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Name of Finished Product: Enzalutamide (MDV3100)		
Name of Active Ingredient: Enzalutamide (MDV3100)		

SYNOPSIS

Title of Study: A Phase I Open-label Study to Evaluate the Effect of Multiple Doses of MDV3100 (ASP9785) on the Pharmacokinetics of Substrates for CYP2C8, CYP2C9, CYP2C19, and CYP3A4 in Patients with Castration-resistant Prostate Cancer

Investigators/Coordinating Investigator:
Site 1: Dr [redacted], [redacted], South Africa;
Site 2: Dr [redacted], [redacted], South Africa

Study Center(s):
Site 1: [redacted], South Africa;
Site 2: [redacted], South Africa

Publication (reference): As of the date of this report, the results of this study have not been published.

Study Period:

Date of first enrollment (Study initiation date): 25 July 2011

Date of last evaluation (Study completion date): 21 February 2012

Phase of Development: Phase 1

Objectives:

Primary Objective:

- To determine the effect of multiple once daily administration of MDV3100 on the pharmacokinetics of a single dose of pioglitazone (CYP2C8 substrate), *S*-warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate) and midazolam (CYP3A4 substrate) in patients with castration resistant prostate cancer (CRPC)

Secondary Objective:

- To evaluate the safety and tolerability of multiple once daily administration of MDV3100 alone and in combination with a single dose of pioglitazone, warfarin, omeprazole and midazolam in patients with CRPC

Methodology: This was a non-randomized, open-label, single sequence crossover drug-drug interaction (DDI) study in 14 male patients with CRPC. 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

Name of Sponsor/Company: Astellas Pharma Europe B.V. (APEB)		
Name of Finished Product: Enzalutamide (MDV3100)		
Name of Active Ingredient: Enzalutamide (MDV3100)		

MDV3100 placebo to match (PTM; 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 MDV3100 (four 40-mg capsules) from day 13 onwards up to day 97 (± 3 days). At day 97 (week 12 of MDV3100 treatment), patients experiencing clinical benefit (as determined by the Investigator in consultation with the physician responsible for treating the patient's prostate cancer) were eligible to continue into an extension study (Study 9785-CL-0121). For patients who did not continue into the extension study, the end-of-study visit was conducted 30 ±7 days after the last dose of MDV3100. Only patients who were enrolled into the extension study continued to receive MDV3100.

Administration of the substrates, in combination with MDV3100 PTM or in combination with 160 mg MDV3100, was done under fasted conditions. Patients fasted overnight for at least 10 hours prior to study drug administration.

Number of Patients (planned, enrolled and analyzed): 14 planned, 37 screened, 14 enrolled, 14 analyzed.

Diagnosis and Main Criteria for Inclusion: Male patient aged 18 years old or above, with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features, with ongoing androgen deprivation therapy with a gonadotropin releasing hormone (GnRH) analogue or orchiectomy (i.e., medical or surgical castration). Progressive disease by prostate-specific antigen (PSA) or imaging; estimated life expectancy of $\geq$ 6 months. Body mass index (BMI) of at least 18.5 kg/m^2 and no greater than 32.0 kg/m^2.

Patients with confirmed CYP2C8, CYP2C9, or CYP2C19 poor metabolizer status based on genotyping analysis were excluded from the study.

Test Product, Dose and Mode of Administration, Batch Numbers:

- 160 mg MDV3100, administered orally as four 40-mg soft capsules. Batch no. [redacted], expiry 09/2012; bulk lot number [redacted].
- Pioglitazone hydrochloride tablets (Actos®, manufactured by Takeda Pharmaceuticals) containing 30 mg pioglitazone (as the base) were from a commercial source; one tablet (30 mg) was taken orally. Batch no. [redacted], expiry 05/2013.
- Midazolam (Dormicum®, manufactured by Roche) was formulated as an intravenous (iv) solution containing 1 mg/mL midazolam and was from a commercial source, packaged as 5 mg/5 mL ampoules; 2 mg midazolam were taken orally. Batch no. [redacted], expiry 03/2015.

Name of Sponsor/Company: Astellas Pharma Europe B.V. (APEB)		
Name of Finished Product: Enzalutamide (MDV3100)		
Name of Active Ingredient: Enzalutamide (MDV3100)		

- Omeprazole tablets (Losec MUPS®, manufactured by AstraZeneca) containing 20 mg omeprazole were from a commercial source; one tablet (20 mg) was taken orally. Batch no. [redacted], expiry 03/2013.
- Warfarin tablets (Aspen warfarin®, manufactured by Aspen Pharmacare) containing 5 mg warfarin were from a commercial source; 10 mg (2 tablets) were taken orally. Batch no. [redacted], expiry 07/2012.

Note: Vitamin K solution (Konakion®, manufactured by Roche) containing 10 mg/mL from a commercial source as 10 mg/1 mL ampoules was also supplied for this study; batch no. [redacted], expiry 06/2013. Vitamin K was to be given intravenously, if needed to counteract the anticoagulant activity of warfarin (i.e., if international normalized ratio [INR] was > 5 on the day after warfarin intake). However, no patients required vitamin K in this study.

