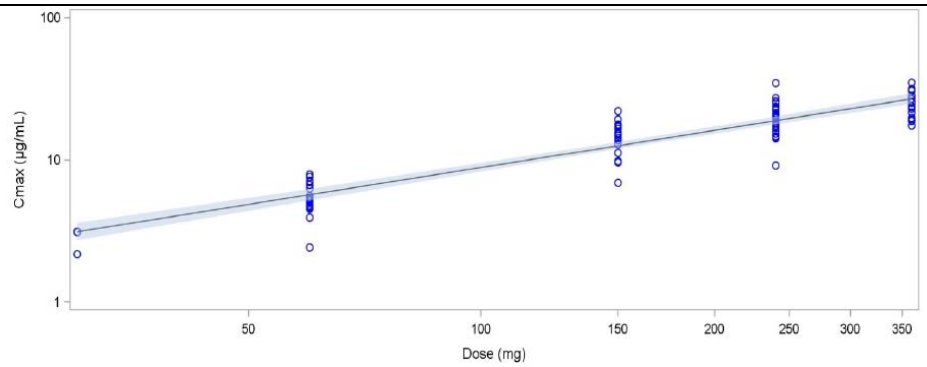
The Day 84 (steady state) noncompartmental model predicted individual time-averaged steady-state $C_{min}$, $C_{max}$ and $AUC_{0-\tau}$ (AUC from time 0 to 24 hours after dosing on Day 84 of the Multiple-Dose Period) obtained from trial S-3100-1-01 were used to asses the dose proportionality of enzalutamide in plasma following daily dosing at 30, 60, 150, 240 and 360 mg. Over the dose range of 30 to 360 mg/day, the slope (90% CI) of the line of the log time-averaged steady-state $C_{min}$ vs. log dose plot was 0.858 (0.798, 0.918). Over the dose range of 30 to 360 mg/day, the slope (90% CI of the line of the $C_{max}$ vs. log dose plot was 0.867 (0.802, 0.933). Over the dose range of 30 to 360 mg/day, the slope (90% CI of the line of the log $AUC_{0-\tau}$ vs. log dose plot was 0.872 (0.799, 0.944). These results from the analyses with time-averaged steady-state $C_{min}$, $C_{max}$ and $AUC_{0-\tau}$ indicate approximately dose-proportional pharmacokinetics of the daily dose range of 30 to 360 mg enzalutamide (Figure 11).

Panel A:



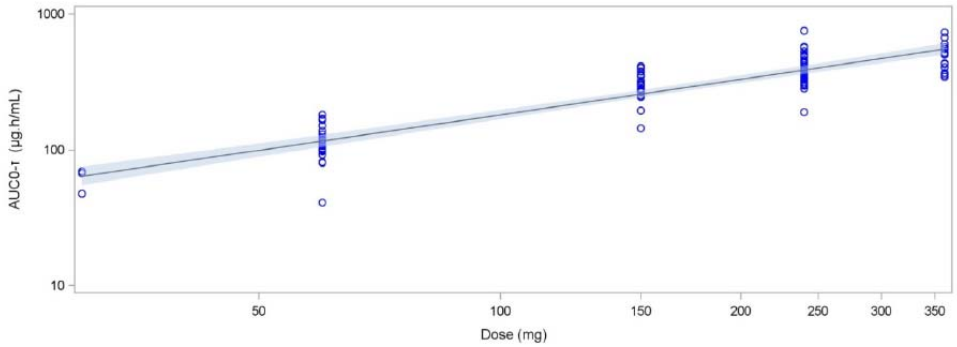

Ln(y)= 0.858 *Ln(x) +b

Panel B:




Ln(y)= 0.867 *Ln(x) +b

Panel C:




Ln(y)= 0.872 *Ln(x) +b

Figure 11. Figure. Panel A: Transformed fit: Multiple dose (Day 84) Log time-averaged steady-state $C_{min}$, vs. Log of Dose over the dose range of 30 to 360 mg in patients. Panel B: Transformed fit: Multiple dose (Day 84) Log $C_{max}$, vs. Log of Dose over the dose range of 30 to 360 mg in patients. Panel C: Transformed fit: Multiple dose (Day 84) Log $AUC_{0-\tau}$, vs. Log of Dose over the dose range of 30 to 360 mg in patients. The shaded area represents the 90% confidence interval of the slope. (Study S-3100-1-01).

**2.2.16 How do the PK parameters change with time following chronic dosing?**

Enzalutamide exposure increases with multiple dosing in patients with CRPC. In the Phase 1 dose-escalation study (S-3100-1-01), plots of mean $C_{min}$ versus time show that steady state was achieved by approximately 1 month (28 days). The steady state (Day 84) peak-to-trough ratio (PTR) ($C_{max}/C_{24h}$) averaged 1.25 (range 1.00 to 1.72) (Study S-3100-1-01). The mean accumulation index was 8.33 (range 4.17 to 13.56) (Study S-3100-1-01).

In patients with CRPC, the interindividual variability (% CV) values for $C_{max}$ and AUC were similar following a single dose (Day 1, 150 mg dose) and multiple doses of enzalutamide to steady state (Day 84, 150 mg/day) (Study S-3100-1-01). On Day 1, the %CV values for $C_{max}$ and $AUC_{0-inf}$ were 23% and 15%, respectively. On Day 84, the %CV values for $C_{max}$ and $AUC_{0-\tau}$ were 23% and 23%, respectively.

**2.2.17 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?**

The intersubject variability in enzalutamide, M1 and M2 PK parameters appeared similar in patients and healthy volunteers.

The intersubject variability of PK parameters in healthy volunteers was determined in the parallel-design food-effect study (MDV3100-05). After administration of a single oral dose under fasted and fed conditions, the intersubject variability (% CV) in $C_{max}$ and $AUC_{inf}$ values were ≤ 31% and ≤ 29% for enzalutamide and M2, respectively, irrespective of food (see Section 2.2.8). For M1, the intersubject variability for $C_{max}$ was ≤ 58% and for $AUC_{inf}$ was 24%. (see Section 2.2.8).

The intersubject and intrasubject variability of PK parameters for enzalutamide were determined in patients with castration-resistant prostate cancer in the Phase 1 dose-escalation study (S-3100-1-01). In the single-dose period, intersubject variability (%CV) in the $C_{max}$ and $AUC_{inf}$ ranged from 15% to 52% (see Section 2.2.8). In the multiple-dose period, intersubject variability (%CV) in the $C_{max}$ and $AUC_{\tau}$ ranged from 19% CV to 30% CV (see Section 2.2.8).

The intersubject variability of steady-state $C_{min}$ values for enzalutamide, M1, and M2 during multiple-dose administration of enzalutamide (160 mg/day) were determined in patients with castration-resistant prostate cancer in the pivotal Phase 3 study (CRPC2). At steady state, the intersubject variability (%CV) in $C_{min}$ values was low for enzalutamide (26%), and M2 (29%) and moderate for M1 (80%) (see Section 2.2.8).

## 2.3 INTRINSIC FACTORS

### 2.3.1 What intrinsic factors (age, race, weight, height, genetic polymorphisms and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

No formal studies have been conducted to assess the effect of age, race, weight, height, genetic polymorphisms or renal dysfunction on exposure and response to enzalutamide. The applicant population pharmacokinetic analysis (ICON 2147014) included data from trial MDV3100-05 (healthy volunteers), S-3100-1-01 (patients), and CRPC2 (patients), and assessed the influence of covariates age, body weight and serum creatinine on the between-patient differences in enzalutamide pharmacokinetic parameters. The population PK model characterized the concentrations of enzalutamide. The FDA pharmacometrics reviewer concluded that the small magnitudes of covariate effects (age, body weight and renal function) on enzalutamide exposure are not clinically relevant and there is no need for dose adjustment based on any of these covariates.

**Relationship between Gender and Exposure**
The proposed indication is for the treatment of patients with castration-resistant prostate cancer, and therefore females were not enrolled in any of the submitted clinical trials.

**Relationship between Race and Exposure**
It was not possible to assess the effect of race due to the limited enrollment of races other than Caucasians in the submitted clinical trials. Pharmacokinetic data were available for the population PK analysis from 985 patient/volunteers, and >92% of these were White.

**Relationship between Weight (BMI) and Exposure**
Based on the pharmacometrics reviewer's review of the population PK model, there was no clinically relevant effect of body weight on enzalutamide exposure (see Pharmacometrics Review).

**Relationship between Age and Exposure**
Based on the pharmacometrics reviewer's review of the population PK analysis, age has no statistically

significant effect on enzalutamide pharmacokinetics.

**Relationship between Renal Impairment and Exposure:**
Based on the pharmacometrics reviewer's analysis of the applicant population pharmacokinetic dataset described above, no dose adjustments are needed for patients with calculated CrCL values ≥ 30 mL/min. The CrCL was calculated by the Cockcroft and Gault equation, and the CL/F was estimated for each individual in the PK data set, i.e. normal renal function (CrCL ≥ 90 mL/min, N=512), mild renal impairment (CrCL 60 to < 90 mL/min, N=332), moderate renal impairment (CrCL 30 to < 60 mL/min, N=88), and severe renal impairment (CrCL < 30 mL/min, N=1). The impact of renal impairment was also examined by calculating the deviation in exposures corresponding to CrCL at the breakpoints of renal impairment categories as compared to the exposure for a "typical patient" ((BW=70 kg; AGE=69 yr; CREA=0.9 mg/dL). The FDA pharmacometrics reviewer concluded that the small magnitude of mild and moderate renal impairment on enzalutamide exposure is not clinically relevant, and there is no need for dose adjustment in patients with CrCL ≥ 30 mL/min. The potential effect of severe renal impairment or end stage renal disease on enzalutamide pharmacokinetics cannot be determined as clinical and pharmacokinetic data are available from only one patient (see Pharmacometrics Review).

**Relationship between Hepatic Impairment and Exposure:**
There were no available PK data to assess the effect of severe hepatic impairment (Child-Pugh class C) on enzalutamide, M1 and M2 pharmacokinetics. Mild and moderate hepatic impairment did not have a significant effect on the **sum of enzalutamide plus M2 exposure**.

A dedicated trial was conducted to assess the effect of mild and moderate hepatic impairment on the enzalutamide, M1 and M2 plasma pharmacokinetics. A single 160 mg oral dose (four 40 mg tablets) of enzalutamide was administered under fasted conditions to male volunteers with mild hepatic impairment (Child-Pugh A score 5-6, N=8), moderate hepatic impairment (Child-Pugh B score 7-9, N=8) and normal hepatic function matched for age and BMI (N=8 and N=9 to match mild and moderate impairment groups, respectively). Blood sampling for determination of plasma concentrations of enzalutamide, M1 and M2 occurred for approximately 5 times the $T_{1/2}$ of the metabolite with the longest half-life (M1) at predose and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8 and 12 (day 1), 24, 36 (day 2), 48 (day 3), 72 (day 4), 120 (day 6), 168 (day 8), 264 (day 12), 336 (day 15), 432 (day 19), 504 (day 22), 600 (day 26), 672 (day 29), 840 (day 36), 1008 (day 43), and 1176 (day 50) hours postdose.

Table 13 summarizes the plasma **enzalutamide** pharmacokinetic parameters for volunteers with mild hepatic impairment and normal hepatic function. The geometric mean ratio (90% CI) of $AUC_{0-\infty}$ between volunteers with mild hepatic impairment and matched control volunteers with normal hepatic function was 1.05 (0.79, 1.39). The geometric mean ratio (90% CI) of $C_{max}$ between volunteers with mild hepatic impairment and matched control volunteers with normal hepatic function was 1.24 (0.92, 1.66). For volunteers with mild hepatic impairment, the inter-patient variability (CV%) values for the arithmetic mean $AUC_{0-\infty}$ and $C_{max}$ were 16.5% and 17.3%, respectively. For volunteers with normal hepatic function, the inter-patient variability (CV%) values for $AUC_{0-\infty}$ and $C_{max}$ were 27.9% and 35.5%, respectively.

Table 13 summarizes the plasma **enzalutamide** pharmacokinetic parameters for volunteers with moderate hepatic impairment and normal hepatic function. The geometric mean ratio (90% CI) of $AUC_{0-\infty}$ between volunteers with moderate hepatic impairment and matched control volunteers with normal hepatic function was 1.29 (1.09, 1.65). The geometric mean ratio (90% CI) of $C_{max}$ between volunteers with moderate hepatic impairment and matched control volunteers with normal hepatic function was 0.89 (0.69, 1.16). For volunteers with moderate hepatic impairment, the inter-patient variability (CV%) values for the arithmetic mean $AUC_{0-\infty}$ and $C_{max}$ were 41.4% and 56.6%, respectively. For volunteers with

normal hepatic function, the inter-patient variability (CV%) values for $AUC_{0-\infty}$ and $C_{max}$ were 22.5% and 21.5%, respectively.

Table 13. Statistical Assessment of enzalutamide exposure parameters after single dose enzalutamide administered in mild (A) and moderate (B) hepatic impaired volunteers, compared to administration in healthy control volunteers with normal hepatic function (9785-CL0009)

| A: Effect of Mild Hepatic Impairment | | | | |
|---|---|---|---|---|
| | Geometric Means | | | |
| Parameter (Units) | Mild Hepatic Impaired (test) | Normal Hepatic Function (reference) | Ratio (Test/ Reference) | 90% CI |
| n | 6 | 6 | | |
| $AUC_{0-inf}$ (h*µg/mL) | 250.07 | 238.34 | 1.05 | 0.79 - 1.39 |
| $C_{max}$ (µg/mL) | 4.38 | 3.55 | 1.24 | 0.92 - 1.66 |
| $AUC_{0-inf,u}$ (h*µg/mL) | 3.70 | 3.71 | 1.00 | 0.66 - 1.52 |
| $C_{max,u}$ (µg/mL) | 0.065 | 0.055 | 1.18 | 0.82 - 1.69 |
| **B: Effect of Moderate Hepatic Impairment** | | | | |
| | Geometric Means | | | |
| Parameter (Units) | Moderate Hepatic Impaired (test) | Normal Hepatic Function (reference) | Ratio (Test/ Reference) | 90% CI |
| n | 8 | 8 | | |
| $AUC_{0-inf}$ (h*µg/mL) | 282.89 | 218.99 | 1.29 | 1.01 - 1.65 |
| $C_{max}$ (µg/mL) | 3.34 | 3.74 | 0.89 | 0.69 - 1.16 |
| $AUC_{0-inf,u}$ (h*µg/mL) | 5.58 | 4.76 | 1.17 | 0.82 - 1.69 |
| $C_{max,u}$ (µg/mL) | 0.066 | 0.081 | 0.81 | 0.59 - 1.11 |

Table 14 summarizes the plasma M2 pharmacokinetic parameters for volunteers with mild or moderate hepatic impairment and normal hepatic function. Administration of a single dose enzalutamide resulted in similar M2 $AUC_{0-inf}$ and $C_{max}$ values in volunteers with mild or moderate hepatic impairment vs. normal hepatic function.

Table 14. Statistical Assessment of M2 exposure parameters after single dose enzalutamide administered in mild (A) and moderate (B) hepatic impaired volunteers, compared to administration in healthy control volunteers with normal hepatic function (9785-CL0009)

| A: Effect of Mild Hepatic Impairment | | | | |
|---|---|---|---|---|
| | Geometric Means | | | |
| Parameter (Units) | Mild Hepatic Impaired (test) | Normal Hepatic Function (reference) | Ratio (Test/ Reference) | 90% CI |
| n | 6 | 6 | | |
| $AUC_{0-inf}$ (h*µg/mL) | 375.81 | 318.45 | 1.18 | 0.90 - 1.54 |
| $C_{max}$ (µg/mL) | 0.75 | 0.59 | 1.26 | 0.92 - 1.72 |
| $AUC_{0-inf,u}$ (h*µg/mL) | 9.95 | 8.29 | 1.20 | 0.82 - 1.75 |
| $C_{max,u}$ (µg/mL) | 0.020 | 0.015 | 1.28 | 0.86 - 1.91 |
| **B: Effect of Moderate Hepatic Impairment** | | | | |
| | Geometric Means | | | |
| Parameter (Units) | Moderate Hepatic Impaired (test) | Normal Hepatic Function (reference) | Ratio (Test/ Reference) | 90% CI |
| n | 8 | 8 | | |
| $AUC_{0-inf}$ (h*µg/mL) | 316.21 | 294.86 | 1.07 | 0.85 - 1.35 |
| $C_{max}$ (µg/mL) | 0.52 | 0.61 | 0.85 | 0.65 - 1.11 |
| $AUC_{0-inf,u}$ (h*µg/mL) | 11.24 | 10.10 | 1.11 | 0.80 - 1.54 |
| $C_{max,u}$ (µg/mL) | 0.018 | 0.021 | 0.88 | 0.62 - 1.24 |

U: Refers to Parameters for unbound concentrations of M2.

The **sum of enzlutamide plus M2** plasma concentrations vs. time profiles for up to 50 hours post dosing

in patients with mild or moderate hepatic impairment and normal hepatic function were used to calculate the plasma PK parameters for the sum of enzalutamide plus M2. Table 15 summarizes the plasma pharmacokinetic parameters for the sum of **enzalutamide plus M2** in volunteers with mild hepatic impairment and normal hepatic function. Administration of a single dose enzalutamide resulted in a similar $AUC_{0\text{-}inf}$ and $C_{max}$ for the sum of enzalutamide plus M2 in volunteers with mild hepatic impairment vs. normal hepatic function. After administration of a single dose of enzalutamide to volunteers with mild hepatic impairment $AUC_{0\text{-}inf}$ and $C_{max}$ for the sum of enzalutamide plus M2 were 13% (GM ratio: 1.13; 90% CI: 0.89 - 1.43) and 23% (GM ratio: 1.23; 90% CI: 0.92 - 1.66) higher, respectively, compared to after administration in healthy control volunteers, matched for BMI and age. The inter-subject variability on AUC was low and comparable in both subject groups (range: 19.2% - 23.1%). Percent CV on $C_{max}$ was 17.0% for volunteers with mild hepatic impairment and 35.2% for healthy control volunteers.

Table 15 summarizes the plasma pharmacokinetic parameters for the **sum of enzalutamide plus M2** in volunteers with moderate hepatic impairment and normal hepatic function. For the sum of enzalutamide plus M2, administration of a single dose enzalutamide resulted in 18% higher $AUC_{0\text{-}inf}$ (GM ratio: 1.18; 90% CI: 0.96 - 1.45) in volunteers with moderate hepatic impairment compared to healthy control volunteers. $C_{max}$ was 11% lower (GM ratio: 0.89; 90% CI: 0.69 - 1.15). The inter-subject variability on AUC was low and comparable in both subject groups (range: 20.4% - 24.6%). Percent CV on $C_{max}$ was higher (56.7%) for volunteers with moderate hepatic impairment compared to the %CV on $C_{max}$ for healthy control volunteers (21.4%).

Table 15. Statistical assessment of enzalutamide + M2 exposure parameters after single-dose enzalutamide administered in mild (A) and moderate (B) hepatic impaired volunteers, compared to administration in healthy control volunteers with normal hepatic function (9785-CL0009).

| **A: Effect of Mild Hepatic Impairment** | | | | |
|---|---|---|---|---|
| | **Geometric Means** | | | |
| **Parameter (Units)** | **Mild Hepatic Impaired (test)** | **Normal Hepatic Function (reference)** | **Ratio (Test/ Reference)** | **90% CI** |
| n | 6 | 6 | | |
| $AUC_{0\text{-}inf}$ (h*µg/mL) | 629.48 | 556.41 | 1.13 | 0.89 - 1.43 |
| $C_{max}$ (µg/mL) | 4.41 | 3.59 | 1.23 | 0.92 - 1.66 |
| **B: Effect of Moderate Hepatic Impairment** | | | | |
| | **Geometric Means** | | | |
| **Parameter (Units)** | **Moderate Hepatic Impaired (test)** | **Normal Hepatic Function (reference)** | **Ratio (Test/ Reference)** | **90% CI** |
| n | 8 | 8 | | |
| $AUC_{0\text{-}inf}$ (h*µg/mL) | 609.97 | 517.45 | 1.18 | 0.96 - 1.45 |
| $C_{max}$ (µg/mL) | 3.35 | 3.76 | 0.89 | 0.69 - 1.15 |

**2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dose adjustments, if any, are recommended for each of these groups? If dose adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

**Renal Impairment:**

The effect of renal impairment on the pharmacokinetics of enzalutamide was investigated in the population PK analysis described above. No dose adjustments are necessary for patients with calculated CrCL values ≥ 30 mL/min. Assessment of the effect of renal impairment on M2 may not be relevant

since M2 has a minor renal clearance component. Thus, M2 exposures are not expected to be modulated to a clinically meaningful extent with mild and moderate renal impairment (see Pharmacometrics Review). There were insufficient pharmacokinetic data available to assess the effect of severe renal impairment (CrCL < 30 mL/min, N=1) or end-stage renal disease (N=0) on enzalutamide pharmacokinetics.