Duration of Treatment (or Duration of Study, if applicable):

Treatment was as follows:

On days 1 and 55, all patients received a single oral dose of 30 mg pioglitazone (CYP2C8 substrate).

On days 5 and 62, all patients received a single oral cocktail of 10 mg warfarin (*S*-warfarin = CYP2C9 substrate), 20 mg omeprazole (CYP2C19 substrate) and 2 mg midazolam (CYP3A4 substrate).

On days 1 and 5, all patients received a single oral dose of MDV3100 PTM.

On days 13 through 97, all patients received once daily oral doses of 160 mg MDV3100.

The duration of the study was 104 to 162 days and consisted of a screening period of 7 to 28 days, a treatment period of 97 days, and an end-of-study visit at day 97 or up to 37 days after day 97, depending on whether or not the patient entered the rollover extension study.

Reference Product, Dose and Mode of Administration, Batch Numbers:

- MDV3100 PTM administered orally as four 40-mg soft capsules. Batch no. [redacted], expiry 09/2012; bulk lot number [redacted].

Name of Sponsor/Company: Astellas Pharma Europe B.V. (APEB)		
Name of Finished Product: Enzalutamide (MDV3100)		
Name of Active Ingredient: Enzalutamide (MDV3100)		

Criteria for Evaluation:

Pharmacokinetics:

The Pharmacokinetic Analysis Set (PKAS) included the patients from the Safety Analysis Set (SAF) population for whom sufficient concentration data were available to facilitate derivation of at least 1 pharmacokinetic parameter.

Primary pharmacokinetic variables (for determining potential for DDI) were as follows:

- for pioglitazone, *S*-warfarin, omeprazole and midazolam: C_{max}, AUC_{0-t}, AUC_{0-inf}

Secondary pharmacokinetic variables (for informational purposes only) were as follows:

- for pioglitazone, *S*-warfarin, omeprazole and midazolam: t_{max}, $t_{1/2,}$ CL/F, V_z/F
- for metabolites pioglitazone M-IV, 7-OH-*S*-warfarin, 5-OH-omeprazole, and 1-OH-midazolam: C_{max}, AUC_{0-t}, AUC_{0-inf}, t_{max}, $t_{1/2}$
- for *R*-warfarin: C_{max}, AUC_{0-t}, AUC_{0-inf}, t_{max}, $t_{1/2}$, CL/F
- for MDV3100: C_{max}, C_{0h}, C_{min}, t_{max}, AUC_{tau}, CL/F (parent only), peak-trough ratio (PTR)
- for MDV3100 metabolites MDPC0001 (M1) and MDPC0002 (M2): C_{max}, C_{0h}, C_{min}, t_{max}, AUC_{tau}, ratio of the metabolite - parent AUC values (MPR) and MPR corrected for the difference in molecular weight (MPR[MWC])

Safety:

For the statistical summary of the safety data, the SAF was used. The SAF consisted of all patients who took at least 1 dose of study medication.

Safety was assessed by evaluation of the nature, frequency and severity of adverse events, physical examination, vital signs, 12-lead ECG and safety laboratory tests (urinalysis, hematology, biochemistry, coagulation, PSA).

Statistical Methods:

Descriptive statistics including the number of patients (n), mean, standard deviation (SD), median, minimum and maximum were used to summarize continuous variables. Medical history and adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 12.0). Previous and concomitant medications were coded with World Health Organization Drug Reference List (WHO-DRL). For continuous pharmacokinetic parameters, coefficient of variation (CV) and geometric mean (GM) were also presented,

Name of Sponsor/Company: Astellas Pharma Europe B.V. (APEB)		
Name of Finished Product: Enzalutamide (MDV3100)		
Name of Active Ingredient: Enzalutamide (MDV3100)		

where the GM of t_{max} was not provided. The number (n) and percentage of patients in each category were used to summarize categorical variables.

Plasma concentrations were listed and summarized by scheduled time points for MDV3100, M1, M2, pioglitazone, pioglitazone M-IV, *R*-warfarin, *S*-warfarin, 7-OH-*S*-warfarin, omeprazole, 5-OH-omeprazole, midazolam and 1-OH-midazolam. Individual and mean plasma concentrations of study drugs were listed and summarized by treatment and time. Values below the lower limit of quantification (LLOQ) were set to 0 for calculation of descriptive statistics. Descriptive statistics were not calculated if all values were less than the LLOQ. If 1 or more values were less than the LLOQ, the GM was not calculated.

Graphics for plasma concentrations, including mean concentration-time profiles (both linear and log-linear), individual patient concentration-time profiles (both linear and log-linear), and overlay ("spaghetti") plots of concentrations-time profiles were produced. Trough plasma concentrations for MDV3100, M1, and M2 in the morning of Days 41, 48, 51, 55, 56, 59, 62, 63, 68 and 72 were graphically displayed to monitor for the achievement of steady-state conditions.