**Hepatic Impairment:**
The effect of hepatic impairment on the pharmacokinetics of enzalutamide (and its metabolites M1 and M2) was investigated in trial 9785-CL-0009 discussed above. Based on the results from this trial, no dose adjustments are needed for use in patients with mild or moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of enzalutamide has not been studied. *Due to the positive risk-benefit relationship for enzalutamide, and the medical need, a PMR will be requested to evaluate the effect of severe hepatic impairment on the PK of enzalutamide and its major metabolites.*

**Pediatric patients**
Enzalutamide has not been studied in pediatric patients.

### 2.3.3 What pregnancy and lactation use information is there in the application?

Enzalutamide was not studied in women, pregnancy and in lactating women.

## 2.4 EXTRINSIC FACTORS

### 2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The effects of extrinsic factors such as herbal products, diet, smoking and alcohol use on the dose-exposure and/or dose-response for enzalutamide were not assessed in a formal study.

**Drug-drug interactions**

### 2.4.2 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

As a substrate (*in vitro*)
The *in vitro* screens (Study 9785-ME-0001 and 9785-ME-0025) indicate that CYP2C8 and CYP3A4/5 are the primary CYP450 isozymes responsible for the metabolism of enzalutamide. Specifically, enzalutamide appears to be metabolized to M6 by CYP2C8 and CYP3A4/5, and M6 degrades to the active metabolite M2 in a reaction that may or may not require metabolic enzymes. These in vitro results combined with the in vivo drug interaction trial (9785-CL-0006) results suggest that CYP2C8 is primarily responsible for the formation of the active metabolite M2. (see Section 2.4.3). Based on the in vitro screen results the effect of a potent CYP2C8 inhibitor and a potent CYP3A4 inhibitor on the PK of enzalutamide was evaluated (9785-CL-0006) in vivo (see Section 2.4.3).

*The effects of CYP2C8 and CYP3A4 inducers on the pharmacokinetics of enzalutamide and M2 were not investigated in vivo, and a PMR will be requested to address this.*

*The metabolism of M2 was not investigated, and a PMR will be requested to address this.*

As an inhibitor (*in vitro*)
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 $IC_{50}$ of CYP2C8 was the lowest. The applicant assessed the effect of enzalutamide on CYP2C8, 2C9, 2C19 and 3A4 mediated metabolism *in vivo* (trial 9785-CL-0007, see Section 2.4.3).

The potential for **enzalutamide** (PRO3100NC24), **M1** (9785-ME-0009), and **M2** (9785-ME-0010) to inhibit 7 major CYP isoform [redacted] (b) (4) It was not possible to test higher concentrations due to solubility limitations. The concentration range of enzalutamide, M1 and M2 evaluated in the study is acceptable, as the range includes clinically relevant concentrations (S-3100-1-01).

Study PRO3100NC24 evaluated enzalutamide for its ability to act as a direct inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 activity. Human liver microsomes from a pool of sixteen individuals were incubated with marker substrates at concentrations approximately equal to their apparent $K_m$, in the presence or absence of enzalutamide. Enzalutamide was further evaluated for its ability to function as a time-dependent inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 [redacted] (b) (4), and in this case enzalutamide was pre-incubated with human liver microsomes and an NADPH generating system for 30-minutes to allow for the generation of metabolites that might inhibit CYP activity. Known direct and metabolism-dependent inhibitors of CYP enzymes were included as positive controls.

Enzalutamide caused direct inhibition of CYP2B6, CYP2C8, CYP2C9 and CYP2C19 with $IC_{50}$ values of 42 µM, 10 µM, 50 µM and 23 µM, respectively (Table 16). The applicant determined the $K_i$ values for enzalutamide mediated inhibition of CYP2C8 and CYP2C19 as 5.5 µM and 8.6 µM, respectively. $K_i$ values for CYP2B6 and 2C9 were estimated based on the FDA Drug Interaction Guidance ($IC_{50}/2$) as 21 µM and 25 µM, respectively. There was also evidence of direct inhibition of CYP2D6 and CYP3A4/5 (as measured by testosterone 6β-hydroxylation) by enzalutamide, as 37% and 26% inhibition was observed at enzalutamide concentrations up to 84 µM; however, the $IC_{50}$ value for these enzymes was reported as greater than 84 µM (estimated $K_i$ values ($IC_{50}/2$) of 42 µM). The calculated R values ($1 + I/K_i$) for CYP2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 at the clinically relevant enzalutamide $C_{max}$ concentration (160 mg/day dose) at steady state (31.13 µM) were all > 1.1 at 2.5, 6.7, 2.2, 4.6, 1.74 and 1.74, respectively. This indicates the potential for in vivo drug-drug interactions is likely for substrates of CYP2B6, 2C8, 2C9, 2C19, 2D6 and 3A4. See Section 2.4.3 for the in vivo study to assess the effect of enzalutamide (and its metabolites M1 and M2) on the PK of specific CYP substrates (trial 9785-CL-0007).

Enzalutamide caused no discernable time-dependent inhibition of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 (using both testosterone and midazolam as marker substrates), as no distinct increase in inhibition was observed upon pre-incubation (Table 16). Enzalutamide caused time-dependent inhibition of CYP1A2, as an increase in inhibition was observed after enzalutamide was pre-incubated with human liver microsomes for 30 minutes. The applicant states that the time-dependent inhibition of CYP1A2 was dependent on NADPH and is not resistant to dilution (Table 16). As the inhibition is not resistant to dilution, the time-dependent inhibition appears not to be metabolism-dependent.

Table 16. Summary of in vitro evaluation of enzalutamide as an inhibitor of major human CYP isozymes (table reproduced from PRO3100NC24)

| | | Direct inhibition | | | | Time-dependent inhibition | | |
|---|---|---|---|---|---|---|---|---|
| | | Zero-minute pre-incubation | | | | 30-minute pre-incubation | | |
| Enzyme | CYP Reaction | $IC_{50}$ (μM) | Maximum inhibition at 84 μM (%) [a] | $K_i$ (μM) | Type of inhibition | $IC_{50}$ (μM) | Maximum inhibition at 84 μM (%) [a] | Potential for time-dependent inhibition [b] |
| CYP1A2 | Phenacetin *O*-deethylation | >84 | 5.4 | ND | ND | 56 | 61 | yes[c] |
| CYP2B6 | Bupropion hydroxylation | 42 | 70 | ND | ND | 53 | 67 | little or no |
| CYP2C8 | Amodiaquine *N*-dealkylation | 10 | 94 | 5.5 | mixed | 7.6 | 95 | little or no |
| CYP2C9 | Diclofenac 4´-hydroxylation | 50 | 66 | ND | ND | 53 | 66 | little or no |
| CYP2C19 | *S*-Mephenytoin 4´-hydroxylation | 23 | 87 | 8.6 | mixed | 19 | 88 | little or no |
| CYP2D6 | Dextromethorphan *O*-demethylation | >84 | 37 | ND | ND | >84 | 36 | little or no |
| CYP3A4/5 | Testosterone 6β-hydroxylation | >84 | 26 | ND | ND | >84 | 33 | little or no |
| CYP3A4/5 | Midazolam 1´-hydroxylation | >84 | NA | ND | ND | >84 | NA | little or no |

Notes: Average data (i.e., percent of control activity) obtained from duplicate samples for each test article concentration were used to calculate IC50 values.
a Maximum inhibition (%) is calculated with the following formula and data for the highest concentration of test article evaluated (results are rounded to two significant figures): Maximum inhibition (%) = 100% – Percent solvent control.
b Time-dependent inhibition was determined by comparison of IC50 values with and without pre-incubation, by comparison of the maximum inhibition
(%) with and without pre-incubation and by visual inspection of the IC50 plot.
c Upon further investigation, the increase in inhibition upon pre-incubation is dependent on NADPH and is not resistant to dilution.
NA Not applicable. No value was obtained as the rates at the highest concentration of MDV3100 evaluated (84 μM) were higher than the control rates.
ND Not determined.

Study 9785-ME-0009 evaluated the ability of M1 to inhibit human CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 (Table 17). M1 directly inhibited CYP2C8 with an $IC_{50}$ value of 20 μmol/L (9.0 μg/mL). M1 caused 45% and 22% inhibition of CYP2B6 and CYP2C19 activities, respectively, at 300 μmol/L. The estimated $K_i$ values ($IC_{50}/2$) for CYP2C8, 2B6 and 2C19 were 10 μM, 150 μM and 150 μM, respectively. M1 did not show evidence of direct inhibition of CYP1A2, CYP2C9, CYP2D6 or CYP3A4/5; therefore, the $IC_{50}$ values for CYP1A2, CYP2C9, CYP2D6 and CYP3A4/5 were reported as >300 μmol/L (>135 μg/mL). The mean M1 steady-state plasma $C_{min}$ in patients taking 160 mg/day enzalutamide is 8.44 μg/mL (18.7 μM). The calculated R values ($1 + I/K_i$) for CYP2C8, 2B6, and 2C19 at the clinically relevant M1 $C_{min}$ concentration (steady state at 160 mg/day enzalutamide) of 18.7 μM were > 1.1 at 2.87, 1.12 and 1.12, respectively. There was no evidence of either time-dependent or metabolism-dependent inhibition of any CYP enzyme examined. See Section 2.4.3 for the in vivo study to assess the effect of enzalutamide (and its metabolites M1 and M2) on the PK of specific CYP substrates (trial 9785-CL-0007).

Table 17. *In Vitro* Evaluation of M1 as an Inhibitor of Human CYP Enzymes (reproduced from 9785-ME-0009).

| Enzyme | Enzyme reaction | Direct inhibition | | Time-dependent inhibition | | Metabolism-dependent inhibition | | |
|---|---|---|---|---|---|---|---|---|
| | | Zero-minute preincubation | | 30-minute preincubation without NADPH | | 30-minute preincubation with NADPH | | |
| | | $IC_{50}$ (µmol/L) [a] | Inhibition observed at 300 µmol/L (%) [b] | $IC_{50}$ (µmol/L) [a] | Inhibition observed at 300 µmol/L (%) [b] | $IC_{50}$ (µmol/L) [a] | Inhibition observed at 300 µmol/L (%) [b] | Potential for metabolism-dependent inhibition [c] |
| CYP1A2 | Phenacetin *O*-dealkylation | >300 | 6.8 | >300 | 10 | >300 | 14 | No |
| CYP2B6 | Efavirenz 8-hydroxylation | >300 | 45 | >300 | 45 | >300 | 46 | No |
| CYP2C8 | Amodiaquine *N*-dealkylation | 20 | 100 | 19 | 100 | 24 | 100 | No |
| CYP2C9 | Diclofenac 4′-hydroxylation | >300 | 15 | >300 | 13 | >300 | 19 | No |
| CYP2C19 | *S*-Mephenytoin 4′-hydroxylation | >300 | 22 | >300 | 18 | >300 | 23 | No |
| CYP2D6 | Dextromethorphan *O*-demethylation | >300 | 0.8 | >300 | 3.4 | >300 | 3.9 | No |
| CYP3A4/5 | Testosterone 6β-hydroxylation | >300 | 2.8 | >300 | 4.3 | >300 | 14 | No |
| CYP3A4/5 | Midazolam 1′-hydroxylation | >300 | NA | >300 | NA | >300 | NA | No |

a Average data (i.e., percent of control activity) obtained from duplicate samples for each test article concentration were used to calculate $IC_{50}$ values.
b Maximum inhibition (%) is calculated with the following formula and data for the highest concentration of test article evaluated (results are rounded to two significant figures): Maximum inhibition (%) = 100% − Percent solvent control.
c Metabolism-dependent inhibition was determined by comparison of $IC_{50}$ values with and without pre-incubation, by comparison of the maximum inhibition (%) with and without pre-incubation and by visual inspection of the $IC_{50}$ plot.
NA Not applicable. No value was obtained as the rates at the highest concentration of MDPC0001 evaluated (300 µmol/L) were higher than the control rates.

Study 9785-ME-0010 evaluated the ability of M2 to inhibit human CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. M2 directly inhibited CYP2B6, CYP2C8, CYP2C9 and CYP2C19 as $IC_{50}$ values for direct inhibition of these enzymes were calculated to be 59 µmol/L (27 µg/mL), 28 µmol/L (13 µg/mL), 56 µmol/L (25 µg/mL), and 40 µmol/L (18 µg/mL), respectively. M2 caused 41% inhibition of CYP2D6 at 100 µmol/L, and did not show evidence of direct inhibition of CYP1A2 or CYP3A4/5; therefore, the $IC_{50}$ values for CYP1A2, CYP2D6, and CYP3A4/5 were reported as > 100 µmol/L (>45 µg/mL). The estimated $K_i$ values ($IC_{50}$/2) for CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 were 30 µM, 14 µM, 28 µM, 20 µM and 50 µM, respectively. The mean M2 steady-state plasma $C_{min}$ in patients taking 160 mg/day enzalutamide is 13.0 µg/mL (28.9 µM). The calculated R values (1 +I/$K_i$) for CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 at the clinically relevant M2 $C_{min}$ concentration (steady state, 160 mg/day enzalutamide) of 28.9 µM were > 1.1 at 1.96, 3.06, 2.03, 2.44 and 1.58, respectively. See Section 2.4.3 for the in vivo study to assess the effect of enzalutamide (and its metabolites M1 and M2) on the PK of specific CYP substrates (trial 9785-CL-0007).

As an inducer (*in vitro*)

The applicant did not study the potential of N-desmethyl enzalutamide to induce CYP1A2, 2B6, and 3A4 in vitro. Study PRO3100NC23 evaluated the potential of enzalutamide to induce enzymatic activity and mRNA of CYP1A2, 2B6, and 3A4 in human primary hepatocyte cultures from three different donors as recommended by FDA (Table 18). The highest concentration of enzalutamide that could be maintained in solution in the cell system studied was 2.5 µM (1.16 µg/mL), and enzalutamide was thus studied at 0.1, 0.5, and 2.5 µM (0.0464, 0.23, and 1.16 µg/mL) [n=3]. The concentration range evaluated in this study was significantly lower than the mean steady state $C_{max}$ for the 150 mg/day dosing regimen is 14.46 µg/mL (31.1 µM) (S-3100-1-01). Induction effects of enzalutamide were directly compared to those of a vehicle control and the following three inducers: (1) 3-methylcholanthrene (a prototypical CYP1A enzyme inducer), (2) phenobarbital (PB) (a prototypical CYP2B inducer), and (3) rifampicin (a prototypical CYP3A enzyme inducer) at FDA recommended concentrations. All three hepatocyte cultures demonstrated appropriate induction of enzyme activity and increases in mRNA expression in response to treatment with the prototypical CYP1A, CYP2B, and CYP3A inducers. Based on the FDA guidance for industry, studies using human hepatocytes in culture are acceptable and if the increase in

enzyme activity for the NME treated cells is > 40% of the positive considered an enzyme inducer and an *in vivo* induction study is recommended. As discussed below, enzalutamide does not appear to be an inducer of CYP1A2 over the concentration range studied, it may be an inducer of CYP2B6, and it appears to be an inducer of CYP3A4.

The data showed that at the concentration range studied, the increase in CYP1A2 enzyme activity ranged from -0.71% to 4.9% of the adjusted positive control response across all hepatocyte cultures treated with enzalutamide (Table 18). Analysis of the CYP1A2 mRNA content also demonstrated that the increase in CYP1A2 mRNA content ranged from 0.47% to 2.5% of the adjusted positive control response across all hepatocyte cultures treated with enzalutamide. The concentration range studied was lower than that observed in patients (approximately 20% of the $C_{max}$ observed in patients), and therefore this study was not able to conclusively determine that enzalutamide was not an inducer of CYP1A2 at clinically relevant concentrations. However, given the small increases in CYP1A2 activity and mRNA content over the concentration range studied, and the lack of concentration-related increases in CYP1A2 activity or mRNA levels, it appears that enzalutamide is not a strong inducer of CYP1A2.

The applicant concluded that enzalutamide is not an inducer of CYP2B6, however based on the data submitted, FDA concludes that induction of CYP2B6 cannot be ruled out, based on results from this in vitro screen (Table 18). Data relevant to CYP2B6 showed a marked induction of hydroxybupropion formation from bupropion with the positive control, PB (1000 μM), in all three human hepatocyte preparations (5.2- to 18.9-fold greater than vehicle control. The data showed that at the enzalutamide concentration range studied, there was some evidence of a concentration-dependent increase in CYP2B6 enzyme activity and mRNA levels. In the culture from one subject, the enzyme activity increased up to 23.9% of the positive control and CYP2B6 mRNA levels increased up to 33.1%. The concentration range studied was lower than that observed in patients (approximately 20% of the $C_{max}$ observed in patients).

Based on the current FDA Drug Interaction Guidance: "*If the result in hepatocytes from at least one donor exceed the predefined threshold (R value estimated using a basic model, or mRNA is > than a pre-defined threshold), the drug is considered an inducer and a follow-up evaluation is needed (e.g., estimate AUCR using a mechanistic model or conduct a clinical study)*". Due to the low concentrations of enzalutamide that could be used in the current study, it could not be determined whether enzalutamide (at clinically relevant concentrations) is an inducer of CYP2B6. The applicant did not conduct an *in vivo* study to assess CYP2B6 induction. An in vivo study does not appear warranted, given the lack of CYP2B6 substrates that are likely to be used in patients with CRPC.

Over the concentration range studied (0.1 - 2.5 μM), there was concentration-dependent, parallel increases in CYP3A4 enzyme activity and CYP3A4 mRNA in 2 out of 3 volunteers (Table 18). The maximum increases in CYP3A4 enzyme activity and mRNA were ≤ 34% of the fold increases observed with the prototypical CYP3A4 inducer (rifampicin). Given that the highest concentration of enzalutamide tested was low relative to steady-state plasma concentrations in patients (1.16 μg/mL tested for *in vitro* induction versus >10 μg/mL in most patients' plasma at the anticipated therapeutic dose), the results indicate that enzalutamide may be a CYP3A4 inducer. Based on the *in vitro* result for CYP3A induction, the applicant evaluated the effect of enzalutamide on the PK of a sensitive CYP3A4 substrate in vivo (trial 9785-CL-0007, see Section 2.4.3).

Table 18. CYP450 mediated induction by enzalutamide (reproduced from PRO3100NC23).

| Enzyme | Known CYP450 Inducer (Concentration) | Probe Substrate (Concentration) | Marker Metabolite | MDV3100 (0.1, 0.5, and 2.5 µM) | |
|---|---|---|---|---|---|
| | | | | Enzyme Activity | mRNA Levels |
| CYP1A2 | 3-Methylcholanthrene (2 µM) | Phenacetin (100 µM) | Acetaminophen | No induction[a] | No induction[a] |
| CYP2B6 | Phenobarbital (1000 µM) | Bupropion (500 µM) | Hydroxybupropion | No induction[a] | No induction[a] |
| CYP3A4 | Rifampicin (10 µM) | Testosterone (200 µM) | 6β-Hydroxytestosterone | Concentration-dependent increases[b] | Concentration-dependent increases[c] |

[a]Enzyme activity and mRNA levels neither showed trends indicative of concentration-response nor surpassed 40% of the respective adjusted positive control.
[b]A concentration-dependent increase was observed in CYP3A4 enzyme activity in 2 out of 3 volunteers. This increase was ≤ 34.2% of the magnitude observed with the positive control (rifampicin).
[c]A concentration-dependent increase was observed in CYP3A4 mRNA levels in 2 out of 3 volunteers. This increase was ≤ 28.3% of the magnitude observed with the positive control (rifampicin). The 2 volunteers showing this increase in CYP3A4 mRNA were the same as those who showed an increase in CYP3A4 enzyme activity.

### 2.4.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

*In vivo evaluation of enzalutamide dosed to steady state on the PK of substrates for CYP2C8, 2C9, 2C19 and 3A4 in patients with castrate-resistant prostate cancer )(9785-CL-0007):*

Results from trial 9785-CL-0007 showed that the potential for an interaction between enzalutamide (and its metabolites M1 and M2) at steady state and pioglitazone (CYP2C8 substrate) is not clinically relevant. Trial 9785-CL-0007 showed that enzalutamide can be classified as a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. Therefore, co-administration of enzalutamide with CYP3A4, 2C9, and 2C19 substrates with a narrow therapeutic index should be avoided. *The in vivo effects of steady state enzalutamide on CYP2D6 and CYP1A2 substrates are not known, and a PMR will be requested to address this.*

The study design and the selection of pioglitazone (CYP2C8 substrate), S-warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate) and midazolam (CYP3A4 substrate) as the sensitive probe substrates were in accordance with the current FDA Drug Interaction Studies Guidance for Industry.