The primary pharmacokinetic parameters for assessment of DDI were the log transformed C_{max}, AUC_{0-t} and AUC_{0-inf} for pioglitazone, omeprazole, midazolam and *S*-warfarin.

Statistical analyses were performed on the pharmacokinetics of pioglitazone, omeprazole, midazolam and *S*-warfarin using the treatment in combination with 160 mg MDV3100 as test and the treatment in combination with MDV3100 PTM as reference. For each substrate, only patients with data for both reference and test treatment were included in the analysis.

For each of the primary pharmacokinetic parameters, an analysis of variance (ANOVA) was performed on the natural logarithm of pharmacokinetic parameter estimates with the treatment (Day) as a fixed effect, and patient as a random effect. Point estimates and 90% confidence intervals (CIs) for the difference in means (test - reference) from the estimated least square means (LS means) and within-patient variance were back-transformed using anti-logarithms to obtain point estimates and 90% CIs for the ratio (test/reference) of the mean C_{max}, AUC_{0-t} and AUC_{0-inf}.

The clinical significance of the GM ratios was interpreted in accordance with the draft DDI guidances of the FDA (Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling, dated Sep 2006) and EMA (Guideline on the Investigation of Drug Interactions, dated Apr 2010). Per these guidance documents, a drug that causes a 1.25- to 2-fold increase in the plasma AUC is classified as a mild (weak) inhibitor, a moderate inhibitor causes a > 2-fold increase in the plasma AUC, and a strong inhibitor causes > 5-fold increase in the plasma AUC. In addition, a drug that causes ≤ 50% reduction in plasma AUC is classified

Name of Sponsor/Company: Astellas Pharma Europe B.V. (APEB)		
Name of Finished Product: Enzalutamide (MDV3100)		
Name of Active Ingredient: Enzalutamide (MDV3100)		

as a mild inducer, a moderate inducer causes > 50% to ≤ 80% reduction in plasma AUC, and a strong inducer causes a > 80% reduction in plasma AUC.

The pharmacokinetic parameters of C_{max}, AUC_{0-t} and AUC_{0-inf} for the metabolites of pioglitazone, *S*-warfarin, omeprazole and midazolam (pioglitazone M-IV, 7-OH-*S*-warfarin, 5-OH-omeprazole and 1-OH-midazolam) and *R*-warfarin (secondary pharmacokinetic endpoints) were analyzed using similar ANOVA models. PTR, MPR and MPR(MWC) were summarized by descriptive statistics.

Summary of Results/Conclusions:

Disposition of Patients and Analysis Sets:

A total of 37 male patients gave consent and were screened for the study (Figure 1). Twenty-three of the patients failed screening: 22 did not meet inclusion/exclusion criteria and 1 withdrew for another reason, i.e., no history or current records could be found. A total of 14 patients were enrolled and dosed in the study. All enrolled patients completed the study except for 1 patient, who withdrew from the study due to a serious adverse event.

All 14 enrolled patients were eligible for inclusion in both the SAF and PKAS analysis sets.

Demographics and Other Baseline Characteristics:

Eleven of the 14 male patients enrolled in this study were white, 3 of the 14 were other (mixed race); none were Hispanic or Latino (Table 1). The mean age was 70.4 years and the mean BMI was 27.09 kg/m^2.

No patient had a positive serology test for HBsAg, anti-HAV (IgM), anti-HCV or anti-HIV 1+2 or a positive test for drugs of abuse. All patients met the limits of alcohol and tobacco use as specified in the protocol. As would be expected from the patient population, most patients had extensive medical histories with a number of ongoing conditions. Listings of each patient's CRPC disease history, metastases, and cancer treatment history are provided in the report appendices. Data on the target disease (CRPC) including its severity were also summarized (Table 2). Approximately 2/3 (64.3%) of the enrolled patients had an Eastern Cooperative Oncology Group (ECOG) grade of 0; the remainder had an ECOG grade of 1 (Table 3).

Patients were assessed for bone and soft tissue metastases by abdominopelvic MRI or CT and bone scan at screening and day 97. The majority of the patients had bone and soft tissue metastases at screening (CT/MRI: 64.3%, bone scan: 57.1%) as well as Day 97 (CT/MRI: 64.3%, bone scan 64.3%) (Table 4). Patients also underwent a normal posterior anterior chest x-ray; in case of pulmonary metastases, a chest CT was also performed. All but 1 of the 14 patients had negative chest x-rays; 2 patients had chest CTs performed, but those results were negative (Table 5).