The applicant concluded that enzalutamide may be an inducer of (b) (4) based on metabolite data from trial 9785-CL-0007. In particular the applicant states that enzalutamide decreased the exposure to several hydroxyl metabolites assessed in the current trial (e.g., 5-OH-omeprazole) that are know or suspected to be substrates of (b) (4) enzymes. Since these probes have not been systematically validated for use in a cocktail drug-drug interaction trials, FDA cannot confirm that enzalutamide is in fact an inducer of (b) (4), and the labeling language proposed by the sponsor will not be acceptable.

This was a non-randomized, open-label, single-sequence crossover DDI study in 14 male patients with castrate-resistant prostate cancer. The oral dose for each probe substrate was selected based upon literature data on validated cocktails. All patients received a single oral dose of 30 mg pioglitazone (CYP2C8 substrate) on day 1, followed by a 4-day washout. On day 5, a single oral cocktail of 10 mg warfarin (S-warfarin = CYP2C9 substrate), 20 mg omeprazole (CYP2C19 substrate) and 2 mg midazolam (CYP3A4 substrate) was administered, followed by a washout period of 8 days. On days 1 and 5, a single oral dose of placebo (4 capsules) was co-administered. A single oral dose of 30 mg pioglitazone was administered on day 55, followed by a 7-day washout. A single oral drug cocktail of 10 mg warfarin, 20

mg omeprazole and 2 mg midazolam was administered on day 62, followed by a 10-day washout. All patients received once daily oral doses of 160 mg enzalutamide (four 40-mg capsules) from day 13 onwards up to day 97 (± 3 days). The dosing of enzalutamide was adequate to assess the potential for the drug interactions at steady state concentrations of enzalutamide and M2 (approximately Day 55 of daily dosing).
Full PK profiles were obtained as follows:

- Pioglitazone and its metabolite pioglitazone M-IV predose and for 96 hours after pioglitazone dosing on days 1 and 55.
- R-warfarin, S-warfarin and its metabolite 7-OH-S-warfarin predose and for 192 hours after warfarin dosing on day 5, and predose and for 240 hours after warfarin dosing on day 62.
- Omeprazole and its metabolite 5-OH-omeprazole predose and for 12 hours after omeprazole dosing on days 5 and 62.
- Midazolam and its metabolite 1-OH-midazolam predose and for 24 hours after midazolam dosing on days 5 and 62.
- Enzalutamide and its metabolites M1 and M2 predose (trough level) on days 41, 51, 55, 56, 59; predose and for 24 hours after 160 mg MDV3100 dosing on day 62; and predose (trough level) on days 68 and 72.

After a single dose of 30 mg **pioglitazone** in the presence of 160 mg enzalutamide (and its metabolites M1 and M2) at steady state, the $AUC_{0\text{-}inf}$ of the CYP2C8 substrate pioglitazone increased by 20% (GM ratio: 1.20; 90% CI: 0.98 - 1.47), while $C_{max}$ of pioglitazone decreased by 18% (GM ratio: 0.82; 90% CI: 0.67 - 1.01), compared to administration of 30 mg pioglitazone alone (Table 19). Therefore, the potential for an interaction between enzalutamide and pioglitazone is not clinically relevant.

Table 19. Statistical Assessment of Effect of Multiple Doses of enzalutamide (MDV3100) on CYP2C8 Substrate Pioglitazone.

| | Geometric Means | | | |
|---|---|---|---|---|
| Parameter (Units) | 30 mg Pioglitazone + 160 mg MDV3100 qd (test) | 30 mg Pioglitazone + MDV3100 PTM (reference) | Ratio (Test/ Reference) | 90% CI |
| n † | 14 | 14 | | |
| $AUC_{0\text{-}t}$ (h*ng/mL) | 10796.66 | 8301.82 | 1.30 | 1.08 – 1.57 |
| $AUC_{0\text{-}inf}$ (h*ng/mL) | 11232.41 | 9369.72 | 1.20 | 0.98 – 1.47 |
| $C_{max}$ (ng/mL) | 571.35 | 695.10 | 0.82 | 0.67 – 1.01 |

MDV3100 PTM: placebo to match MDV3100; qd: once daily
† AUC0-inf n=12 for test and n=14 for reference. There are 12 volunteers with AUC0-inf for both test and reference.

After a single oral dose of 10 mg **warfarin** in the presence of 160 mg enzalutamide (and its metabolites M1 and M2) at steady state, the $AUC_{0\text{-}inf}$ of the CYP2C9 substrate S-warfarin decreased by 56% (GM ratio: 0.44; 90% CI: 0.41 - 0.48), compared to administration of 10 mg warfarin alone, while $C_{max}$ of S-warfarin was comparable between both treatments (GM ratio: 0.93; 90% CI: 0.86 -0.99) (Table 20). Therefore, enzalutamide can be classified as a **moderate CYP2C9 inducer** as it caused a > 50% to ≤ 80% reduction in plasma AUC of warfarin. Co-administration of enzalutamide with narrow therapeutic index CYP2C9 substrates should be avoided, as enzalutamide may decrease the exposure to these substrates.

Table 20. Statistical Assessment of Effect of Multiple Doses of enzalutamide (MDV3100) on CYP2C9 Substrate S-warfarin.

| | Geometric Means | | | |
|---|---|---|---|---|
| Parameter (Units) | 10 mg Warfarin + 160 mg MDV3100 qd (test) | 10 mg Warfarin + MDV3100 PTM (reference) | Ratio (Test/ Reference) | 90% CI |
| n | 14 | 14 | | |
| $AUC_{0-t}$ (h*ng/mL) | 6605.71 | 14700.12 | 0.45 | 0.42 – 0.49 |
| $AUC_{0-inf}$ (h*ng/mL) | 6886.22 | 15587.77 | 0.44 | 0.41 – 0.48 |
| $C_{max}$ (ng/mL) | 367.61 | 396.80 | 0.93 | 0.86 – 0.99 |

MDV3100 PTM: placebo to match MDV3100; qd: once daily.

After a single oral dose of 20 mg **omeprazole** in the presence of 160 mg enzalutamide (and its metabolites M1 and M2) at steady state, the $AUC_{0-inf}$ and $C_{max}$ of the CYP2C19 substrate omeprazole decreased by 70% (GM ratio: 0.30; 90% CI: 0.24 - 0.36) and 62% (GM ratio: 0.38; 90% CI: 0.26 - 0.54), respectively, compared to administration of 20 mg omeprazole alone (Table 21). Therefore, enzalutamide can be classified as a **moderate CYP2C19 inducer** as it caused a > 50% to ≤ 80% reduction in plasma AUC of omeprazole. Co-administration of enzalutamide with narrow therapeutic index CYP2C19 substrates should be avoided, as enzalutamide may decrease the exposure to these substrates.

Table 21. Statistical Assessment of Effect of Multiple Doses of enzalutamide (MDV3100) on CYP2C19 Substrate Omeprazole.

| | Geometric Means | | | |
|---|---|---|---|---|
| Parameter (Units) | 20 mg Omeprazole + 160 mg MDV3100 qd (test) | 20 mg Omeprazole + MDV3100 PTM (reference) | Ratio (Test/ Reference) | 90% CI |
| n † | 14 | 14 | | |
| $AUC_{0-t}$ (h*ng/mL) | 238.54 | 845.46 | 0.28 | 0.23 – 0.34 |
| $AUC_{0-inf}$ (h*ng/mL) | 281.80 | 955.20 | 0.30 | 0.24 – 0.36 |
| $C_{max}$ (ng/mL) | 125.84 | 333.22 | 0.38 | 0.26 – 0.54 |

MDV3100 PTM: placebo to match MDV3100; qd: once daily.
† AUC0-inf n=10 for test and n=13 for reference. There are 10 volunteers with AUC0-inf for both test and reference.

After a single oral dose of 2 mg **midazolam** in the presence of 160 mg enzalutamide (and its metabolites M1 and M2) at steady state, the $AUC_{0-inf}$ and $C_{max}$ of CYP3A4 substrate midazolam decreased by 86% (GM ratio: 0.14; 90% CI: 0.12 - 0.17) and 77% (GM ratio: 0.23; 90% CI: 0.20 - 0.27), respectively, compared to administration of 2 mg midazolam alone (Table 22). Therefore, enzalutamide can be classified as a **strong CYP3A4 inducer** as it caused ≥ 80% reduction in plasma AUC of midazolam. Co-administration of enzalutamide with narrow therapeutic index CYP3A4 substrates should be avoided, as enzalutamide may decrease the exposure to these substrates.

Table 22. Statistical Assessment of Effect of Multiple Doses of enzalutamide (MDV3100) on CYP3A4 Substrate Midazolam.

| | Geometric Means | | | |
|---|---|---|---|---|
| Parameter (Units) | 2 mg Midazolam + 160 mg MDV3100 qd (test) | 2 mg Midazolam + MDV3100 PTM (reference) | Ratio (Test/ Reference) | 90% CI |
| n † | 14 | 14 | | |
| $AUC_{0-t}$ (h*ng/mL) | 4.01 | 29.50 | 0.14 | 0.11 – 0.16 |
| $AUC_{0-inf}$ (h*ng/mL) | 4.23 | 29.97 | 0.14 | 0.12 – 0.17 |
| $C_{max}$ (ng/mL) | 2.18 | 9.45 | 0.23 | 0.20 – 0.27 |

MDV3100 PTM: placebo to match MDV3100; qd: once daily.
† n = AUC0-inf n=13 for test and n=12 for reference. There are 11 volunteers with AUC0-inf for both test and reference.

*In vivo evaluation of the effect of a potent CYP2C8 inhibitor and a potent CYP3A4 inhibitor on single dose enzalutamide pharmacokinetics in healthy volunteers (9785-CL-0006):*

Results from trial 9785-CL-0006 showed that multiple oral doses of gemfibrozil (strong CYP2C8 inhibitor) resulted in an increase in the single dose plasma pharmacokinetics of enzalutamide. Gemfibrozil increased the mean **sum of enzalutamide and M2** $AUC_{0-inf}$ by 2.17-fold and decreased the mean sum of enzalutamide and M2 $C_{max}$ by 16%. Based on the assumption of approximately linear pharmacokinetics, a starting dose 80 mg per day is recommended when enzalutamide is co-administered with strong CYP2C8 inhibitors. The 80 mg once daily dose, co-administered with a strong CYP2C8 inhibitor is predicted to result in an area under the sum of the enzalutamide and M2 plasma concentration curve that matches the AUC at the recommended dose of 160 mg once daily.

Results from trial 9785-CL-0006 showed that multiple oral doses of itraconazole (strong CYP3A4 inhibitor) resulted in an increase in the single dose plasma pharmacokinetics of enzalutamide. Itraconazole increased the mean **sum of enzalutamide and M2** $AUC_{0-inf}$ by 1.28-fold, and did not affect the mean sum of enzalutamide and M2 $C_{max}$. No specific enzalutamide dose reduction recommendation is needed when enzalutamide must be co-administered with strong CYP3A4 inhibitors. If patients experience enzalutamide-associated adverse events when it is co-administered with strong CYP3A4 inhibitors, the general enzalutamide toxicity-associated dose modification instructions, as indicated in Section 2.2 of the package insert, are adequate.

Trial 9785-CL-0006 was an open-label, 3-arm, randomized, parallel DDI study performed in 42 healthy male volunteers aged from 18 to 55 years. CYP2C8 poor metabolizers (PM) were excluded from enrollment. The primary objectives were:

- To investigate the effect of multiple oral doses of 600 mg gemfibrozil (potent CYP2C8 inhibitor) twice daily on the pharmacokinetics of a single oral dose of 160 mg enzalutamide.
- To investigate the effect of multiple oral doses of 200 mg itraconazole (potent CYP3A4 inhibitor) once daily on the pharmacokinetics of a single oral dose of 160 mg enzalutamide.

The doses and inhibitors chosen are appropriate based on the current FDA Drug Interaction Studies Guidance.

In all 3 study arms, pharmacokinetic sampling to determine plasma enzalutamide, M1 and M2 concentrations continued for 49 days after receiving the single oral dose of 160 mg enzalutamide. All 3 treatment arms received a single oral dose of enzalutamide.

● Arm 1: Volunteers received a single oral dose of 160 mg enzalutamide on Day 1.
● Arm 2: Volunteers received twice daily 600 mg gemfibrozil (CYP2C8 inhibitor) doses on Day 1 through Day 21. On Day 4, volunteers received a single oral dose of 160 mg enzalutamide with the morning dose of gemfibrozil.
● Arm 3: Volunteers received 200 mg itraconazole (CYP3A4 inhibitor) once daily from Day 1 through Day 21. On Day 4, volunteers received a single oral dose of 160 mg enzalutamide.
- PK sampling to measure enzalutamide, M1, and M2 was performed pre-dose and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 120, 168, 264, 336, 432, 504, 600, 672, 768, 840, 936, 1008, 1104, and 1176 hours post-dose.

In the analysis of data from Study 9785-CL-006, semi-logarithmic PK profiles showed that the rates of enzalutamide elimination was slower in the presence of gemfibrozil compared to when enzalutamide was administered by itself after the gemfibrozil dosing period ended (i.e., 432 h). Due to these changes, the drug-drug interaction assessments for gemfibrozil treatment included results for both $AUC_{0-432h}$ and AUC $AUC_{0-inf}$ (Figure 12 to Figure 15 and Table 23 to Table 26). As the 432 h time frame for PK collection only spans three elimination half-lives for enzalutamide and less than three elimination half-lives for M2, the $AUC_{0-inf}$ parameter will be used for the dose-adjustment recommendations.

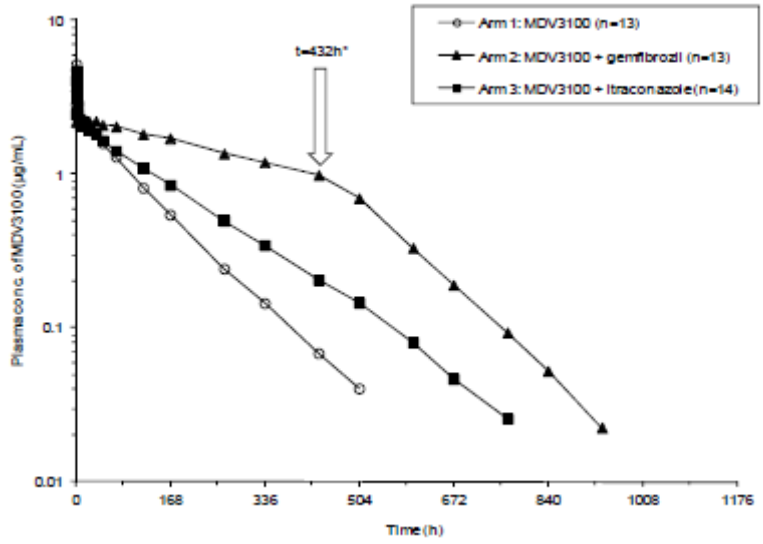



Figure 12. Plasma mean enzalutamide concentrations in each treatment arm (9785-CL-0006).

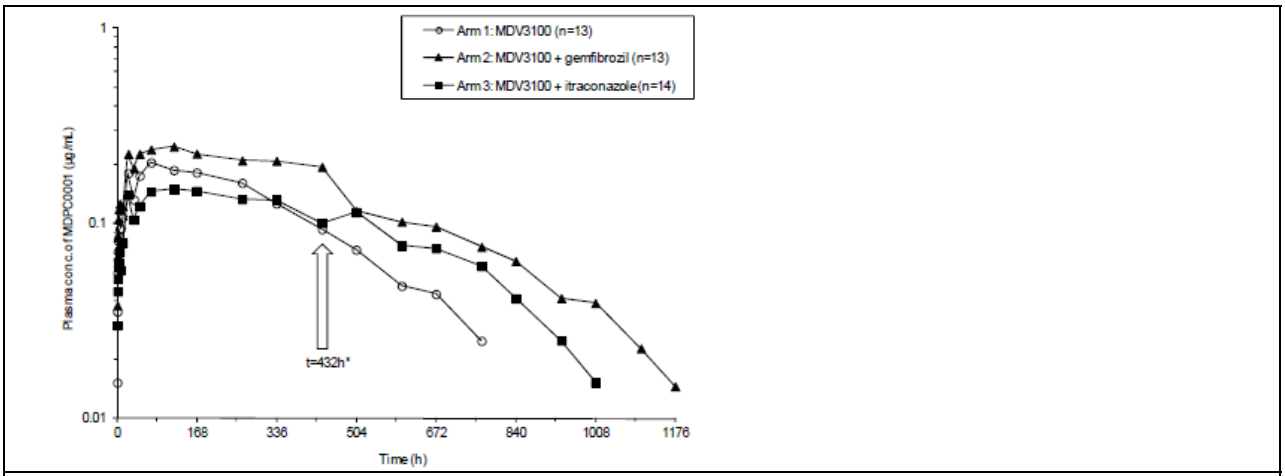



Figure 13. Plasma mean M1 concentrations in each treatment arm (9785-CL-0006).

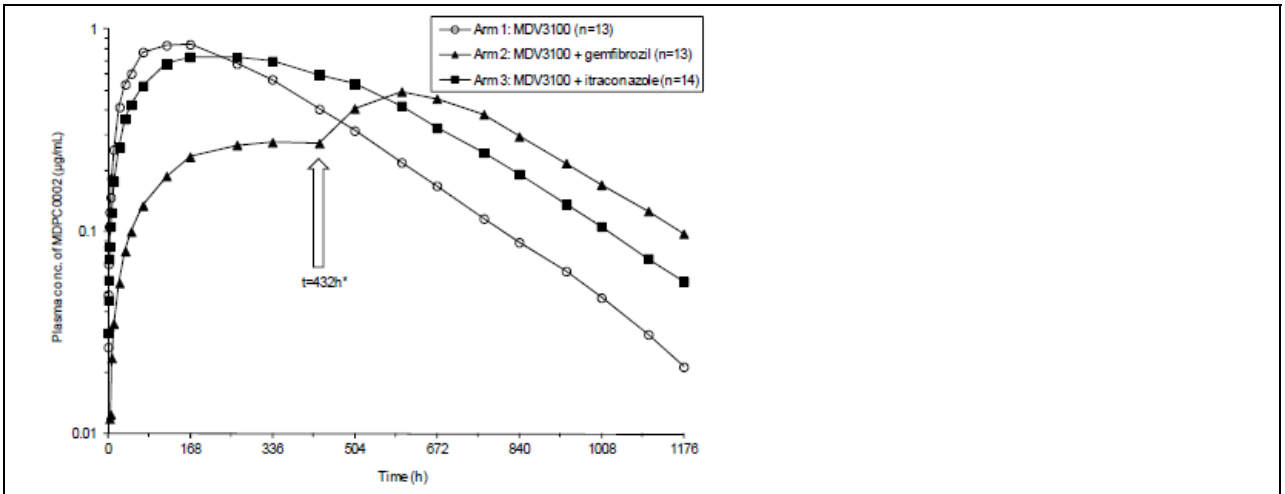



Figure 14. Plasma mean M2 concentrations in each treatment arm (9785-CL-0006).

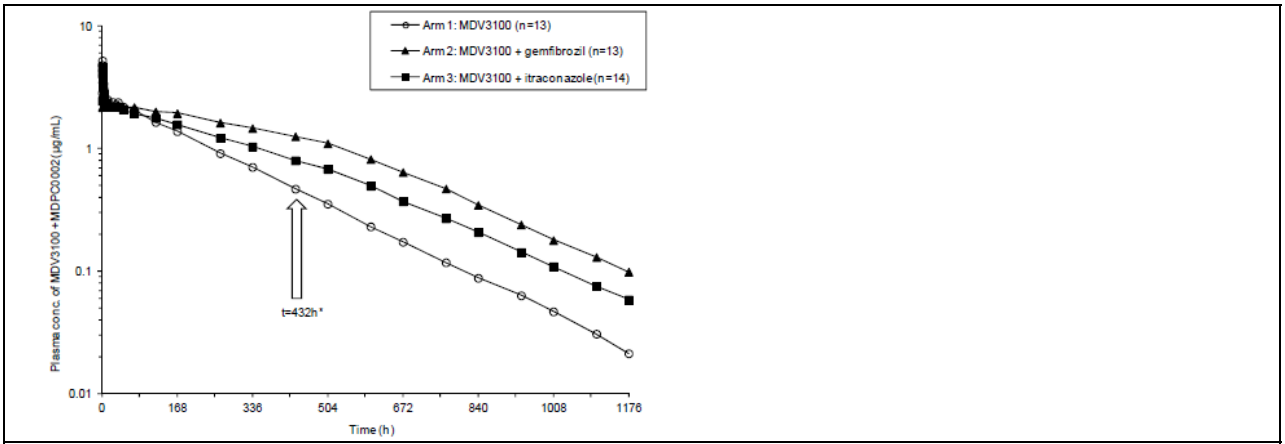



Figure 15. Plasma mean enzalutamide (MDV3100) plus M2 concentrations (µg/mL) in in each treatment arm (9785-CL-0006).