Name of Sponsor/Company: Astellas Pharma Europe B.V. (APEB)		
Name of Finished Product: Enzalutamide (MDV3100)		
Name of Active Ingredient: Enzalutamide (MDV3100)		

Pharmacokinetic Results:

After a single dose of 30 mg pioglitazone in the presence of 160 mg MDV3100 at steady state, AUC_{0-t} and AUC_{0-inf} of CYP2C8 substrate pioglitazone increased by 30% (GM ratio: 1.30; 90% CI:1.08 - 1.57) and 20% (GM ratio: 1.20; 90% CI: 0.98 - 1.47), respectively, 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 6; Figure 2). The t_{max} was comparable for both treatments, with comparable ranges. Exposure parameters of pioglitazone M-IV AUC_{0-t}, AUC_{0-inf} and C_{max} decreased by 36% (GM ratio: 0.64; 90% CI: 0.54 - 0.76), 37% (GM ratio: 0.63; 90% CI 0.52 - 0.77) and 40% (GM ratio: 0.60; 90% CI: 0.52 - 0.70), respectively. Based upon the 20% increase in the AUC_{0-inf} of pioglitazone and the 90% CIs on the GM ratio (0.98 - 1.47), MDV3100 has no clinically relevant effect on CYP2C8.

After a single oral dose of 10 mg warfarin in the presence of 160 mg MDV3100 at steady state, AUC_{0-t} and AUC_{0-inf} of CYP2C9 substrate *S*-warfarin decreased by 55% (GM ratio: 0.45; 90% CI: 0.42 - 0.49) and 56% (GM ratio: 0.44; 90% CI: 0.41 - 0.48), respectively 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 6; Figure 2). The t_{max} was also comparable. Exposure parameters of 7-OH-*S*-warfarin AUC_{0-t}, AUC_{0-inf} and C_{max} decreased by 56% (GM ratio: 0.44; 90% CI: 0.33 - 0.59), 53% (GM ratio: 0.47; 90% CI: 0.35 - 0.63) and 17% (GM ratio: 0.83; 90% CI: 0.71 - 0.99), respectively. Based upon the 56% decrease in the AUC_{0-inf} of *S*-warfarin, MDV3100 is considered to be a moderate inducer of CYP2C9.

After a single oral dose of 10 mg warfarin in the presence of 160 mg MDV3100 at steady state, AUC_{0-t} and AUC_{0-inf} of *R*-warfarin decreased by 41% (GM ratio: 0.59; 90% CI: 0.56 - 0.63) and 45% (GM ratio: 0.55; 90% CI: 0.51 - 0.58), respectively, while C_{max} was comparable between both treatments (GM ratio: 0.99; 90% CI: 0.93 - 1.05). The t_{max} was also comparable.

After a single oral dose of 20 mg omeprazole in the presence of 160 mg MDV3100 at steady state, AUC_{0-t}, AUC_{0-inf} and C_{max} of CYP2C19 substrate omeprazole decreased by 72% (GM ratio: 0.28; 90% CI: 0.23 - 0.34), 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 6; Figure 2). The t_{max} was comparable for both treatments, with comparable ranges. Exposure parameters of 5-OH-omeprazole AUC_{0-t}, AUC_{0-inf} and C_{max} decreased by 56% (GM ratio: 0.44; 90% CI: 0.39 - 0.50), 54% (GM ratio: 0.46; 90% CI: 0.39 - 0.53) and 36% (GM ratio: 0.64; 90% CI: 0.50 - 0.83), respectively. Based upon the 70% decrease in the AUC_{0-inf} of omeprazole, MDV3100 is considered to be a moderate inducer of CYP2C19.

After a single oral dose of 2 mg midazolam in the presence of 160 mg MDV3100 at steady state, AUC_{0-t}, AUC_{0-inf} and C_{max} of CYP3A4 substrate midazolam decreased by 86% (GM ratio: 0.14; 90 % CI: 0.11 - 0.16),

Name of Sponsor/Company: Astellas Pharma Europe B.V. (APEB)		
Name of Finished Product: Enzalutamide (MDV3100)		
Name of Active Ingredient: Enzalutamide (MDV3100)		

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 6; Figure 2). The t_{max} was comparable for both treatments, with comparable ranges. Exposure parameters of 1-OH-midazolam AUC_{0-t}, AUC_{0-inf} and C_{max} decreased by 78% (GM ratio: 0.22; 90% CI: 0.18 - 0.26), 76% (GM ratio: 0.24; 90% CI: 0.20 - 0.28) and 71% (GM ratio: 0.29; 90% CI: 0.24-0.35), respectively. Based upon the 86% decrease in the AUC_{0-inf} of midazolam, MDV3100 is considered to be a strong inducer of CYP3A4.

Fluctuations in the steady-state plasma concentrations of MDV3100, M1, M2, and for the sum of MDV3100 plus M2 during a dosing interval were small, resembling a constant infusion (Figure 3). The mean PTR of MDV3100 was 1.27 (range: 1.09 - 1.51). Mean (SD) steady-state C_{max} of MDV3100, M1 and M2 were 16.6 (3.81) µg/mL, 8.87 (6.52) µg/mL and 12.7 (3.77) µg/mL, respectively. AUC_{tau} of M1 at steady state was approximately 40% lower compared to that of MDV3100. AUC_{tau} of M2 after multiple dosing was comparable to that of the parent.

Safety Results:

All 14 patients experienced 1 or more treatment-emergent adverse events (TEAEs) (Table 7). A TEAE was an adverse event that started any time after the first study drugs (pioglitazone and MDV3100 PTM) were given on day 1 to the end of the study. Thirteen of the 14 patients experienced a TEAE on day 13 or later (daily dosing with 160 mg MDV3100 began on day 13). Eight patients had a TEAE considered possibly or probably related to MDV3100 (Table 8), including 1 patient who had a serious TEAE (grand mal convulsion) that was considered probably related to study drug.

Three patients reported at least 1 serious adverse event (SAE). Two patients experienced 5 treatment-emergent SAEs (1 patient: grand mal convulsion on study day 89; 1 patient: chest pain, dizziness, dyspnea, and nausea on study day 55). The other SAE (retinal detachment) occurred during the screening period in a patient who did not meet inclusion/exclusion criteria, was never dosed in the study, and was not included in the Safety Analysis Set.

One patient with a serious TEAE (grand mal convulsion) permanently discontinued study drug due to the SAE. For this patient, plasma concentrations of MDV3100 were consistently high (approximately twice as high compared to other values). On day 62, C_{max} and AUC_{tau} of MDV3100 for this patient were 28.0 µg/mL (C_{max} mean [SD]: 16.6 [3.81] µg/mL) and 593 µg*h/mL (AUC_{tau} mean [SD]: 322 [85.4] µg*h/mL), respectively. In addition, for this patient C_{max} and AUC_{tau} for M2 were the highest observed values. C_{max} and AUC_{tau} of M2 were 19.6 µg/mL (C_{max} mean [SD]: 12.7 [3.77] µg/mL) and 442 µg*h/mL (AUC_{tau} mean [SD]: 278 [85.5] µg*h/mL), respectively. All other enrolled patients completed the study.

Name of Sponsor/Company: Astellas Pharma Europe B.V. (APEB)		
Name of Finished Product: Enzalutamide (MDV3100)		
Name of Active Ingredient: Enzalutamide (MDV3100)		

The most frequently reported TEAEs by MedDRA preferred term were nausea (35.7%), constipation (28.6%), dizziness (28.6%), arthropod bite (21.4%), fatigue (21.4%), and hot flush (21.4%) (Table 8). Of the TEAEs considered related to MDV3100, the most frequently reported were fatigue (21.4%), nausea (14.3%), constipation (14.3%), dizziness (14.3%), and hot flush (14.3%) (Table 8).

The majority of patients experienced TEAEs that were NCI-CTCAE grade 1 or 2 in intensity [End-of-Text Table 12.6.1.4.1]. Two (14.3%) patients each experienced a grade 1 TEAEs; 10 (71.4%) patients experienced a total of 17 grade 2 TEAEs. Two (14.3%) patients experienced a total of five grade 3 TEAEs: nausea, chest pain, diverticulitis, dizziness, and dyspnea. No patients experienced any grade 4 or grade 5 TEAEs. For the 8 patients with TEAEs considered related to MDV3100, only 1 patient experienced a TEAE (diverticulitis) that was NCI-CTCAE grade 3 in intensity [End-of-Text Table 12.6.1.5.1].

No clinically important mean changes from baseline were noted for hematology, urinalysis or coagulation testing [End-of-Text Table 12.6.2.1.1, End-of-Text Table 12.6.2.3.1, End-of-Text Table 12.6.2.1.3, End-of-Text Table 12.6.2.1.4, End-of-Text Table 12.6.2.2.4, End-of-Text Table 12.6.2.3.3].

The following trends were noted for serum chemistry [End-of-Text Table 12.6.2.1.2]:

- Mean ALT decreased over time from baseline (22.6 U/L, n = 14) to day 97 (17.0 U/L, n = 12) or End of Treatment (17.0 U/L, n = 12).
- Mean ALP increased from a baseline value of 122.9 U/L (n = 14) to around 140 U/L (n = 14) between days 13 and 56, decreasing slightly at days 62 and 63, and increasing to 139.3 U/L at day 97 (n = 12) or End of Treatment (n = 12). Two patients ([redacted], [redacted]) had ALP values above the normal range at baseline and throughout the study, with peak elevations noted between days 13 and 56. Patient [redacted], who had normal ALP values at screening (64 U/L) and baseline (65 U/L), began experiencing steady increases in ALP that were still within the normal range, between day 13 (74 U/L) and day 63 (94 U/L); at an unscheduled visit on day 72, his ALP had increased above the normal range to 319 U/L. At an unscheduled visit on day 83 and at day 97, his ALP was still above the normal range but had decreased to 142 U/L and 134 U/L, respectively [Appendix 13.2.8.1.2.1].
- Mean gamma-glutamyl transferase (GGT) decreased over time from baseline (24.5 U/L, n = 14) to day 97 (19.3 U/L, n = 12) or End of Treatment (19.3 U/L, n = 12).
- Mean PSA decreased over time from baseline (130.49 μg/L, n = 14) to day 97 (20.72 μg/L, n = 13) or End of Treatment (20.72 μg/L, n = 13).