The mean **enzalutamide $AUC_{0-432h}$** and **$AUC_{0-inf}$** were higher when enzalutamide was given in the presence of **gemfibrozil**, compared to enzalutamide alone. The $AUC_{0-432h}$ was 153% (GM ratio: 2.53; 90% CI: 2.19 – 2.91) higher and the mean enzalutamide $C_{max}$ was 18% lower (GM ratio: 0.82; 90% CI: 0.72 – 0.93) in the presence of gemfibrozil compared to enzalutamide alone (Figure 12 and Table 23). The enzalutamide **$AUC_{0-inf}$** was increased by 4.26-fold (GM ratio: 4.26; 90% CI: 3.59 – 5.05) higher (Figure 12 and Table 23). The mean **M1 $AUC_{0-432h}$** and **$AUC_{0-inf}$** were higher when enzalutamide was given in the presence of **gemfibrozil**, compared to enzalutamide alone. The **M1 $AUC_{0-432h}$** and $C_{max}$ were increased by 38% (GM ratio: 1.38; 90% CI: 1.18 - 1.61) and 18% (GM ratio: 1.18; 90% CI: 1.02 – 1.37), respectively, in the presence of gemfibrozil compared to enzalutamide alone (Figure 13 and Table 24). The **M1 $AUC_{0-inf}$** was increased by 2.70-fold (GM ratio: 4.26; 90% CI: 2.24 – 3.26) higher (Figure 13 and Table 24). The mean **M2 $AUC_{0-432h}$** and **$AUC_{0-inf}$** were decreased when enzalutamide was given in the presence of **gemfibrozil**, compared to enzalutamide alone. The **M2 $AUC_{0-432h}$** was decreased by 67% (GM ratio: 0.33; 90% CI: 0.28 – 0.38) compared to enzalutamide alone and $C_{max}$ was 44% lower (GM ratio: 0.56; 90% CI: 0.49 – 0.65) (Figure 14 and Table 25). The mean **M2 $AUC_{0-inf}$** was decreased when enzalutamide was given in the presence of **gemfibrozil**, compared to enzalutamide alone. The **$AUC_{0-inf}$** was decreased by 25% (GM ratio: 0.75; 90% CI: 0.64 – 0.87) compared to enzalutamide alone (Figure 14 and Table 25). Based on in vitro data, enzalutamide and M2 have similar affinities for the human androgen receptor (AR) and pharmacodynamic potency for inhibiting AR activation. Therefore, the effect of gemfibrozil on the combined exposure to enzalutamide and M2 should be evaluated. The sum of enzlutamide plus M2 plasma concentrations vs. time profiles in volunteers who received enzalutamide alone or who received enzalutamide in the presence of gemfibrozil were used to calculate the plasma PK parameters for the sum of enzalutamide plus M2. The mean **$AUC_{0-432h}$** and **$AUC_{0-inf}$** for the **sum of enzalutamide and M2 concentrations** were higher when enzalutamide was given in the presence of gemfibrozil, compared to enzalutamide alone. The **sum of the enzalutamide and M2 $AUC_{0-432h}$** was 39% (GM ratio: 1.39; 90% CI: 1.26 – 1.53) higher and the mean sum of the enzalutamide and M2 $C_{max}$ was 16% lower (GM ratio: 0.84; 90% CI: 0.75 – 0.95) in the presence of gemfibrozil compared to enzalutamide alone (Figure 15 and Table 26). The **sum of the enzalutamide and M2 $AUC_{0-inf}$** was 2.17-fold (GM ratio: 2.17; 90% CI: 1.91 – 2.47) higher in the presence of gemfibrozil, compared to enzalutamide alone (Figure 15 and Table 26).

Mean **enzalutamide** $AUC_{0-inf}$ was higher when enzalutamide was given in the presence of **itraconazole**, compared to enzalutamide alone. The $AUC_{0-inf}$ of enzalutamide was 41% (GM ratio: 1.41; 90% CI: 1.20 – 1.65) higher in the presence of itraconazole compared to enzalutamide alone. $C_{max}$ was comparable in the presence and absence of itraconazole (GM ratio: 0.98; 90% CI: 0.86 – 1.11) (Figure 12 and Table 23). The **M1** $AUC_{0-inf}$ was similar in the presence and absence of itraconazole (GM ratio 1.06; 90% CI: 0.89 – 1.26). The M1 $C_{max}$ was decreased by 25% (GM ratio: 0.75; 90% CI: 0.65 – 0.87) in the presence of itraconazole compared to enzalutamide alone (Figure 13 and Table 24). The **M2** $AUC_{0-inf}$ was increased by 21% (GM ratio: 1.21; 90% CI: 1.08 – 1.36) in the presence of itraconazole compared to enzalutamide alone . The M2 $C_{max}$ was decreased by 14% (GM ratio: 0.86; 90% CI: 0.75 – 0.99) in the presence of itraconazole compared to enzalutamide alone (Figure 14 and Table 25). The mean $AUC_{0-inf}$ for the **sum of enzalutamide and M2 concentrations** was higher when enzalutamide was given in the presence of itraconazole, compared to enzalutamide alone. The sum of the enzalutamide and M2 $AUC_{0-inf}$ was 28% (GM ratio: 1.28; 90% CI: 1.17 – 1.41) higher, and the sum of the enzalutamide and M2 $C_{max}$ was similar (GM ratio: 0.97; 90% CI: 0.87 – 1.09) in the presence of itraconazole compared to enzalutamide alone (Figure 15 and Table 26).

These results indicate that CYP2C8 plays an important role in the metabolism of enzalutamide and the formation of M2, while CYP3A4 plays a role in the metabolism of enzalutamide.

Table 23. Statistical assessment of enzalutamide exposure parameters of single-dose enzalutamide

(MDV-3100) co-administered with multiple doses of gemfibrozil (A) or with multiple doses of itraconazole (B) (source: 9785-CL-0002 and 9785-CL-0006).

| A: Effect of CYP2C8 Inhibitor Gemfibrozil | | | | |
|---|---|---|---|---|
| **Parameter (Units)** | **MDV3100 SD (R) GM** | **MDV3100 SD + Gemfibrozil MD (T) GM** | **GM Ratio (T/R)** | **90% CI for GM Ratio** |
| $AUC_{0\text{-}432h}$ (h*µg/mL) | 267 | 674 | 2.53 | 2.19 – 2.91 |
| $AUC_{0\text{-}inf}$ (h*µg/mL) | 275.9 | 1174 | 4.26 | 3.59 – 5.05 |
| $C_{max}$ (µg/mL) | 5.62 | 4.61 | 0.82 | 0.72 – 0.93 |
| **B: Effect of CYP3A4 Inhibitor Itraconazole** | | | | |
| **Parameter (Units)** | **MDV3100 SD (R) GM** | **MDV3100 SD + Itraconazole MD (T) GM** | **GM Ratio (T/R)** | **90% CI for GM Ratio** |
| $AUC_{0\text{-}432h}$ (h*µg/mL) | 267 | 356 | 1.34 | 1.16 – 1.54 |
| $AUC_{0\text{-}inf}$ (h*µg/mL) | 279 | 392 | 1.41 | 1.20 – 1.65 |
| $C_{max}$ (µg/mL) | 5.62 | 5.50 | 0.98 | 0.86 – 1.11 |

Table 24. Statistical assessment of M1 exposure parameters of single-dose enzalutamide (MDV-3100) co-administered with multiple doses of gemfibrozil (A) or with multiple doses of itraconazole (B) (source: 9785-CL-0002 and 9785-CL-0006).

| A: Effect of CYP2C8 Inhibitor Gemfibrozil | | | | |
|---|---|---|---|---|
| **Parameter (Units)** | **MDV3100 SD (R) GM** | **MDV3100 SD + Gemfibrozil MD (T) GM** | **GM Ratio (T/R)** | **90% CI for GM Ratio** |
| $AUC_{0\text{-}432h}$ (h*µg/mL) | 64.9 | 89.3 | 1.38 | 1.18 – 1.61 |
| $AUC_{0\text{-}inf}$ (h*µg/mL) | 95.86 | 259.3 | 2.70 | 2.24 – 3.26 |
| Cmax (µg/mL) | 0.23 | 0.28 | 1.18 | 1.02 – 1.37 |
| **B: Effect of CYP3A4 Inhibitor Itraconazole** | | | | |
| **Parameter (Units)** | **MDV3100 SD (R) GM** | **MDV3100 SD + Itraconazole MD (T) GM** | **GM Ratio (T/R)** | **90% CI for GM Ratio** |
| $AUC_{0\text{-}432h}$ (h*µg/mL) | 64.9 | 55.4 | 0.85 | 0.73 – 0.99 |
| $AUC_{0\text{-}inf}$ (h*µg/mL) | 91.2 | 96.3 | 1.06 | 0.89 – 1.26 |
| Cmax (µg/mL) | 0.23 | 0.18 | 0.75 | 0.65 – 0.87 |

Table 25. Statistical assessment of M2 exposure parameters of single-dose enzalutamide (MDV-3100) co-administered with multiple doses of gemfibrozil (A) or with multiple doses of itraconazole (B) (source: 9785-CL-0002 and 9785-CL-0006).

| A: Effect of CYP2C8 Inhibitor Gemfibrozil |
|---|

| | MDV3100 SD (R) | MDV3100 SD + Gemfibrozil MD (T) | GM Ratio | 90% CI for GM Ratio |
|---|---|---|---|---|
| **Parameter (Units)** | **GM** | **GM** | **(T/R)** | |
| $AUC_{0\text{-}432h}$ (h*μg/mL) | 276 | 90.0 | 0.33 | 0.28 – 0.38 |
| $AUC_{0\text{-}inf}$ (h*μg/mL) | 399.7 | 298.8 | 0.75 | 0.64 – 0.87 |
| Cmax (μg/mL) | 0.87 | 0.49 | 0.56 | 0.49 – 0.65 |
| **B: Effect of CYP3A4 Inhibitor Itraconazole** | | | | |
| | **MDV3100 SD (R)** | **MDV3100 SD + Itraconazole MD (T)** | **GM Ratio** | **90% CI for GM Ratio** |
| **Parameter (Units)** | **GM** | **GM** | **(T/R)** | |
| $AUC_{0\text{-}432h}$ (h*μg/mL) | 276 | 264 | 0.96 | 0.83 – 1.11 |
| $AUC_{0\text{-}inf}$ (h*μg/mL) | 391 | 473 | 1.21 | 1.08 – 1.36 |
| Cmax (μg/mL) | 0.87 | 0.75 | 0.86 | 0.75 – 0.99 |

Table 26. Statistical assessment of enzalutamide (MDV-3100) plus M2 exposure parameters of single-dose enzalutamide co-administered with multiple doses of gemfibrozil (A) or with multiple doses of itraconazole (B) (source: 9785-CL-0002 and 9785-CL-0006).

| **A: Effect of CYP2C8 Inhibitor Gemfibrozil** | | | | |
|---|---|---|---|---|
| | **MDV3100 SD (R)** | **MDV3100 SD + Gemfibrozil MD (T)** | **GM Ratio** | **90% CI for GM Ratio** |
| **Parameter (Units)** | **GM** | **GM** | **(T/R)** | |
| $AUC_{0\text{-}432h}$ (h*μg/mL) | 551 | 766 | 1.39 | 1.26 – 1.53 |
| $AUC_{0\text{-}inf}$ (h*μg/mL) | 681.4 | 1480 | 2.17 | 1.91 – 2.47 |
| Cmax (μg/mL) | 5.67 | 4.77 | 0.84 | 0.75 – 0.95 |
| **B: Effect of CYP3A4 Inhibitor Itraconazole** | | | | |
| | **MDV3100 SD (R)** | **MDV3100 SD + Itraconazole MD (T)** | **GM Ratio** | **90% CI for GM Ratio** |
| **Parameter (Units)** | **GM** | **GM** | **(T/R)** | |
| $AUC_{0\text{-}432h}$ (h*μg/mL) | 551 | 628 | 1.14 | 1.03 – 1.26 |
| $AUC_{0\text{-}inf}$ (h*μg/mL) | 678 | 871 | 1.28 | 1.17 – 1.41 |
| Cmax (μg/mL) | 5.67 | 5.53 | 0.97 | 0.87 – 1.09 |

### 2.4.4 Are other metabolic/transporter pathways important?

Enzalutamide, M1 and M2 are not substrates for human P-gp. Enzalutamide and M2 are inhibitors of P-gp, while M1 is not an inhibitor of P-gp.

An in vitro study was done to assess whether enzalutamide, M1 and M2 are substrates and inhibitors of human P-gp (9785-ME-0026). In study 9785-ME-0026, the bi-directional transport [Basolateral to apical (B→A) and from apical to basolateral (A→B)] of [$^{14}$C]enzalutamide, M1 and M2 were evaluated (tested at 0.5, 2.5, and 25 μM; 4 hour end-point assay) in LLC-PK1 cells and in LLC-PK1 cells stably transfected with a human MDR1 cDNA. To quantify their potential as P-gp substrates, the ratio of efflux with MDR1-expressing cells to efflux with control cells was expressed as the corrected Papp value (this value must be > 2 to be considered a P-gp substrate). For enzalutamide, M1, and M2, the corrected Papp values

were ≤ 1.3, ≤ 1.7, and ≤ 1.5, respectively, and there was no concentration dependency; therefore, these molecules are not substrates for P-gp.

In the inhibition experiments, efflux of $^3$H-digoxin (1 μM) was measured in the presence of enzalutamide (0.3 to 50 μM), M1 (0.3 to 80 μM), or M2 (0.1 to 25 μM). Inhibition-effect versus concentration curves were used to determine $IC_{50}$ values. Enzalutamide and M2 showed concentration-dependent inhibition of $^3$H-digoxin efflux with $IC_{50}$ values of 1.67 μM (0.776 μg/mL) and 1.09 μM (0.491 μg/mL), respectively. With M1, $^3$H-digoxin efflux was essentially unchanged; therefore, the estimated $IC_{50}$ was > 80 μM (> 36.1 μg/mL).

Based on the published FDA decision tree for P-gp interactions an *in vivo* study with the P-gp substrate digoxin is needed if $[I]_1/IC_{50} \geq 0.1$, or $R > 1.1$, or $[I]_2/IC_{50} \geq 10$ is met, where $[I]_1$ is the mean steady-state total $C_{max}$, $R = 1 + [I]_1/IC_{50}$, and $[I]_2$ is the maximal gastrointestinal concentration. For enzalutamide The $[I]_1/IC_{50}$ ratio and R value at the $C_{max}$ at steady state (160 mg daily dose) for enzalutamide are 18.6 (31.1/1.67) and 19.6, respectively. This indicates that the risk for an *in vivo* drug-drug interaction is likely. The mean steady-state plasma $C_{min}$ in patients taking 160 mg/day enzalutamide is 13.0 μg/mL (28.9 μM). For M2 The $[I]_1/IC_{50}$ ratio and R value at the $C_{min}$ at steady state (160 mg daily dose) for M2 are 26.5 (28.9/1.09) and 27.5, respectively. This indicates that the risk for an *in vivo* drug-drug interaction is likely.

**2.4.5 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?**

The label does not specify co-administration of another drug with enzalutamide.

**2.4.6 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?**

See section 2.4.3.

## 2.5 GENERAL BIOPHARMACEUTICS

**2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?**

The drug product is a liquid-filled capsule of enzalutamide fully dissolved in (b) (4). Enzalutamide exhibits limited aqueous solubility and high permeability, and according to the principles of the Biopharmaceutics Classification System (BCS), the applicant classifies enzalutamide as a low solubility, high permeability BCS Class 2 drug substance.

Solubility:

The partition coefficient (Log P) was determined by the applicant by a calculation due to the low solubility of enzalutamide Drug Substance in water. The calculated distribution coefficient (cLog P) of enzalutamide was 2.98. The solubility profile of enzalutamide in pH adjusted aqueous solutions and a variety of solvents is shown in Table 27. Enzalutamide has no ionic forms at biologically-relevant pH; therefore, enzalutamide solubility is not affected by pH over the physiological range.

Table 27. Enzalutamide solubility profile.

| Solvent | Solubility (mg/mL) |
|---|---|
| Methanol | 49 mg/mL (Soluble) |
| 1-Methyl 2-pyrrolidinone | $5.3 \times 10^{2}$ mg/mL (Freely soluble) |
| Absolute ethanol | 12 mg/mL (Sparingly soluble) |
| Acetonitrile | $3.4 \times 10^{2}$ mg/mL (Freely soluble) |
| Water | $2.0 \times 10^{-3}$ mg/mL (Practically insoluble) |
| Aqueous solution [a], pH 1.0 | $2.0 \times 10^{-3}$ mg/mL (Practically insoluble) |
| Aqueous solution [b], pH 3.0 | $2.0 \times 10^{-3}$ mg/mL (Practically insoluble) |
| Aqueous solution [b], pH 5.0 | $2.0 \times 10^{-3}$ mg/mL (Practically insoluble) |
| Aqueous solution [b], pH 7.0 | $2.0 \times 10^{-3}$ mg/mL (Practically insoluble) |
| Aqueous solution [b], pH 9.0 | $1.0 \times 10^{-3}$ mg/mL (Practically insoluble) |
| Aqueous solution [b], pH 11.0 | $3.0 \times 10^{-3}$ mg/mL (Practically insoluble) |

[a] The result was determined using 0.1 mol/L hydrochloric acid.
[b] The results were determined using Carmody buffer (a mixture of 0.2 mol/L boric acid, 0.05 mol/L citric acid and 0.1 mol/L trisodium phosphate).

Permeability:

Enzalutamide appears to be a high permeability compound that crosses Caco-2 cell monolayers by passive diffusion. $^{14}$C-enzalutamide was evaluated for membrane permeability and bidirectional permeability using Caco-2 cells (9785-ME-0031). The results showed that enzalutamide has high apparent permeability across Caco-2 cell monolayers (Papp $\geq 31 \times 10^{-6}$ cm/s) with no significant transport asymmetry between absorptive apical-to-basolateral (A→B) and secretory (B→A) flux determinations.

### 2.5.2 What is the composition of the to-be-marketed formulation?

The to-be-marketed formulation is a liquid-filled capsule of enzalutamide fully dissolved in (b) (4). The composition of the enzalutamide solution in the capsules has remained unchanged throughout clinical development. For the first-in-human, dose-escalation Phase 1 study (S-3100-1-01), the liquid formulation was initially filled into hard gelatin capsules containing 30 mg of enzalutamide per capsule. During the Phase 1 study, the liquid formulation was filled into more robust, soft gelatin capsules containing 40 mg enzalutamide. The difference in capsule dose strength is strictly a function of the capsule fill volume, and there were no changes in the composition of the liquid formulation. The soft gelatin capsule was used in all subsequent clinical studies and is the intended commercial presentation. The dose regimen in the pivotal Phase 3 study (CRPC2) was four 40 mg capsules once a day (160 mg/day). The composition of the to-be marketed formulation is summarized in Table 28.

Table 28. Composition of a single enzalutamide to-be-marketed tablet.

| Component | Reference to Quality Standard | Function | Amount (mg) per Capsule |
|---|---|---|---|
| (b) (4) | | | (b) (4) |
| MDV3100 | Section 2.3.S.4 | Active Ingredient | 40.0 |
| Caprylocaproyl Polyoxylglycerides | NF | (b) (4) | (b) (4) |
| Butylated Hydroxyanisole | NF | | |
| Butylated Hydroxytoluene | NF | | |
| (b) (4) | | | (b) (4) |
| | | **Capsule Fill Solution Weight:** | **946.0** |
| (b) (4) | | | (b) (4) |

DMF, drug master file; mg, milligrams; NF, national formulary. MDV3100: enzalutamide

### 2.5.3 What moieties should be assessed in bioequivalence studies?

Enzalutamide and M2 should be assessed in bioequivalence studies.

**2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**

A food-effect trial (MDV3100-05) indicated that high-fat, high-calorie meal had no effect on the extent of enzalutamide absorption, and enzalutamide was administered without regard to food in the phase 3 trial (CRPC2). Therefore, the dosing recommendation is for enzalutamide administration with or without food.

A parallel design food-effect trial (MDV3100-05) involved administration of a single 160 mg oral dose of enzalutamide to healthy volunteers (30 volunteers per arm) under fasting conditions and with a high-fat, high-calorie meal. On Day 1, 60 volunteers were randomized to receive a single oral dose of 160 mg enzalutamide (4 × 40 mg capsules) under fasted conditions (a minimum 10 hour fast from food) or under fed conditions. In the fed condition, volunteers consumed a standard FDA high-fat, high-calorie breakfast, containing 800 to 1000 calories with approximately 50% of this caloric content as fat (the breakdown was approximately 150 calories from protein, 250 calories from carbohydrate, and 500 to 600 calories from fat). PK samples were collected up to Day 42 postdose and analyzed for plasma concentrations of enzalutamide, M1, and M2 using a validated LC-MS/MS method. The primary food-effects comparison by the applicant was based on parent molecule enzalutamide.