Only 2 patients had NCI-CTCAE grade 3 results in serum chemistry analyses [End-of-Text Table 12.6.2.3.2]:

- 1 patient (patient [redacted]) had grade 3 elevations in ALP from screening and baseline and throughout the study; this was considered due to bone metastases [Appendix 13.2.8.1.2.1].

Name of Sponsor/Company: Astellas Pharma Europe B.V. (APEB)		
Name of Finished Product: Enzalutamide (MDV3100)		
Name of Active Ingredient: Enzalutamide (MDV3100)		

- 1 patient (patient [redacted]) had a grade 3 elevation in potassium at baseline only [Appendix 13.2.8.1.2.4].

No grade 4 results were reported.

No clinically important changes were noted in mean systolic or mean diastolic BP, pulse rate, or oral temperature [End-of-Text Table 12.6.3.1]. No patients had any clinically significant abnormal 12-lead ECG results at baseline or any time during the study [End-of-Text Table 12.6.4.1, End-of-Text Table 12.6.4.2, End-of-Text Table 12.6.4.3].

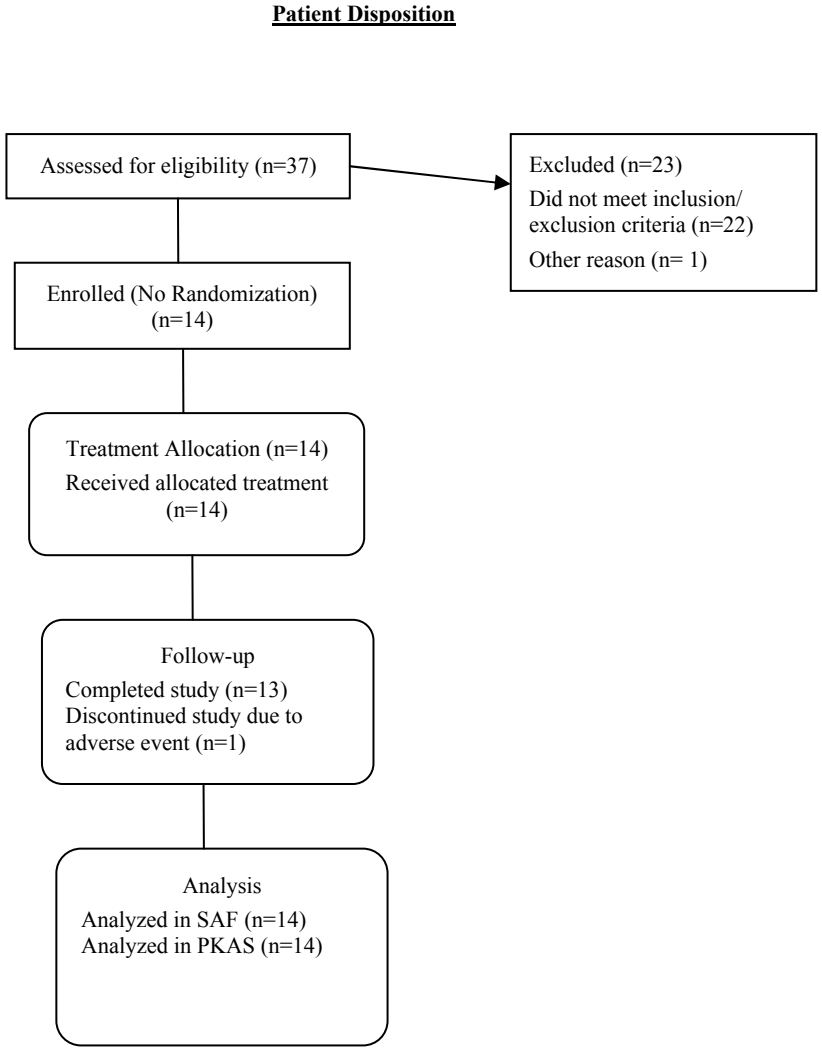
CONCLUSIONS:

- MDV3100 (160 mg once daily to steady state) has no clinically relevant effect on CYP2C8, is a moderate inducer of CYP2C9 and CYP2C19, and is a strong inducer of CYP3A4 based on changes in plasma $AUC_{0\text{-}inf}$ for single oral doses of the sensitive substrates pioglitazone, *S*-warfarin, omeprazole and midazolam, respectively.
- Mean (SD) steady-state C_{max} of MDV3100, M1 and M2 were 16.6 (3.81) µg/mL, 8.87 (6.52) µg/mL and 12.7 (3.77) µg/mL, respectively. Fluctuations in the steady-state plasma concentrations for MDV3100, M1, M2, and for the sum of MDV3100 and M2 during a dosing interval were small, resembling a constant infusion.
- The most frequently reported (i.e., in ≥ 3/14 patients, ≥ 21.4%) TEAEs were nausea, constipation, dizziness, arthropod bite, fatigue, and hot flush. The majority of the reported TEAEs were NCI-CTCAE grade 1 or 2 in intensity. One patient experienced a single and transient episode of [redacted] which was assessed as probably related to MDV3100 and led to discontinuation of study treatment with MDV3100. No clinically significant changes were noted for the safety laboratory tests or ECGs.