The geometric mean AUC values were approximately 1% lower in fed than in fasted volunteers, and the 90% confidence intervals (CI) for the ratio of treatment mean AUC values were within the 80% to 125% range. Based on $C_{max}$ and $T_{max}$ values, the rate of absorption following a high-fat meal was slower than under fasted conditions. Geometric mean $C_{max}$ was approximately 30% lower and median $T_{max}$ was approximately 1 hour later with food. The 90% CI for the ratio of treatment mean $C_{max}$ values was 63.24 to 78.50 (Table 29). Overall, these results support the dosing recommendation of enzalutamide with or without food.

Table 29. Statistical summary of the food-effect comparison for enzalutamide following a single 160 mg dose under fed and fasted conditions (MDV3100-05).

| PK Parameter (Unit) | Adjusted Geometric Means | | Ratio (Test/Reference) (%) | 90% CI for Ratio (%) | |
|---|---|---|---|---|---|
| | Capsule - Fed (Test) | Capsule - Fasted (Reference) | | Lower | Upper |
| N, n | 30, 30 | 27, 27 | -- | -- | -- |
| $AUC_{0-t}$ (µg·h/mL) | 269 | 270 | 99.61 | 87.77 | 113.05 |
| $AUC_{inf}$ (µg·h/mL) | 276 | 279 | 98.98 | 87.31 | 112.21 |
| $C_{max}$ (µg/mL) | 3.61 | 5.13 | 70.45 | 63.24 | 78.50 |

N = number of volunteers in the PK Evaluable Population; n = number of volunteers for whom $AUC_{inf}$ was determined.
$AUC_{0-t}$, area under the plasma concentration versus time curve from time zero to the last measurable concentration; $AUC_{inf}$, area under the plasma concentration versus time curve from time zero to infinity; CI, confidence interval; $C_{max}$, maximum observed plasma concentration,

The applicant's exploratory analyses of the adjusted geometric mean ratios for $AUC_{0-t}$, $AUC_{0-inf}$ and $C_{max}$ for both M1 and M2 under fed conditions, relative to fasted conditions are summarized in Table 30, and in general indicate equivalence under fed and fasted conditions.

Table 30. Statistical Summary of food-effect comparison for M1 and M2 for the liquid-filled capsule formulation

Metabolite M1:

| Pharmacokinetic Parameters (Units) | Adjusted Geometric Means | | Ratio (Test/Reference) (%) | 90% CI for Ratio (%) | |
|---|---|---|---|---|---|
| | Capsule - Fed (Test) | Capsule – Fasted (Reference) | | Lower | Upper |
| N, n | 30, 22 | 27, 17 | -- | -- | -- |
| $AUC_{0-t}$ (µg·h/mL) | 73.6 | 73.9 | 99.59 | 86.59 | 114.53 |
| $AUC_{0-inf}$ (µg·h/mL) | 81.5 | 90.0 | 90.56 | 79.78 | 102.79 |
| $C_{max}$ (µg/mL) | 0.20 | 0.20 | 98.61 | 82.29 | 118.17 |

Metabolite M2:

| Pharmacokinetic Parameters (Units) | Adjusted Geometric Means | | Ratio (Test/Reference) (%) | 90% CI for Ratio (%) | |
|---|---|---|---|---|---|
| | Capsule - Fed (Test) | Capsule - Fasted (Reference) | | Lower | Upper |
| N, n | 30, 30 | 27, 25 | -- | -- | -- |
| $AUC_{0-t}$ (µg·h/mL) | 386 | 355 | 108.68 | 97.95 | 120.58 |
| $AUC_{0-inf}$ (µg·h/mL) | 410 | 379 | 108.15 | 96.46 | 121.26 |
| $C_{max}$ (µg/mL) | 0.81 | 0.76 | 106.14 | 95.18 | 118.37 |

n, number of volunteers for whom $AUC_{0-inf}$ was determined and included in the analysis.

**2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure *in vivo* performance and quality of the product?**

Yes.

## 2.6 ANALYTICAL SECTION

**2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?**

Yes, the major inactive metabolite MDPC0001 (M1) and major active metabolite MDPC0002 (M2) plasma and urine concentrations were measured in the clinical pharmacology and biopharmaceutics studies using validated LC-MS/MS methods.

**2.6.2 Which metabolites have been selected for analysis and why?**

The major metabolites MDPC0001 (M1) MDPC0002 (M2) were selected for analysis in plasma and urine. In the later stages of development it was determined that M1 is a major inactive metabolite, and M2 is a major active metabolite.

**2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?**

The total plasma concentrations of enzalutamide, M1 and M2 in plasma were measured in the clinical trials. This was appropriate due to the constant plasma protein binding of enzalutamide, M1 and M2 over the clinically relevant concentration range.

**2.6.4 What bioanalytical methods are used to assess concentrations? (Refer to the guidance for industry on Bioanalytical Method Validation, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf)**

Methods for the analysis of enzalutamide, M1 and M2 concentrations in human urine (9785-ME-0013) and plasma (PRO3100NC33 and PRO3100NC86) samples collected during clinical studies are described below. Methods PRO3100NC33, PRO3100NC86 and 9785-ME-0013 were developed and validated by (b) (4) respectively.

**Plasma Assays:**
Two validated LC-MS/MS methods were used for concentration determinations in human plasma (PRO3100NC33 and PRO3100NC86). The first method (PRO3100NC33) was applied in trial S-3100-1-01. The second method (PRO3100NC86) was applied in trials 9785-LC-0001, MDV3100-05 and CRPC2, and measured enzalutamide, M1, and M2.

**Urine Assay:**
One LC-MS/MS method was validated for human urine (9785-ME-0013). This method was applied in trial 9785-CL-0001.

**Itraconazole Plasma Concentrations:**
Plasma samples obtained in protocol 9785-CL-0006 were analyzed for itraconazole concentrations by (b) (4) using LC-MS/MS. The lower limit of quantitation (LLOQ) was 5.00 ng/mL and the linear calibration range was 5.00 ng/mL to 1000 ng/mL. The concentration range in the calibration curve was in the appropriate range for analysis of itraconazole concentrations.

**Gemfibrozil Plasma Concentrations:**
Plasma samples obtained in protocol 9785-CL-0006 were analyzed for gemfibrozil concentrations by (b) (4) using LC-MS/MS. The lower limit of quantitation (LLOQ) was 32.44 ng/mL and the linear calibration range was 32.44 ng/mL to 6487.50 ng/mL. The concentration range in the calibration curve was in the appropriate range for analysis of gemfibrozil concentrations.

**Pioglitazone Plasma Concentrations:**
Plasma samples obtained in protocol 9785-CL-0007 were analyzed for pioglitazone concentrations by (b) (4) using LC-MS/MS. The lower limit of quantitation (LLOQ) was 10.05 ng/mL and the linear calibration range was 10.05 ng/mL to 3016.20 ng/mL. The concentration range in the calibration curve was in the appropriate range for analysis of pioglitazone concentrations.

**S-Warfarin Plasma Concentrations:**
Plasma samples obtained in protocol 9785-CL-0007 were analyzed for S-warfarin concentrations by (b) (4) using LC-MS/MS. The lower limit of quantitation (LLOQ) was 5.00 ng/mL and the linear calibration range was 5.00 ng/mL to 1500 ng/mL. The concentration range in the calibration curve was in the appropriate range for analysis of S-warfarin concentrations.

**Omeprazole Plasma Concentrations:**
Plasma samples obtained in protocol 9785-CL-0007 were analyzed for omeprazole concentrations by (b) (4) using LC-MS/MS. The lower limit of quantitation (LLOQ) was 1.00 ng/mL and the linear calibration range was 1.00 ng/mL to 1000 ng/mL. The concentration range in the calibration curve was in the appropriate range for analysis of omeprazole concentrations.

**Midazolam Plasma Concentrations:**
Plasma samples obtained in protocol 9785-CL-0007 were analyzed for midazolam concentrations by (b) (4) using LC-MS/MS. The lower limit of quantitation (LLOQ) was 0.100 ng/mL and the linear calibration range was 0.100 ng/mL to 100 ng/mL. The concentration range in the calibration curve was in the appropriate range for analysis of midazolam concentrations.

### 2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

*Linearity:*
Method PRO3100NC33 was applied in trial S-3100-1-01 and measured only plasma enzalutamide. Weighted (weighting factor=*1/y*) least squares regression calibration curves were constructed by plotting the peak area ratios of analyte to internal standard *versus* standard concentration. The linear calibration range for spanned from 0.002 to 5.0 µg/mL. Dilution integrity data (PRO3100NC33) of enzalutamide in human plasma indicated that enzalutamide samples diluted up to 50 times were observed to be within the ± 15% deviation of expected concentrations. The accuracy of dilution integrity enabled the quantitation of enzalutamide at concentrations up to 250 µg/mL. Considering the defined upper limit of quantification (ULOQ) and supportive data on dilution integrity, samples were reliably quantified method PRO3100NC33. The lowest plasma concentrations occurred in studies in which enzalutamide was administered as a single dose. The LLOQ of the assay for these studies (≤ 0.02 µg/mL) was sufficiently sensitive to measure plasma concentrations of enzalutamide at least 3 half-lives after administration of a single oral dose of 160 mg, ensuring that the terminal elimination rate constant (λz) could be estimated accurately. The concentration range in the calibration curve using diluted samples was in the appropriate range for analysis of enzalutamide concentrations.

Method PRO3100NC86 was applied in trials 9785-LC-0001, MDV3100-05 and CRPC2, and measured plasma enzalutamide, M1, and M2. Weighted (weighting factor=$1/x^2$) least squares regression calibration curves were constructed by plotting the peak area ratios of analyte to internal standard *versus* standard concentration. The linear calibration ranges for enzalutamide, M1 and M2 spanned from 0.02 to 50 µg/mL. Dilution integrity data (PRO3100NC86) indicated that samples diluted up to 50 times were observed to be within the ± 15% deviation of expected concentrations. Considering the defined upper limit of quantification (ULOQ) and supportive data on dilution integrity, samples were reliably quantified method PRO3100NC86. The lowest plasma concentrations occurred in studies in which enzalutamide was administered as a single dose. The LLOQ of the assay for these studies (≤ 0.02 µg/mL) was sufficiently sensitive to measure plasma concentrations of enzalutamide, M1 and M2 for at least 3 half-lives after administration of a single oral dose of 160 mg, ensuring that the terminal elimination rate constant (λz) could be estimated accurately. The concentration range in the calibration curve using diluted samples was in the appropriate range for analysis of enzalutamide concentrations.

Method 9785-ME-0013 was applied in trial 9785-CL-0001, and measured urine enzalutamide, M1 and M2. Weighted (weighting factor=$1/x^2$) least squares regression calibration curves were constructed by plotting the peak area ratios of analyte to internal standard *versus* standard concentration. The linear calibration ranges for enzalutamide, M1 and M2 spanned from 50 to 10000 ng/mL. Tests for dilution integrity demonstrated that enzalutamide measurements were accurate with sample dilutions up to 10-fold. Following enzalutamide administration as a single oral dose, and urine was collected for approximately 2 months. The validated LC-MS/MS method was sufficiently sensitive to verify that enzalutamide is excreted in human urine at trace concentrations.

### 2.6.6 What is the QC sample plan?

The QC sample plan, and the assay accuracy and precision for methods PRO3100NC33, PRO3100NC86 and 9785-ME-0013 are acceptable (Table 31).

Table 31. QC Sample plan.

| **Study Number** | **PRO3100NC33** | **PRO3100NC86** | | | **9785-ME-0013** | | |
|---|---|---|---|---|---|---|---|
| Analyte | **Enzalutamide** | **Enzalutamide** | **M1** | **M2** | **Enzalutamide** | **M1** | **M2** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Accuracy (%Bias) LLOQ | −0.2% (2 ng/mL) | −0.50% (0.02 µg/mL) | 9.00% (0.02 µg/mL) | 1.00% (0.02 µg/mL) | 4.3% (50 ng/mL) | −1.5% (50 ng/mL) | 0.3% (50 ng/mL) |
| Low QC | 1.9% (5 ng/mL) | −2.83% (0.06 µg/mL) | −4.67% (0.06 µg/mL) | −1.67% (0.06 µg/mL) | 3.2% (150 ng/mL) | 0.4% (150 ng/mL) | 3.8% (150 ng/mL) |
| Medium QC | 1.3% (1500 ng/mL) | 2.00% (1.00 µg/mL) | 3.00% (1.00 µg/mL) | 2.00% (1.00 µg/mL) | 0.5% (1000 ng/mL) | −2.8% (1000 ng/mL) | 2.0% (1000 ng/mL) |
| High QC | −2.1% (4000 ng/mL) | −3.75% (40.0 µg/mL) | 6.75% (40.0 µg/mL) | −3.00% (40.0 µg/mL) | 1.3% (8000 ng/mL) | −2.3% (8000 ng/mL) | 3.3% (8000 ng/mL) |
| Precision (%CV) LLOQ | 9.1% (2 ng/mL) | 4.87% (0.02 µg/mL) | 4.72% (0.02 µg/mL) | 4.37% (0.02 µg/mL) | 3.2% (50 ng/mL) | 4.2% (50 ng/mL) | 3.2% (50 ng/mL) |
| Low QC | 8.0% (5 ng/mL) | 5.75% (0.06 µg/mL) | 5.33% (0.06 µg/mL) | 4.68% (0.06 µg/mL) | 3.3% (150 ng/mL) | 5.5% (150 ng/mL) | 4.8% (150 ng/mL) |
| Medium QC | 4.1% (1500 ng/mL) | 5.69% (1.00 µg/mL) | 5.61% (1.00 µg/mL) | 4.99% (1.00 µg/mL) | 2.9% (1000 ng/mL) | 4.6% (1000 ng/mL) | 4.1% (1000 ng/mL) |
| High QC | 3.3% (4000 ng/mL) | 3.09% (40.0 µg/mL) | 4.47% (40.0 µg/mL) | 4.61% (40.0 µg/mL) | 3.5% (8000 ng/mL) | 5.5% (8000 ng/mL) | 3.6% (8000 ng/mL) |

## 3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. The red text is the proposed changes added by the clinical pharmacology reviewer and the applicant's proposed language that has not been accepted is crossed out.

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

# 4 APPENDICES

## 4.1 PHARMACOMETRICS REVIEW

| | |
|---|---|
| **Application Number** | NDA 203415 |
| **Compound** | Enzalutamide, MDV3100 (Xtandi); 40 mg IR Capsule |
| **Indication** | Treatment of patients with castration-resistant prostate cancer who have received docetaxel (b) (4) |
| **Submission Date** | 05/22/2012 |
| **Sponsor** | Medivation, Inc. |
| **PM Reviewer** | Dhananjay D. Marathe, PhD |
| **PM Team Leader** | Nitin Mehrotra, PhD |
| **Related IND** | 74563 |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# 1 SUMMARY OF FINDINGS

## 1.1 Key Review Questions

The purpose of this review is to address the following key questions:

### 1.1.1 What are the characteristics of the exposure-response relationships for efficacy and safety for Enzalutamide?

**Efficacy: No exposure-response relationship for overall survival (OS) could be identified for enzalutamide (MDV3100) within a single fixed dose of 160 mg/day in the phase 3 trial.** As shown in **Figure 1** and **Figure 2** below, there was no significant difference in survival between the four quartiles and all the exposure quartiles were uniformly beneficial relative to placebo in overall survival.

For the phase 3 AFFIRM study with 160 mg/day fixed dose, in a pair-wise comparisons versus placebo, all the active treatment exposure quartile groups, based on Cmin for either MDV3100 (parent drug) alone, or M2 (N-desmethyl MDV3100, an active metabolite with similar potency, molecular weight and steady state plasma concentrations as the parent drug) alone, or MDV3100 + M2 combined, were statistically significant (p-values $\leq$ 0.0039) in favor of active treatment, for all of the efficacy endpoints including overall survival, radiographic progression-free survival, and time to PSA progression. Overall, the active treatment Cmin quartile groups were uniformly beneficial relative to placebo, and there was no specific threshold of plasma concentrations in patients receiving MDV3100 that was associated with achieving a significantly better response.

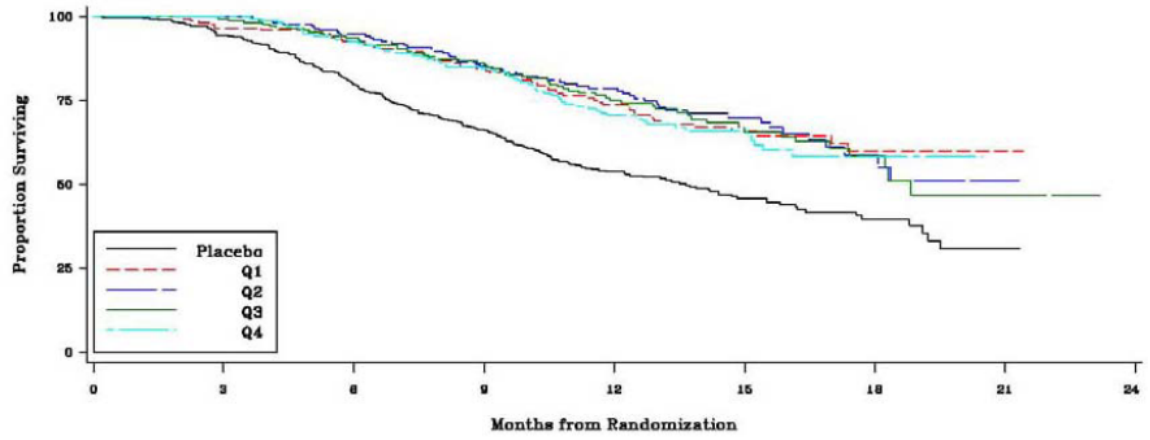



**Figure 1: Kaplan-Meier Exposure-Response Analysis for Overall Survival (MDV3100+M2 Cmin is used for exposure quartiles in treatment arm)** *Source: Sponsor's Exposure-Response Report, Figure 7.13, Page 56*





Reference ID: 3175035

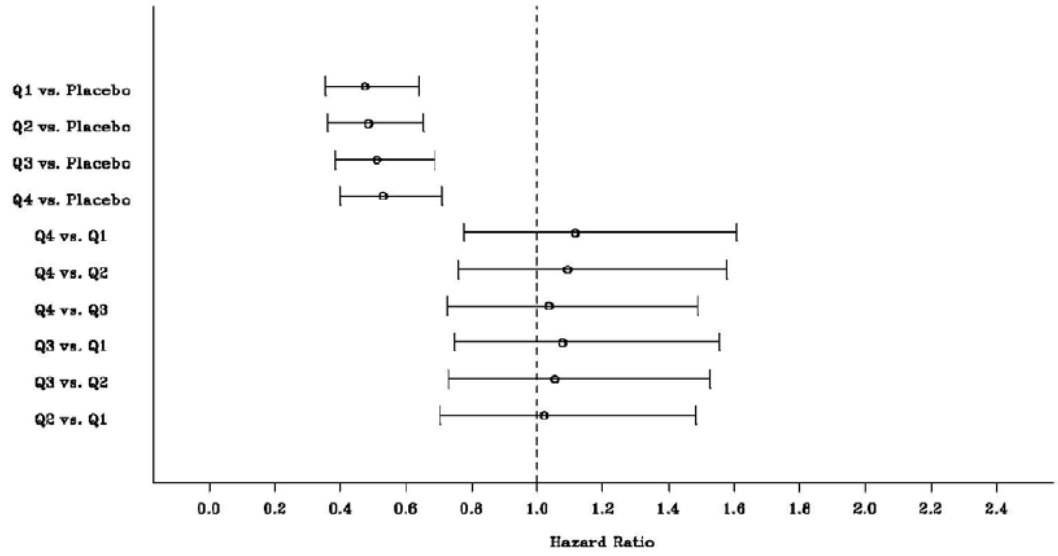



**Figure 2: Cox-Proportional Hazard Model Exposure-Response Analysis for Overall Survival (MDV3100+M2 Cmin is used for exposure quartiles in treatment arm and placebo arm is assigned an exposure of zero)** *Source: Sponsor's Exposure-Response Report, Figure 7.14, Page 58*

**Safety: There was no clinically meaningful exposure-response relationship for adverse events (AE) of clinical interest (Fatigue, Flushing, Headache, Hypertension, Seizure) within the limited exposure range of a single dose (160mg/day) explored in phase 3 (Figure 3).**

For AEs of clinical interest (mentioned above) the logistic regression analysis indicated statistically significant positive slopes for either MDV3100, M2, or MDV3100 + M2 Cmin values as continuous variables (with placebo= 0 exposure). The analysis with pair-wise comparison (odds ratio) of exposure quartiles indicated that the associations of higher risk with greater exposures were inconsistent between active treatment Cmin quartiles. Thus, there was no specific threshold of plasma concentrations in patients receiving MDV3100 that was associated with a greater risk of experiencing any of the AEs of clinical interest. For seizure, the incidence rate and the number of patients in the exposure categories was very low. Only 4 (of 6) patients who had seizures had parent drug exposure data (2 each belonged to Q3 and Q4 quartiles) and only 2 patients had M2 exposure data. This precluded having a meaningful analysis of association between exposure and incidence rates for seizures.

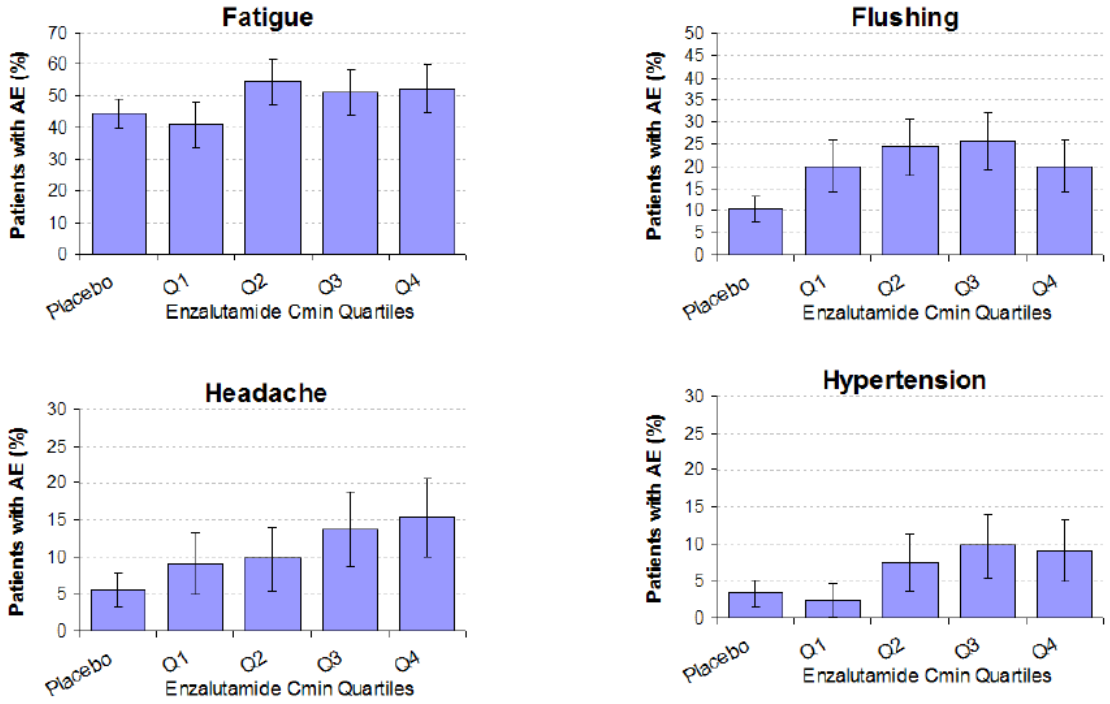



**Figure 3: Incidence rates (with 95% CI) for AEs of Clinical Interest (Safety events of all grades for Fatigue, Flushing, Headache, Hypertension) for Placebo and Enzalutamide Exposure Quartiles in Phase 3 (MDV3100+M2 Cmin is used for exposure quartiles in treatment arm)** *Source: Reviewer's analysis of sponsor's data in Exposure-Response Report, Page 113-122*

### 1.1.2 Is the dose and dosing regimen selected for phase 3 (AFFIRM) appropriate?

**The 160 mg/day dose selected for the Phase 3 seems reasonable.**

- In Phase 3 pivotal study, there was no exposure-OS relationship with 160 mg/day dose, and all the exposure quartiles were better than placebo in OS.
- There was no clinically meaningful exposure-response relationship for adverse events (AE) of clinical interest (Fatigue, Flushing, Headache, Hypertension, Seizure) within the limited exposure range of a single dose (160mg/day) explored in phase 3.
- In phase 1 dose escalation study, there was a dose/concentration dependant increase in proportion of patients showing a 50% decrease from baseline in PSA for doses from 30mg/day to 150 mg/day and this effect saturated at higher doses.
- The maximum tolerated dose (MTD) was determined to be 240 mg/day, based on occurrence of dose-limiting toxicities (seizure, rash, confusion) and fatigue adverse events that led to dose reduction in phase 1.
- Also a dose-dependent increase in fatigue adverse events occurred in phase 1, with incidences of 2.9%, 7.5% and 20.0% at 240 mg, 360 mg and 480 mg daily dosing respectively. Overall, there was comparable PSA inhibition response (proportion of patients

with 50% reduction in PSA from baseline) for doses ≥ 150 mg/day, and increasing safety issues at higher doses (≥ 240 mg/day) in phase 1.

Thus, with these cumulative evidences a dose of 160 mg/day selected for the Phase 3 AFFIRM study seems reasonable.

The half life of parent drug is 5.8 days, thus it takes about 28 days for drug plasma concentration to reach steady state. The choice of a high loading dose followed by maintenance dose could have been a viable alternative strategy. But the lack of safety indices upon application of a high loading dose and the evidence of severe adverse events at higher (≥ 240 mg/day) daily dose intake might have precluded consideration of such strategy.

### 1.1.3 Is a dose adjustment required based on age, weight or renal impairment?

Based on the pop-pk analysis, an estimated 18% decrease in systemic exposure of parent drug is predicted for subject with a weight of 120 kg and a ~13% increase in exposure for a 50 kg subject as compared to a median subject with a weight of 70 kg (**Table 1**). The moderate renal impairment is predicted to increase the exposures by ~12% over a median subject with normal renal function. Age covariate is expected to change the parent drug exposures by less than 5%. The sponsor's simulations also show that these covariates changed the steady state Cmin by less than 20% from the typical value (**Figure 4**). None of these patient-specific covariates are known to be associated with variability in the drug's pharmacodynamic response. Taken together, none of these covariates (age, weight, mild/moderate renal impairment) warrant any dose adjustment.

**Table 1: Covariate Effects on Population Estimate of Steady State Exposures[†]**

| *Covariate Effect* | *Change in AUCss (%)** |
|---|---|
| *No RI (at CRCL=80 ml/min)* | *-0.5* |
| *Mild RI (at CRCL=50 ml/min)* | *5.5* |
| *Moderate RI (at CRCL=30 ml/min)* | *12.4* |
| *Age=94 yr* | *2.2* |
| *Age=39 yr* | *-4.0* |
| *WT=120 kg* | *-17.7* |
| *WT=50 kg* | *12.9* |

**Calculated as population estimates, with respect to reference subject of age=69 yr, creatinine=0.9 mg/dl (CRCL=76.7 ml/min) and WT=70 kg; RI=Renal impairment*

[†]The range of relevant covariates in the POP-PK dataset: Age range is 19 to 92 yr with a median of 68 yr; WT range is 46 to 163 with a median of 83 kg; serum creatinine range is 0.47 to 2.53 with a median of 0.9 mg/dL; CRCL range is 19.6 to 224 with a median of 93.1 mL/min.

*Source: Reviewer's Assessment of final POP-PK model. The covariate ranges in POP-PK dataset are from Sponsor's Population PK Study Report, Table 6, Page 49*

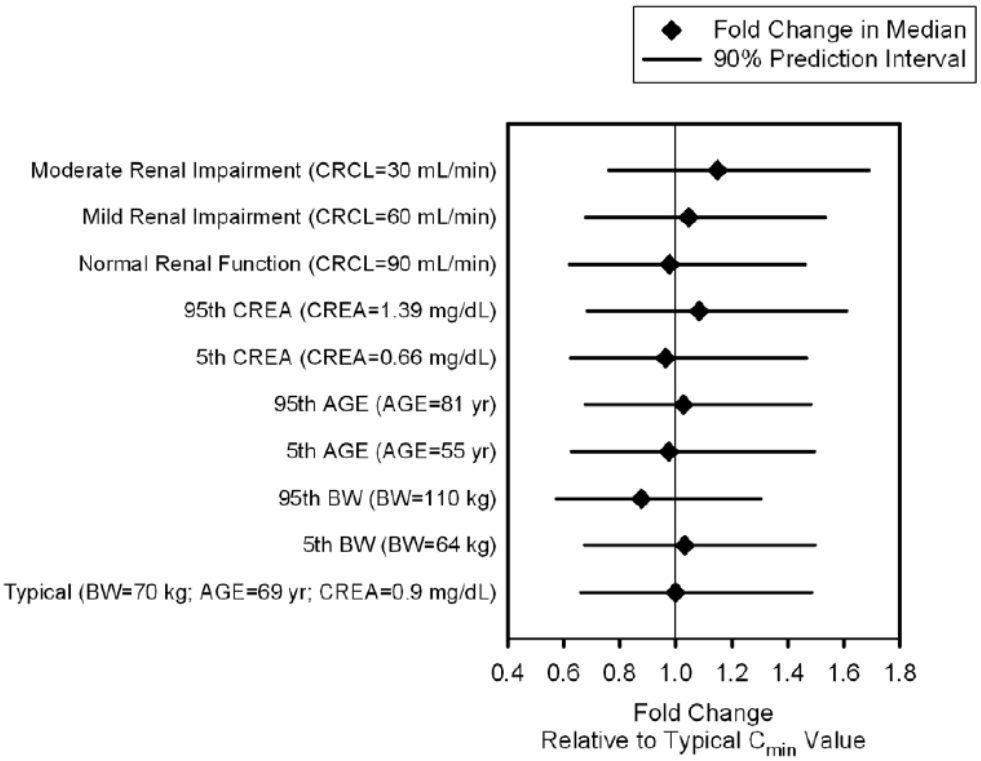



**Figure 4: Plot for Predicted Fold Change in Steady-State Cmin Relative to a Typical Patient under Various Covariate Scenarios** *Source: Sponsor's Population PK Study Report, Figure 56, Page 132*

### 1.2 Recommendations

Division of Pharmacometrics finds the NDA acceptable from a clinical pharmacology perspective.

### 1.3 Label Statements

Please refer to Section 3, Detailed Labeling Recommendations in Clinical Pharmacology Review.

## 2 PERTINENT REGULATORY BACKGROUND

Enzalutamide (MDV3100), an oral androgen receptor (AR) signaling inhibitor designed to block multiple steps in the AR signaling pathway and to be devoid of receptor agonist activity, is currently being developed by Medivation, Inc. and Astellas Pharma for the treatment of prostate cancer. The sponsor is seeking the indication for the treatment of patients with castration-resistant prostate cancer (CRPC) who have received docetaxel therapy. The previously approved therapies for this indication include Cabazitaxel and Abiraterone Acetate.

In the pivotal phase 3 trial for cabazitaxel, the median overall survival in the cabazitaxel (+ prednisone) arm was 15.1 months compared to 12.7 months in the mitoxantrone (+ prednisone) arm. Thus, cabazitaxel and prednisone improved survival by median 2.4 months compared with mitoxantrone and prednisone (hazard ratio [HR]=0.70; p<0.0001). However, patients treated with cabazitaxel experience a high incidence of Grade 3 or 4 neutropenia and febrile neutropenia.

In the pivotal phase 3 trial for abiraterone acetate (AA), the median overall survival in the AA arm was 14.8 months compared to 10.9 months in the placebo (standard of care) arm (P < 0.0001) with a hazard ratio of 0.646. Thus, AA improved survival by median 3.9 months compared with placebo (standard of care). AEs of special interest for AA included liver function abnormalities and mineralocorticoid-related toxicities such as hypertension, hypokalemia, and peripheral edema.

In the pivotal phase 3 trial for enzalutamide (MDV3100), the median overall survival in the enzalutamide arm was 18.4 months compared to 13.6 months in the placebo (standard of care) arm (P < 0.0001) with a hazard ratio of 0.631. Thus, enzalutamide improved survival by median 4.8 months compared with placebo (standard of care). AEs of clinical interest for enzalutamide included fatigue, flushing, headache, hypertension and seizure risk. In the phase 3 clinical trial, six patients (0.75%) experienced a seizure out of 800 patients treated with a daily dose of 160 mg enzalutamide, as compared to none in placebo arm.

Following 3 clinical studies for the MDV3100 program are main contributors to this review:

1. a phase 1 food-effect study (MDV3100-05)
2. an open-label Phase 1 dose escalation study (S-3100-1-01)
3. a pivotal Phase 3 randomized, double-blind, placebo-controlled efficacy, safety and PK study (CRPC2 AFFIRM).

The food-effect study enrolled healthy young subjects while the dose escalation study and pivotal study enrolled patients with castration-resistant prostate cancer. The dose escalation study involved daily doses of 30, 60, 150, 240, 360, 480 (240 mg twice per day) and 600 mg (300 mg twice per day). Phase 3 study involved once daily dose of 160 mg.

The sponsor provided pharmacometric reports for a population PK model developed based on all 3 studies mentioned above and exposure-response analysis for efficacy and safety.

# 3 RESULTS OF SPONSOR'S ANALYSIS AND REVIEWER'S COMMENTS

## 3.1 Dose Selection

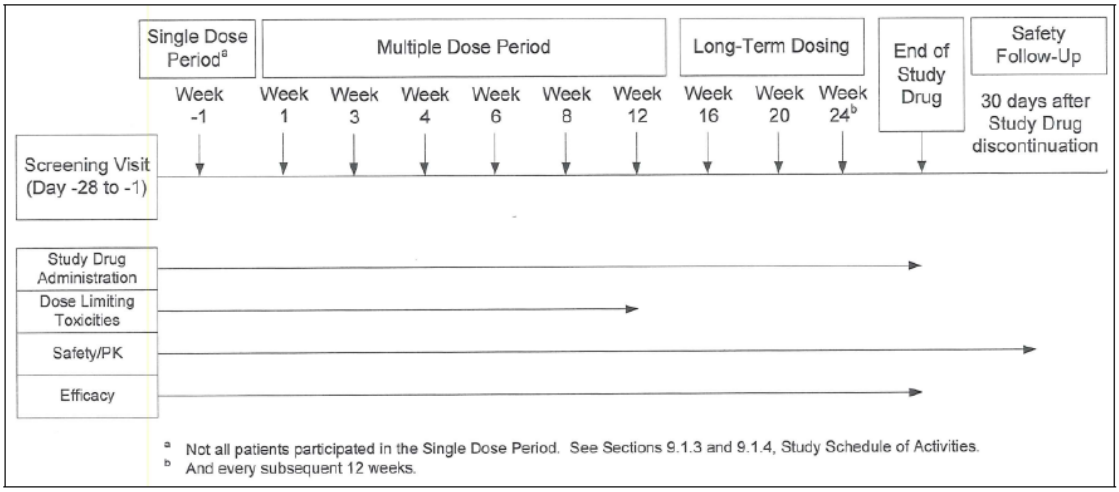
Dose selection was based on Phase 1 dose escalation study in CRPC patients. In the phase 1 dose escalation study, the proportion of patients showing a 50% decrease from baseline in PSA increased in a dose-dependent manner up to 150 mg/day (33.3% of patients at 30 mg/day, 59.3% at 60 mg/day and 66.7% at 150 mg/day) and there was no efficacy endpoint benefit beyond this at higher doses (58.6% at 240 mg/day, 67.9% at 360 mg/day, 28.6% at 480 mg/day, and 66.7% at 600 mg/day).

*Source: Sponsor's Clinical Study Report (CRPC2), Section 9.4.4, Page 34*

### 3.2 Phase 1 Dose Escalation Study (S-3100-1-01) and Phase 3 Pivotal Trial (CRPC2 AFFIRM)

A brief description of Phase 1 dose ranging study and Phase 3 pivotal trial is given in **Figure 5**.

A.




B.

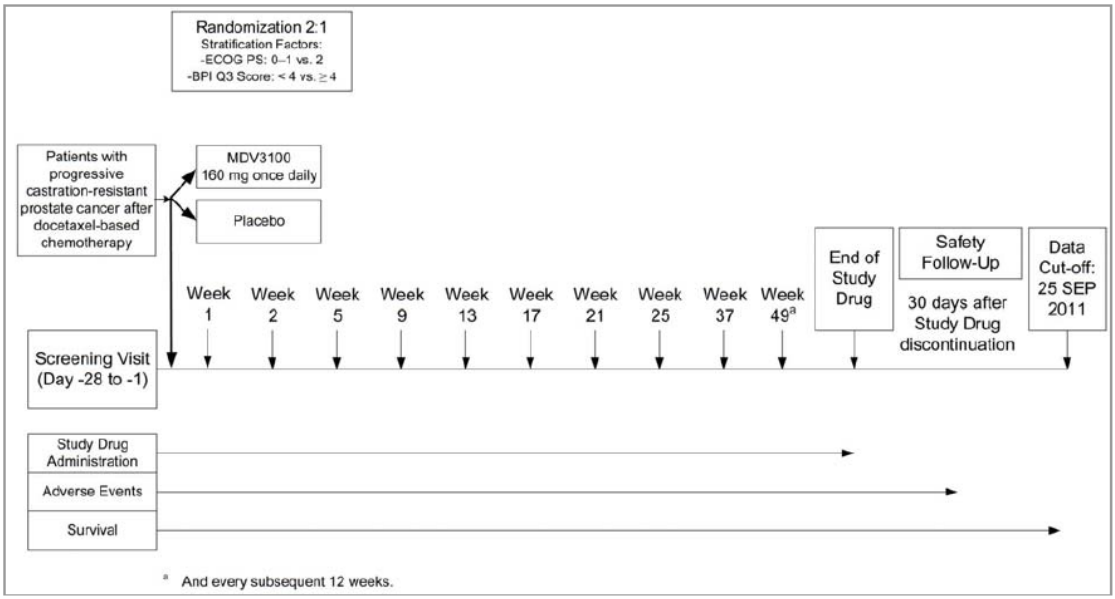



**Figure 5: Overview for Phase 1 Dose Escalation Study (A) and Phase 3 Pivotal Trial CRPC2 AFFIRM (B)**. *Source: Sponsor's Clinical Study Report (S-3100-1-01), Figure 9.1.1-1, Page 19 and Clinical Study Report (CRPC2), Figure 9.1-1, Page 25*

### 3.3 Population Pharmacokinetic Analysis

The sponsor performed population pharmacokinetic (PPK) analyses in patients to:

1. Characterize the inter-individual variability and influence of covariates on PK parameters in healthy subjects and CRPC patients.





Reference ID: 3175035

2. Evaluate the need for dosing adjustments based on patient covariates (weight, age, creatinine clearance values) in typical CRPC patients to support label statements.

### 3.3.1 Methods

The PK data was available from 985 subjects (59 healthy and 926 patients) across 3 different studies. The final pop-PK model was built based on data from 932 subjects (59 healthy and 873 patients) and 6672 observations as summarized in **Table 2**. In phase 1 food effect study MDV3100-05 intensive PK samples (21 samples per subject) were obtained over 42 days after a single 160 mg dose under either fasted conditions or after a high-fat meal. In phase 1 dose escalation study S-3100-1-01 intensive PK samples (11 samples per patient) were obtained over 7 days in a subset of patients in each dose category. Later predose trough (Cmin) PK samples were collected from all patients approximately once per month, and multiple PK samples were collected on Day 84. In phase 3 study (AFFIRM) predose Cmin samples were collected from all patients on Day 1, Week 2, every four weeks for the first 25 weeks, and then every 12 weeks thereafter. Doses were taken without regard to food intake.