In summary, multiple once daily administration of MDV3100 160 mg alone and in combination with a single dose of pioglitazone, warfarin, omeprazole and midazolam in patients with CRPC was observed to be generally safe and well-tolerated.

Date of Report: 31 May 2012

Figure 1 Patient Disposition



Subject [redacted] withdrew from the study due to an treatment-emergent serious adverse event but was included in the SAF and PKAS.

Source: [End-of-text Table 12.1.2.1, Appendix 13.2.1.1, Appendix 13.2.1.2, Appendix 13.2.4.1, Appendix 13.2.7.1]

Table 1 Demographics and Other Baseline Characteristics (Safety Analysis Set)

Parameter	Category/ Statistic	Total (N = 14)
Race, n (%)	White	11 (78.6)
	Other	3 (21.4)
Ethnicity, n (%)	Not Hispanic or Latino	14 (100.0)
Sex, n (%)	Male	14 (100.0)
Age (years) †	n	14
	Mean	70.4
	SD	7.59
	Minimum	54
	Median	71.0
	Maximum	83
Weight (kg) ‡	n	14
	Mean	82.90
	SD	14.864
	Minimum	58.1
	Median	83.80
	Maximum	107.5
Height (cm) ‡	n	14
	Mean	174.34
	SD	7.889
	Minimum	164.5
	Median	172.75
	Maximum	191.0
BMI (kg/m^2) §	n	14
	Mean	27.09
	SD	3.182
	Minimum	20.5
	Median	28.10
	Maximum	31.0

† Age was calculated from date of consent and date of birth.

‡ Height and weight were taken from the screening vital signs evaluations.

§ BMI (kg/m^2) = weight (kg) / height $(m)^2$

Source: [End-of-text Table 12.1.3.1 and Appendix 13.2.4.1]

Table 2 Disease History (Safety Analysis Set)

Test Findings	Total (N = 14) n (%)
Distant Metastasis Initial Diagnosis	
M0 - No distant metastasis	4 (28.6)
M1 - Distant metastasis	1 (7.1)
MX - Distant metastasis cannot be assessed (not evaluated by any modality)	3 (21.4)
Unknown	6 (42.9)
Clinical Lymph Node Stage Initial Diagnosis	
N0 - No regional lymph node metastasis	6 (42.9)
NX - Regional lymph nodes were not assessed	8 (57.1)
Pathological Lymph Node Stage Initial Diagnosis	
PNX - Regional lymph nodes not sampled	6 (42.9)
pN0 - No positive regional nodes	6 (42.9)
Unknown	2 (14.3)
Pathologic Tumor Stage Initial Diagnosis	
pT2 - Organ Confined	3 (21.4)
pT3 - Extraprostatic extension	4 (28.6)
Unknown	7 (50.0)
Primary Gleason Score Initial Diagnosis	
3	8 (57.1)
4	3 (21.4)
Unknown	3 (21.4)
Secondary Gleason Score Initial Diagnosis	
3	3 (21.4)
4	6 (42.9)
5	2 (14.3)
Unknown	3 (21.4)
Total Gleason Score Initial Diagnosis	
6	2 (14.3)†
7	8 (57.1)†
8	1 (7.1)†
9	1 (7.1)†
Unknown	2 (14.3)†
Clinical Tumor Stage Initial Diagnosis	
T2 - Tumor confined within the prostate	3 (21.4)
T3 - Tumor extends through the prostatic capsule	5 (35.7)
Unknown	6 (42.9)

† Where the total Gleason score was not supplied in the electronic Case Report Forms, the total score was calculated from primary and secondary components. The results for the Pharmacokinetic Analysis Set (PKAS) were identical (see [End-of-Table 12.1.7.2]).
Source: [End-of-text Table 12.1.7.1]

Table 3 Eastern Cooperative Oncology Group Performance Status (Safety Analysis Set)

Eastern Cooperative Oncology Group Performance Status	Total (N = 14) n (%)
Grade 0	9 (64.3)
Grade 1	5 (35.7)
Grade 2	0
Grade 3	0
Grade 4	0
Grade 5	0

Grade 0: Fully active, able to carry on all pre-disease performance without restriction.
Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
Grade 2: Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
Grade 3: Capable of only limited self care, confined to bed or chair more than 50% of waking hours.
Grade 4: Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.
Grade 5: Dead.
Source: [End-of-text Table 12.1.6.1 and Appendix 13.2.4.9]

Table 4 CT/MRI and Bone Scan (Safety Analysis Set)

Time Point	Parameter	Category	Total (N = 14) n (%)
Screening	Abdominopelvic CT/MRI Scan	Positive	9 (64.3)
		Negative	5 (35.7)
	Bone Scan	Positive	8 (57.1)
		Negative	6 (42.9)
Day 97	Abdominopelvic CT/MRI Scan	Positive	9 (64.3)
		Negative	4 (28.6)
	Bone Scan	Positive	9 (64.3)
		Negative	4 (28.6)