**Table 2: Pharmacokinetic datasets**

| Dataset/Covariate | Statistic | MDV3100-05 | S-3100-1-01 | AFFIRM | All |
|---|---|---|---|---|---|
| ALL_DATA_v2.csv [excluding nominal doses > 240 mg] | | | | | |
| No. Subjects * (Subject Status) | n | 59 (Healthy) | 86 (Patient) | 787 (Patient) | 932 (Healthy & Patient) |
| Nominal Dose (mg/day) | | 160 | 30 (n=3)<br>60 (n=27)<br>150 (n=27)<br>240 (n=29) | 160 | 30 (n=3)<br>60 (n=27)<br>150 (n=27)<br>160 (n=846)<br>240 (n=29) |
| No. Observations | n | 953 (all single-dose) | 1437 (141 single-dose; 1296 multiple-dose) | 4282 (all multiple-dose) | 6672 (1094 single-dose; 5578 multiple-dose) |

* Number of patients with concentration data and included in the population PK analysis. Doses greater than 240 mg were excluded from final Pop-PK analysis. *Source: Sponsor's Population PK Study Report, Table 6, Page 49*

### 3.3.2 Results

The final Pop-PK model was based on MDV3100 PK in healthy volunteers receiving 160 mg and CRPC patients receiving 30 to 240 mg/day. It consisted of two-compartments with first-order absorption, absorption lag time ($T_{lag}$), and a separate absorption rate constant ($k_a$) for a high-fat meal. The model contained covariates for weight (WT) on oral and intercompartmental clearance (CL/F and Q/F), central volume of distribution ($V_2$/F), and peripheral volume of distribution ($V_3$/F); covariates for age (AGE) on CL/F and $V_2$/F; and a covariate for serum creatinine (CREA) on CL/F. Final parameter estimates for the population PK model are summarized in **Table 3**. The point estimates in the table represent typical values for a subject of



Reference ID: 3175035

**Figure 6.**

**Table 3: Pharmacokinetic and covariate parameter estimates of the final model**

| Parameter [Units] | NONMEM Estimates for Final Pop PK Model (MDV3026s) | | | | |
|---|---|---|---|---|---|
| | Point Estimate [a] | RSE (%) | | 95% CI | |
| CL/F [L/h]* | 0.507 | 1.63 | | 0.496 - 0.518 | |
| $V_2$/F [L]* | 38.5 | 1.58 | | 34.5 - 42.9 | |
| $k_a$ [$h^{-1}$]* | 0.872 | 138 | | 0.602 - 1.26 | |
| Q/F [L/h]* | 9.12 | 4.57 | | 7.46 - 11.1 | |
| $V_3$/F [L]* | 41.7 | 1.27 | | 38.1 - 45.6 | |
| Lag Time (h) | 0.230 | 0.243 | | 0.229 - 0.231 | |
| High fat meal $k_a$ [$h^{-1}$]* | 0.705 | 142 | | 0.267 - 1.865 | |
| WT~CL/F | 0.361 | 11.7 | | 0.278 - 0.444 | |
| WT~$V_2$/F | 0.954 | 21.6 | | 0.550 - 1.36 | |
| WT~Q/F | 0.783 | 49.8 | | 0.0186 - 1.55 | |
| WT~$V_3$/F | 2.04 | 7.40 | | 1.74 - 2.34 | |
| CREA~CL/F | -0.125 | 22.8 | | -0.181 - -0.0691 | |
| AGE~CL/F | -0.0715 | 37.8 | | -0.124 - -0.0186 | |
| AGE~$V_2$/F | 0.863 | 7.14 | | 0.742 - 0.984 | |
| **Inter-individual variability** | | | **ETAshrink (%)** | | **CV%/R** |
| $\omega^2_{CL/F}$ | 0.0407 | 4.05 | 3.15 | 0.0375 - 0.0439 | 20.2 |
| corr($\eta_{CL/F}$, $\eta_{V2/F}$) | 0.00214 | 178 | . | -0.00533 - 0.00961 | 0.0542 |
| $\omega^2_{V2/F}$ | 0.0383 | 35.5 | 37.7 | 0.0116 - 0.0650 | 19.6 |
| $\omega^2_{Q/F}$ | 0.162 | 35.9 | 74.7 | 0.0481 - 0.276 | 41.9[b] |
| corr($\eta_{Q/F}$, $\eta_{V3/F}$) | 0.0401 | 40.6 | | 0.00815 - 0.0720 | 0.503 |
| $\omega^2_{V3/F}$ | 0.0393 | 17.2 | 49.3 | 0.0260 - 0.0526 | 19.8 |
| corr($\eta_{Q/F}$, $\eta_{ka}$) | 0.486 | 36.2 | | 0.141 - 0.831 | 0.733 |
| corr($\eta_{V3/F}$, $\eta_{ka}$) | 0.0834 | 71.0 | | -0.0326 - 0.199 | 0.256 |
| $\omega^2_{ka}$ | 2.71 | 13.5 | 60.4 | 1.99 - 3.43 | 375[b] |
| $\omega^2(\sigma^2)$ | 0.180 | 6.94 | 18.3 | 0.156 - 0.204 | 44.4[b] |
| **Residual variability** | | | **EPSshrink (%)** | | **CV%** |
| $\sigma^2_{prop, SD}$ | 0.0349 | 11.3 | 1.41 | 0.0272 - 0.0426 | 18.7 |
| $\sigma^2_{prop, MD}$ | 0.0116 | 4.52 | 4.37 | 0.0106 - 0.0126 | 10.8 |

Abbreviations: RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; 95% CI= 95% confidence interval on the parameter; R = correlation coefficient; $\omega^2$ = variance of inter-individual random effect; corr($\eta_1$, $\eta_2$) = covariance between $\eta_1$ and $\eta_2$; $\sigma^2_{prop, SD}$ = proportional residual error for single dose data; $\sigma^2_{prop, MD}$ = proportional residual error for multiple dose data.

* Estimate and 95% CI back-transformed from $\log_e$ scale

[a] The typical value represents the expected value for an individual weighing 70 kg with AGE (69 yr) and CREA (0.9 mg/dL), typical for patients in the AFFIRM study.

[b] Computed as $\sqrt{e^{\omega^2} - 1}$

*Source: Sponsor's Population PK Study Report, Page 6*

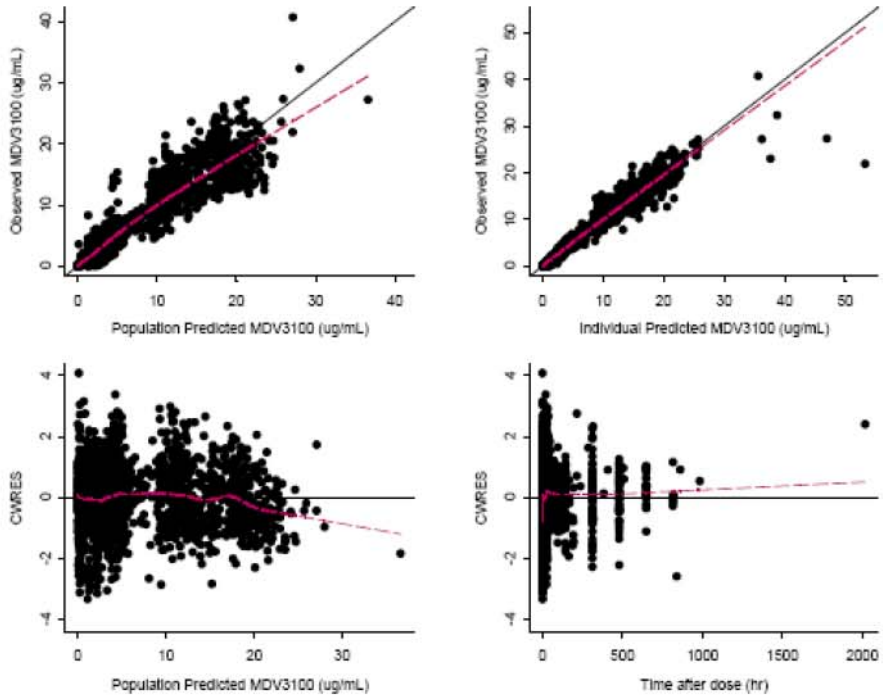



**Figure 6: Goodness-of-Fit Diagnostic Plots for the Final Pop-PK Model** *Source: Sponsor's Population PK Study Report, Figure 41, Page 114*

### 3.3.3 Covariate effects

The final Pop PK model was used to assess the effects of the covariates WT, AGE, and CREA.

- With body weight of 60 and 120 kg, the model estimates of CL/F were 5% below and 21% above the typical value for a 70 kg individual.
- AGE had a minor effect with a 4% increase and a 2% decrease in CL/F at the extremes in the AFFIRM data (41 to 92 yr).
- CREA (serum creatinine) had a minor effect on CL/F, with an 8% increase and a 12% decrease at the extremes in the AFFIRM data (0.47 to 2.53 mg/dL).
- Thus, dosing adjustments based on WT, AGE or CREA are not indicated.

The impact of covariates in the final Pop PK model was further examined by simulation with perturbation of only one covariate from its typical (median) value in each scenario. The results in the form of median and 90% prediction interval for fold-change in steady state Cmin values are summarized in **Figure 4**.

*Reviewer's comments:*

1. *The sponsor's Pop-PK model provides reasonable description of MDV3100 concentrations for individual predictions (observed vs. individual predicted concentrations in **Figure 6**). Visual inspection shows that the model reasonably predicts individual data over a range of concentrations in the phase 1 and phase 3 study. There appears to be some over-estimation at higher observed concentrations for a limited number of observations.*

2. *The model characterizes the concentrations of parent drug but not the major active metabolite M2 which is almost equally potent in inhibitory function. The metabolite was excluded from pop-PK analysis since the Phase 1 dose ranging study did not collect M2 concentration data. Like the parent drug, this metabolite has only a minor component of clearance by renal pathway (<0.5% of dose is cleared renally as M2) and its observed steady state Cmin concentrations are found to be equivalent or slightly higher as compared to parent drug. Since this metabolite has only a minor renal clearance component, M2 exposures are not expected to be modulated to a clinically meaningful extent with mild/moderate renal impairment.*
3. *Among the list of covariates for clearance, effect of body weight on clearance was the most significant covariate (reviewer's assessment summarized in **Table 1**). However, the small magnitudes of covariate effects (age, body weight and renal function) on exposure are not clinically relevant and there is no need for dose adjustment based on any of these covariates.*

## 3.4 Exposure-Response Analysis

### 3.4.1 Objective

The sponsor conducted the exposure-response analysis to evaluate the relationship of patient plasma exposure to MDV3100 and its major active metabolite M2 with following outcomes in phase 3 study:

- efficacy endpoints- overall survival, radiographic progression free survival, time to prostate-specific antigen progression, PSA response and
- adverse events- treatment-emergent adverse events and adverse events of clinical interest that include diarrhea, fatigue, flushing/hot flush, headache, hypertension and seizure.

Treatment-emergent period was defined as the time period from first dose of study drug till 30 days after the date of last dose or the day before the initiation (after discontinuation of study drug) of another systemic antineoplastic therapy, whichever occurred first.

### 3.4.2 Exposure Parameters

Average of steady-state Cmin for each subject was taken as the exposure parameter (detailed in Sponsor's Exposure-Response Report, Section 5.3.1, page 24-25), and the exposure-response analysis was conducted using either MDV3100 alone, M2 alone or MDV3100+M2 exposure for each subject. The exposures were grouped into quartiles and compared with placebo patients who were assigned a Cmin=0.

### 3.4.3 Methods

Both continuous and quartile grouped exposure parameters were used in the exposure-response analysis. Exposure effects on overall survival were evaluated based on a stratified log-rank test of the exposure categories. Kaplan-Meier estimates were used to estimate the distribution of duration and median duration of overall survival. In cases where the median was not reached as of the data cutoff, the 25th percentile values were estimated. Further Cox regression analysis (stratified by the two randomization factors) was performed with continuous exposure

parameters to determine the slope estimate and with categorical (quartile) exposure parameters to determine the hazard ratios between each pair of exposure categories. Exposure effects on safety were evaluated using logistic regression model, first with continuous exposure and if found significant, later with exposure categories to determine the pairwise odds ratios.

### 3.4.4 Datasets

Of the 800 patients randomized to active treatment, 763 active-treatment subjects had qualified MDV3100 Cmin data, while 704 active-treatment subjects had qualified M2 and MDV3100+M2 Cmin data that were used for this analysis. All 399 patients randomized to placebo formed the placebo category in this analysis. The summary of exposure quartiles is shown in **Table 4**.

**Table 4: Summary of Exposure Quartiles for Exposure-Response Analysis**

| Exposure Variable | $C_{min}$ (µg/mL) Quartile | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Q1 | | | Q2 | | | Q3 | | | Q4 | | |
| | n | Median | Min, Max | n | Median | Min, Max | n | Median | Min, Max | n | Median | Min, Max |
| MDV3100 | 192 | 8.926 | 0.56,10.15 | 190 | 10.833 | 10.16,11.57 | 191 | 12.175 | 11.57, 12.96 | 190 | 14.400 | 12.97, 22.80 |
| M2 | 176 | 9.428 | 0.71,10.57 | 176 | 11.586 | 10.59,12.53 | 176 | 13.690 | 12.54, 14.90 | 176 | 16.675 | 14.95, 32.40 |
| MDV3100 + M2 | 176 | 19.350 | 0.82 ,21.34 | 176 | 22.951 | 21.35,24.33 | 176 | 25.833 | 24.39, 27.55 | 176 | 29.655 | 27.58 , 42.40 |

*Source: Sponsor's Exposure-Response Report, Table 7.1, Page 36*

### 3.4.5 Results

***Exposure-Overall Survival Results***

In a pair-wise comparisons versus placebo using Kaplan-Meier estimates, all the active treatment exposure quartile groups (based on MDV3100, M2, or MDV3100 + M2 Cmin) were statistically significant (p-values $\leq 0.0039$) in favor of active treatment, for overall survival. A representative K-M plot for analysis with MDV3100 + M2 exposure is shown in **Figure 1**. (For more information, refer to section 7.3.1 in *Sponsor's Exposure-Response Report*). Although Cmin values as continuous variable showed statistically significant positive slope for efficacy endpoints with placebo and active treatment data, the pairwise comparisons (hazard ratios) between each exposure quartile using cox-proportional hazard model did not show any difference in risk of efficacy events (**Figure 2**). Overall, the active treatment Cmin quartile groups were uniformly beneficial relative to placebo, and there was no specific threshold of plasma concentrations in patients receiving MDV3100 that was associated with achieving a significantly better or worse response.

Thus, based on the efficacy results of Phase 3 trial, no exposure-response relationship for survival could be identified for enzalutamide (MDV3100) within a single fixed dose of 160 mg/day. As shown in **Figure 1** and **Figure 2** above, there was no significant difference in survival between the four quartiles but all the exposure quartiles were better than placebo.

*Reviewer's comments:*

1. *Since the M2 metabolite has almost similar potency for drug action as the parent drug compound, M2 is circulating in plasma at approximately the same concentrations as the parent drug and their molecular weights are not very different (464 Da for MDV3100 and*


Reference ID: 3175035

*450 Da for M2), it is appropriate to take the non-weighted sum of their mass concentrations as the drug exposure parameter for analyzing and deriving exposure-response related conclusions. The final conclusion for the exposure-efficacy analysis was the same irrespective of whether parent drug alone, M2 alone or parent+M2 combined were used as exposure parameter.*

2. *The cox-proportional hazard model analysis not only includes the categorical Cmin exposures but also takes into account the stratification by two risk factors which are considered clinically associated with disease state/likelihood of survival, viz. Baseline ECOG performance status (0-1 vs 2) and Brief Pain Inventory (Short Form) Mean Score for question #3 (<4 vs >=4), and thus the analysis seems reasonably balanced for deriving meaningful conclusions about pairwise comparisons of exposure categories. In this analysis, the patients in lesser exposure quartile(s) did not appear to be at more risk (for overall survival) than the ones in higher exposure quartile.*

3. *Preliminary PK/PD cell-growth model[*] for MDV3100 that was developed by sponsor using phase 1 dose escalation study for PSA response had estimated that the PSA inhibition response is already at a maximum even at the lowest dose range studied (30 mg/day) since the EC50 value for inhibition of PSA response was <100 ng/ml. This EC50 value is lesser by atleast an order of magnitude than the lowest drug+M2 plasma concentration observed at steady state with 160 mg/day dose. This PK/PD analysis gives additional evidence that the exposure-efficacy relationship could be shallow within the exposures achieved with 160 mg/day dose. ([*]Source: Sponsor's Report: PK/PD Modeling of MDV3100 on PSA and Fatigue, Section 4.3.2, Page 49)*

***Exposure-Safety Results***

In the phase 3 study, the majority of treatment-emergent adverse events showed no significant linear association between incidence and MDV3100, M2, or MDV3100 + M2 exposure categories. For the cases where treatment-emergent adverse events showed a statistically significant linear association between increased exposure (MDV3100 + M2) and incidence (Anxiety, dizziness, dyspepsia, headache, hot flush, hypertension, pollakiuria, and pruritus), the overall incidence was generally low, and the statistical findings are of uncertain clinical relevance.

For other adverse events of clinical interest (hypertension, flushing, headache and seizure) the logistic regression analysis indicated statistically significant positive slopes for either MDV3100, M2, or MDV3100 + M2 Cmin values as continuous variables (this analysis included placebo, assigned with an exposure of zero). The analysis with pair-wise odds ratio of exposure quartiles indicated that the associations of higher risk with greater exposures were either inconsistent between active treatment Cmin quartiles or nonexistent. Thus, there was no specific threshold of plasma concentrations in patients receiving MDV3100 that was associated with a greater risk of experiencing any of the adverse events of clinical interest.

For seizure, the number of patients in the exposure categories was too low (4 patients who had seizures had exposure data, 2 each belonged to Q3 and Q4 quartiles) to support a meaningful analysis of association between exposure and seizure incidence rates.

*Reviewer's comments:*

1. *As per the reviewer's assessment, the number of seizure events is small and the exposures for these subjects are distributed across Q3 and Q4 exposure categories (**Figure 7**; Red dots correspond to the exposures for patients who had seizure event). Within the limited exposure range for this single dose study there is insufficient evidence for necessity to recommend dose adjustment for seizure concern based on exposures.*

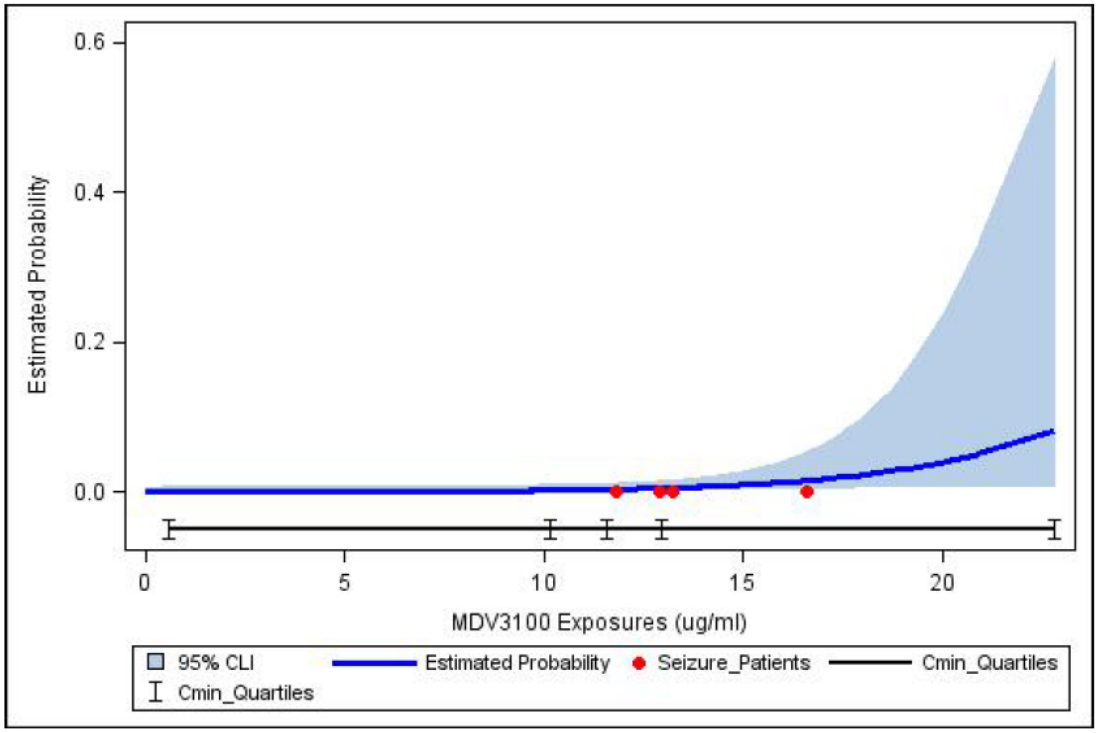



***Figure 7: Logistic Regression Model Exposure-Response Analysis for Seizure (with MDV3100 as exposure parameter)*** *Source: Reviewer's Assessment*

# 4 LISTING OF ANALYSES DATASETS, CODES AND OUTPUT FILES

## Table 5: Analysis Data Sets

| Study Number | Name | Link to EDR |
|---|---|---|
| CRPC2<br>AFFIRM | mdv3026s-ctl.txt (Nonmem control stream) | \\cdsesub1\EVSPROD\NDA203415\\0000\m5\datasets\pop-pk-icon2147014\analysis\datasets\mdv3026s-ctl.txt |
| | aderpk.xpt (ER parameter analysis dataset) | \\cdsesub1\EVSPROD\NDA203415\\0000\m5\datasets\exposure-response-icon-2147016\analysis\datasets\aderpk.xpt |
| | adaei.xpt (Adverse events of clinical interest dataset) | \\cdsesub1\EVSPROD\NDA203415\\0000\m5\datasets\exposure-response-icon-2147016\analysis\datasets\adaei.xpt |

## Table 6: Codes and Output Files

| File Name | Description | Location in \\cdsnas\pharmacometrics\ |
|---|---|---|
| PK_diff_POPPK.xls | Excel file for calculation of population estimates of change in clearance with change in covariates, worked out from final POP-PK model | \\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Enzalutamide_NDA203415_DDM\PPK Analyses\PK_diff_POPPK.xls |
| import.sas | SAS macro for batch converting .xpt files to sas datasets and sas code for Logistic Regression analysis for exposure-seizure events | \\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Enzalutamide_NDA203415_DDM\ER Analyses\data\ER\import.sas |

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

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/s/

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JEANNE FOURIE ZIRKELBACH
08/28/2012

DHANANJAY D MARATHE
08/28/2012

YANING WANG
08/28/2012
Sign for Nitin Mehrotra

QI LIU
08/28/2012

NAM ATIQUR RAHMAN
08/28/2012

| BIOPHARMACEUTICS NDA REVIEW<br>Office of New Drug Quality Assessment | | | |
|---|---|---|---|
| **Application No.:** | NDA 203-415 | **Reviewer:** Deepika Arora Lakhani, PhD | |
| **Submission Date:** | May 22, 2012<br>July 17, 2012 | | |
| **Division:** | Division of Drug Oncology Products 1 | **Team Leader:** Angelica Dorantes, PhD | |
| **Sponsor:** | Medivation, Inc. | **Biopharmaceutics Supervisor (Acting):** Richard Lostritto, PhD | |
| **Trade Name:** | -Xtandi- (under review) Capsules | **Date Assigned:** | Apr 12, 2012 |
| **Generic Name:** | Enzalutamide (MDV 3100) | **Date of Review:** | July 27, 2012 |
| **Indication:** | Castration-resistant prostate cancer who have received docetaxel (b) (4) | **Type of Submission:** New Drug Application 505b(1) | |
| **Formulation/ strengths** | Liquid-filled soft gelatin capsule, 40 mg strength | | |
| **Route of Administration** | Oral | | |

## SUMMARY OF BIOPHARMACEUTICS FINDINGS:

The NDA submission is a 505(b)(1) application for a liquid-filled soft gelatin capsule (40 mg strength) with a dosage of 160 mg orally once daily, with or without food. This NDA was granted a priority expedited review. The capsule contains 40 mg MDV3100 (or enzalutamide) which is a new chemical entity (NCE) being developed for the treatment of patients with castration-resistant prostate cancer who have received docetaxel (b) (4). MDV3100 is an androgen receptor signaling inhibitor that targets several steps in the androgen receptor signaling pathway.

MDV3100 Drug Product 40 mg is an opaque white to off-white, liquid filled soft gelatin capsule. During product development, a rupture method was used (instead of dissolution) throughout product development for batch release and stability evaluation. However, upon Agency's recommendation (Sep 2009), the Applicant developed a dissolution method to replace the rupture method. This review focuses on: a) the acceptability of the dissolution method and acceptance criteria; b) acceptability of rupture test during product development; c) correlation between rupture test and dissolution.

**a) Dissolution Method and Acceptance Criteria:**

The following method to assay the dissolution of enzalutamide liquid filled capsules was developed. The following acceptance criterion was recommended by the Agency and accepted by the Applicant on 17-July-2012.

| Drug Name | Dosage Form | USP Apparatus | Speed (rpm) | Medium | Volume (mL) | Acceptance criterion |
|---|---|---|---|---|---|---|
| Enzalutamide (MDV-3100) | Capsule | II (paddle) | 50 | Tier-1: 0.1N HCl/ 0.3% CTAB, Tier-2: 0.1N HCl/ 0.3% CTAB/pepsin | 900 mL | Q= (b) (4) % at 15 minutes |

The robustness of the dissolution method was evaluated by assessing the effect of changing dissolution parameters (HCl concentration, surfactant level and paddle speed). The discriminating capacity of the dissolution method was evaluated by testing stressed capsules that show crosslinking and crystallization of

the drug substance. The proposed dissolution method discriminates for cross-linked capsules and crystallized API inside the capsule and has been deemed acceptable.

**b) Rupture Test and Correlation between Rupture and Dissolution**
Prior to the development of the dissolution method, capsule rupture testing was performed during stability and this testing was continued throughout the stability program. Upon FDA's recommendation, the dissolution method was developed. Both rupture and dissolution methods were compared by demonstrating that the performance of in- and out- of specification batches were directly correlated.

**RECOMMENDATION:**
The ONDQA/Biopharmaceutics team has reviewed NDA 203-415 and its amendments submitted on May 20, 2012 and Jun 27, 2012. The following dissolution method for enzalutamide capsules is deemed acceptable:

**USP Apparatus II**
**Paddle speed: 50 rpm**
**Volume/Temp: 900 ml / 37°C**
**Tier-1: 0.1N HCl/0.3% CTAB,**
**Tier-2: 0.1N HCl/ 0.3% CTAB/pepsin;**

The following dissolution acceptance criterion has been recommended (and agreed by the Applicant, refer to submission dated 17-JULY-2012) for enzalutamide capsules.

**Q= (b) (4) % at 15 minutes**

From the Biopharmaceutics perspective NDA 203-415 for Xtandi (enzalutamide) Capsules is recommended for APPROVAL.

Deepika Arora Lakhani, PhD
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, PhD
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc. *on file; RLostritto*

## INTRODUCTION

Enzalutamide (an androgen receptor signaling inhibitor that targets several steps in the androgen receptor signaling pathway) is a new chemical entity (NCE) being developed for the treatment of patients with castration-resistant prostate cancer who have received docetaxel (b) (4). The drug product contains 40 mg API and is an opaque white to off-white, liquid filled soft gelatin capsule. The API is in a dissolved state in the capsule. The clinical presentation is a 40-mg gelatin capsule, requiring 4 capsules per day to provide the clinical dose of 160 mg daily.

### Drug Substance

Enzalutamide is a poorly soluble, non-hygroscopic, crystalline solid that remains un-ionized over the physiologic pH range. It is defined as a Class 2 drug using the Biopharmaceutics Classification System because it has high membrane permeability and limited aqueous solubility

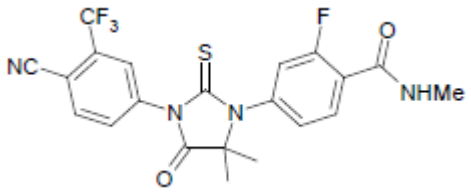


**Figure 1.** Chemical Structure of Enzalutamide

The solubility profile of enzalutamide shows that the API is poorly soluble in aqueous solution across the pH range.

**Table 1.** Enzalutamide Solubility Profile

| Solvent | Solubility (mg/mL) |
|---|---|
| Methanol | 49 mg/mL (Soluble) |
| 1-Methyl 2-pyrrolidinone | $5.3\times10^{2}$ mg/mL (Freely soluble) |
| Absolute ethanol | 12 mg/mL (Sparingly soluble) |
| Acetonitrile | $3.4\times10^{2}$ mg/mL (Freely soluble) |
| Water | $2.0\times10^{-3}$ mg/mL (Practically insoluble) |
| Aqueous solution [a], pH 1.0 | $2.0\times10^{-3}$ mg/mL (Practically insoluble) |
| Aqueous solution [b], pH 3.0 | $2.0\times10^{-3}$ mg/mL (Practically insoluble) |
| Aqueous solution [b], pH 5.0 | $2.0\times10^{-3}$ mg/mL (Practically insoluble) |
| Aqueous solution [b], pH 7.0 | $2.0\times10^{-3}$ mg/mL (Practically insoluble) |
| Aqueous solution [b], pH 9.0 | $1.0\times10^{-3}$ mg/mL (Practically insoluble) |
| Aqueous solution [b], pH 11.0 | $3.0\times10^{-3}$ mg/mL (Practically insoluble) |

[a] The result was determined using 0.1 mol/L hydrochloric acid.
[b] The results were determined using Carmody buffer (a mixture of 0.2 mol/L boric acid, 0.05 mol/L citric acid and 0.1 mol/L trisodium phosphate).

### Drug Product

The Drug Product contains 40 mg API and is an opaque white to off-white, liquid filled soft gelatin capsule. The gelatin capsule is an oblong modified size 12 shell with product identifiers printed in black ink. Caprylocaproyl polyoxylglycerides (b) (4) (b) (4) greatest solubility for the API. This excipient is the major component of capsules. In addition, the fill formulation contains the

antioxidants butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). The composition of the capsules is provided in Table 1.

**Table 1**. Composition of Enzalutamide Capsules

| Component | Reference to Quality Standard | Function | Amount (mg) per Capsule |
|---|---|---|---|
| (b) (4) | | | |
| Enzalutamide | Section 2.3.S.4 | Active Ingredient | 40.0 |
| Caprylocaproyl Polyoxylglycerides | NF | | (b) (4) |
| Butylated Hydroxyanisole | NF | | |
| Butylated Hydroxytoluene | NF | | |
| (b) (4) | | | |
| | | **Capsule Fill Solution Weight:** | **946.0** |
| (b) (4) | | | |

**Formulation Development**

Early nonclinical studies indicated that formulations where the drug substance was in the fully dissolved state exhibited higher oral bioavailability than formulations where the drug substance was presented in the solid state (suspension and solid dose formulations). Therefore, the primary goal of the pharmaceutical development program was to formulate API in the dissolved state, to ensure that the drug absorption would not be hindered by the slow dissolution rate of the drug substance. A liquid filled soft gelatin capsule dosage form was identified as meeting the primary development goal.

The composition of the enzalutamide solution in the capsules has remained unchanged throughout clinical development. For the first-in-human, dose-escalation **Phase 1** study (S-3100-1-01), the liquid formulation was initially filled into hard gelatin capsules containing 30 mg of API per capsule. During the Phase 1 study, the liquid formulation was filled into more robust, soft gelatin capsules containing 40 mg enzalutamide. The difference in capsule dose strength is strictly a function of the capsule fill volume, and there were no changes in the composition of the liquid formulation. **The soft gelatin capsule has been used in all subsequent clinical studies and is the intended commercial presentation. The dose regimen in the pivotal Phase 3 study (CRPC2 [AFFIRM]) was four 40 mg capsules once a day (160 mg/day).**

A brief overview of the manufacture of the drug product is summarized in the diagram below.

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## DISSOLUTION ACCEPTANCE CRITERIA

The following dissolution acceptance criterion was originally proposed by the Applicant as a QC for the release of enzalutamide capsules:

| Dissolution Acceptance Criterion |
|---|
| Q= (b)(4)% at 30 mins |

According to the Applicant, this criterion is being proposed since rupture data from both the water and acid methods at release and on stability support the time point. Further, dissolution batch analyses data and stability data also support the acceptance criterion.

### Reviewer's Recommended Dissolution Acceptance Criteria

The following dissolution acceptance criterion is recommended as a QC for release and on stability for enzalutamide capsules:

| Dissolution Acceptance Criteria |
|---|
| Q= (b)(4)% at 15 mins |

The dissolution acceptance criteria of Q= (b)(4)% in 15 min for enzalutamide capsules was established based on the following information:

- Mean dissolution values from the limited data from drug product release and the drug product stability testing.

The Applicant has very limited data available from the clinical development as rupture test was used during that phase. The dissolution data are available starting from 12 months' time point for stability and consistently show more than (b)(4)% dissolution by 15 mins. Batch release data are provided only from a single batch and support the recommended acceptance criterion.

### Reviewer's Comments

*This NDA is an expedited priority review. Overall, the batch release and stability data are very limited due to nature of NDA. Based upon the submitted data, the dissolution acceptance criterion of Q= (b)(4)% at 15 minutes is the most suitable.*

# CONCLUSIONS

NDA 203-415 is recommended for Approval from a Biopharmaceutics perspective. The following dissolution method and acceptance criterion for the enzalutamide capsules are acceptable:

| USP Apparatus | Speed (rpm) | Volume (ml) & Temperature | Medium | Acceptance Criterion |
|---|---|---|---|---|
| II (paddle) | 50 | 900 mL<br>37°C | Tier-1: 0.1N HCl/0.3% CTAB<br>Tier-2: 0.1N HCl/0.3% CTAB/pepsin | 900 mL |

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/s/

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DEEPIKA LAKHANI
08/15/2012
Recommend Approval from Biopharmaceutics perspective.

ANGELICA DORANTES
08/15/2012

| Clinical Pharmacology Review | |
|---|---|
| **FDA** | 20-3415 (IND 74,563) |
| **Submission Date:** | 5/22/12 |
| **Brand Name:** | (b) (4) |
| **Generic Name:** | Enzalutamide |
| **Formulation:** | 40 mg capsules |
| **OCP Reviewer:** | Jeanne Fourie Zirkelbach, PhD |
| **OCP Team Leader:** | Qi Liu, PhD |
| **Pharmacometrics Reviewer:** | Dhananjay Marathe, PhD |
| **Pharmacometrics Team Leader:** | Nitin Mehrotra, PharmD |
| **OCP Division:** | Division of Clinical Pharmacology V |
| **ORM Division:** | Division of Drug Oncology Products |
| **Sponsor:** | Medivation Inc. |
| **Submission Type; Code:** | NDA 0000/01 |
| **Dosing regimen:** | Once daily oral dose of 160 mg of enzalutamide. |
| **Indication:** | For the treatment of castration-resistant prostate cancer who have received docetaxel (b) (4). |

## NDA FILING AND REVIEW FORM

| Office of Clinical Pharmacology | | | |
|---|---|---|---|
| General Information About the Submission | | | |
| **NDA Number** | NDA 203415<br>IND 74,563 | **Brand Name** | (b) (4) |
| **DCP Division (I, II, III, IV, V)** | V | **Generic Name** | Enzalutamide (MDV3100) |
| **Medical Division** | Oncology | **Drug Class** | Androgen receptor antagonist |
| **OCP Reviewer** | Jeanne Fourie Zirkelbach, Ph.D. | **Indication(s)** | Castration resistant prostate cancer |
| **OCP Team Leader** | Qi Liu, Ph.D. | **Dosage Form** | Immediate-release, liquid filled soft-gelatin capsules containing 40 mg enzalutamide. |
| | | **Route of Administration** | Oral administration, without regard to food, of 160 mg (four 40 mg tablets) once daily. |
| **Sponsor** | Medivation Inc. | **Priority Classification** | Expedited Review |
| **Date of Submission** | 5/22/12 | **Estimated Due Date of OCP Review** | |
| **PDUFA Due Date** | Expedited (Aug 31/2012 action date) | **Division Due Date** | |

### *Clinical Pharmacology Information*

| | **"X" if included at filing** | **Number of studies submitted** | **Number of studies reviewed** | **Critical Comments If any** |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | **X** | | | |

| | | | | |
|---|---|---|---|---|
| **Tabular Listing of All Human Studies** | **X** | | | |
| **HPK Summary** | **X** | | | |
| **Labeling** | **X** | | | |
| **Reference Bioanalytical and Analytical Methods** | **X** | **7** | | PRO3100NC33, PRO3100NC86: Quantification of MDV3100, M1 and M2 in plasma from humans. Probe drug quantification for DDI trials.<br>9785-ME-0013: Quantification of MDV3100, M1 and M2 in urine from humans.<br>Probe drug quantification for DDI trials. |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | **x** | **1** | | 9785-CL-0001: in healthy adult male subjects (single dose). |
| **Metabolic profiling** | **x** | **6** | | 9785-ME-0001 and 9785-ME-0025: metabolite pattern id using human liver microsomes and hepatocytes and cDNA expressed human CYPs. |
| **Isozyme characterization:** | **x** | **2** | | 9785-ME-0001 and 9785-ME-0025: |
| **Active Metabolites** | | | | 2 major metabolites: M1 inactive, M2 active. |
| **Transporters** | **x** | **3** | | 9785-ME-0026 and 9785-ME-0026: P-pg inhibition, Pgp substrate assays for MDV3100, M1 and M2 using cell lines.<br>9785-ME-0031: Permiability, Caco2. |
| **Blood/plasma ratio:** | **x** | **1** | | 9785-CL-0001: in vitro blood/plasma partition. |
| **Plasma protein binding:** | **x** | **3** | | PRO3100NC32: in vitro human plasma protein binding of MDV3100<br>ME-0018: M1 and M2 in vitro plasma protein binding.<br>ME-0008: binding of MDV3100 to major human plasma proteins. |
| **Pharmacokinetics (e.g., Phase I)** | | | | |
| Healthy volunteers | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Patients- | **X** | | | |
| single dose: | **x** | **1** | | S-3100-1-01: Open label dose escalation with PK in patients. |
| multiple dose: | **x** | **2** | | S-3100-1-01: Open label dose escalation with PK in patients.<br>CRPC2: Multiple dose Cmin |
| | | | | |
| **Dose proportionality -** | **x** | | | S-3100-1-01: Open label dose escalation with PK. |
| **Drug-drug interaction studies** | | | | |
| In-vivo effects on primary drug: | **x** | **2** | | Effect of CYP 3A4 and 2C8 inhibitor/inducer on MDV3100 PK. To be submitted June 29, 2012. |
| In-vivo effects of primary drug on other drugs: | **x** | **1** | | DDI cocktail study to be submitted in June 2912 |

| | | | | |
|---|---|---|---|---|
| In-vitro: | **x** | **3** | | PRO3100NC23: P450 Induction in vitro. PRO3100NC24, 9785-ME-0009, 9785-ME-0010: P450 inhibition by MDV3100, M1 and M2. |
| **Subpopulation studies -** | | | | |
| Body size | | | | |
| gender: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| Race/Ethnicity: | | | | |
| hepatic impairment: | **x** | **1** | | Hepatic insufficiency (to be submitted June 29th 2012) |
| pediatrics: | | | | |
| **PD:** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD:** | **x** | **2** | | ICON 2147016: Exposure response for safety and efficacy using phase 3 trial data. (b) (4) 9785-PK-0001: Exposure response using study S-3100-01. |
| **Population Analyses -** | **x** | | | |
| Data rich: | **x** | **1** | | (b) (4) 9785-PK-0001: Pop PK analysis with covariates age, wt and CLCr > 30 mL/min. |
| Data sparse: | | | | |
| | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | **x** | **1** | | MDV3100-05: high fat breakfast in healthy male subjects. |
| **$QT_C$ studies** | **x** | **1** | | CRPC2, eRT Cardiac Safety Report: Substudy in phase 3 trail (CRPC2). |
| **In-Vitro Release BE** | | | | |
| **(IVIVC):** | | | | |
| **Bio-wavier request based on BCS** | | | | |
| **BCS class** | | | | Class II. |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies:** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | | | | |
| Filability and QBR comments | | | | |
| | **"X" if yes** | **Comments** | | |
| **Comments sent to firm?** | | | | |
| **QBR questions (key issues to be considered)** | | | | |
| **Other comments or information not included above** | | | | |
| **Primary reviewer Signature and Date** | | Jeanne Fourie Zirkelbach, Ph.D. 08/26/2011 | | |

| Secondary reviewer Signature and Date | Qi Liu, PhD |
|---|---|

CC: HFD-150 (CSO – C Cottrell; MTL –V Maher; MO –M Ning, W Pierce)

HFD-860 (Reviewer – J Fourie Zirkelbach; TL – Q Liu; DDD-B Booth; DD - A Rahman)

On **initial** review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|---|---|---|---|
| **Criteria for Refusal to File (RTF)** | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | | | X | N/A as the TBM product is the same as that used in the pivotal trial. |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | X | | | |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | X | | | |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | X | | | |
| 5 | Has a rationale for dose selection been submitted? | X | | | |
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin? | X | | | |
| 7 | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin? | X | | | |
| 8 | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work? | X | | | |
| **Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)** | | | | | |
| | **Data** | | | | |
| 9 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | | x | | No NCA datasets or analysis provided –IR submitted to sponsor 5/30/12 and at later dates prior to filing. |
| 10 | If applicable, are the | | | | No PG data, or review. |

| | | | | | |
|---|---|---|---|---|---|
| | pharmacogenomic data sets submitted in the appropriate format? | | | | |
| | **Studies and Analyses** | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | X | | | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | X | | | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | X | | | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | X | | | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | | | X | |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | X | |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | X | | | |
| | **General** | | | | |
| 18 | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to | X | | | |

| | | | | | |
|---|---|---|---|---|---|
| | meet basic requirements for approvability of this product? | | | | |
| 19 | Was the translation (of study reports or other study information) from another language needed and provided in this submission? | | | X | |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _Yes__**

| | |
|---|---|
| Jeanne Fourie Zirkelbach Ph.D. | 5/26/2012 |
| Reviewing Clinical Pharmacologist | Date |
| Qi Liu, Ph.D. | 5/26/2012 |
| Team Leader/Supervisor | Date |
| DJ Marathe, Ph.D. | 5/5/2011 |
| Reviewing Pharmacometrician | Date |
| Nitin Mehrotra, PhD | 5/26/2012 |
| Pharmacometrics Reviewer | Date |

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

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/s/

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JEANNE FOURIE ZIRKELBACH
06/14/2012

QI LIU
06/15/2012