Source: [End-of-text Table 12.1.4.1]

Table 5 Chest X-Ray and Chest CT (Safety Analysis Set)

Parameter	Category	Total (N = 14) n (%)
Normal Posterior to Anterior Chest X-Ray	Positive	1 (7.1)
	Negative	13 (92.9)
Chest CT Scan	Positive	0
	Negative	2 (14.3)

Source: [End-of-text Table 12.1.5.1]

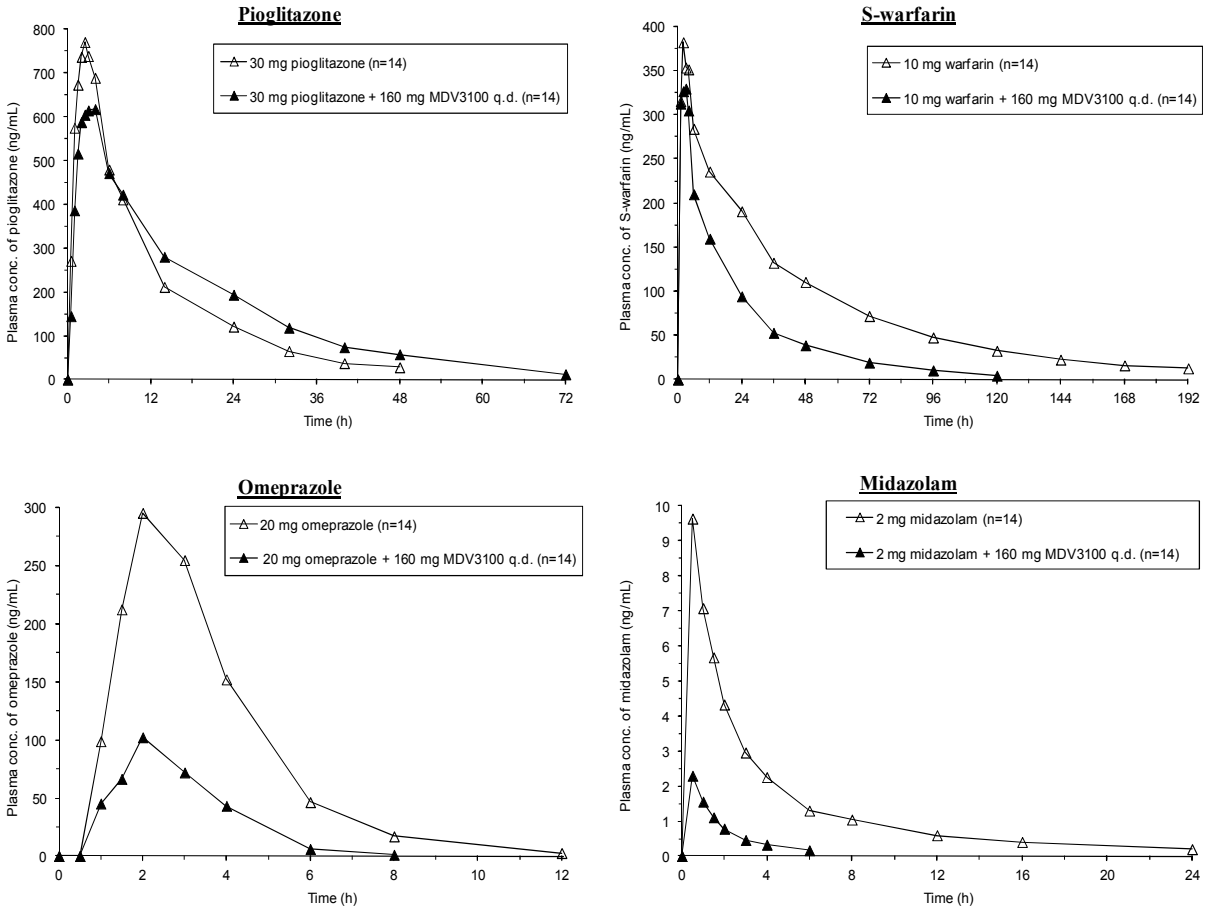
Table 6 Statistical Assessment of Effect of Multiple Doses MDV3100 on CYP-Substrates Pioglitazone, *S*-warfarin, Omeprazole and Midazolam

	Geometric Means		GM Ratio (Test/ Reference)	90% CI
	CYP-Substrate + 160 mg MDV3100 qd (Test)	CYP-Substrate + MDV3100 PTM (Reference)		
Pioglitazone (CYP2C8)				
$AUC_{0\text{-}inf}$ (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
***S*-warfarin (CYP2C9)**				
$AUC_{0\text{-}inf}$ (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
Omeprazole (CYP2C19)				
$AUC_{0\text{-}inf}$ (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
Midazolam (CYP3A4)				
$AUC_{0\text{-}inf}$ (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

GM: geometric mean; MDV3100 PTM: placebo to match MDV3100; qd: once daily.

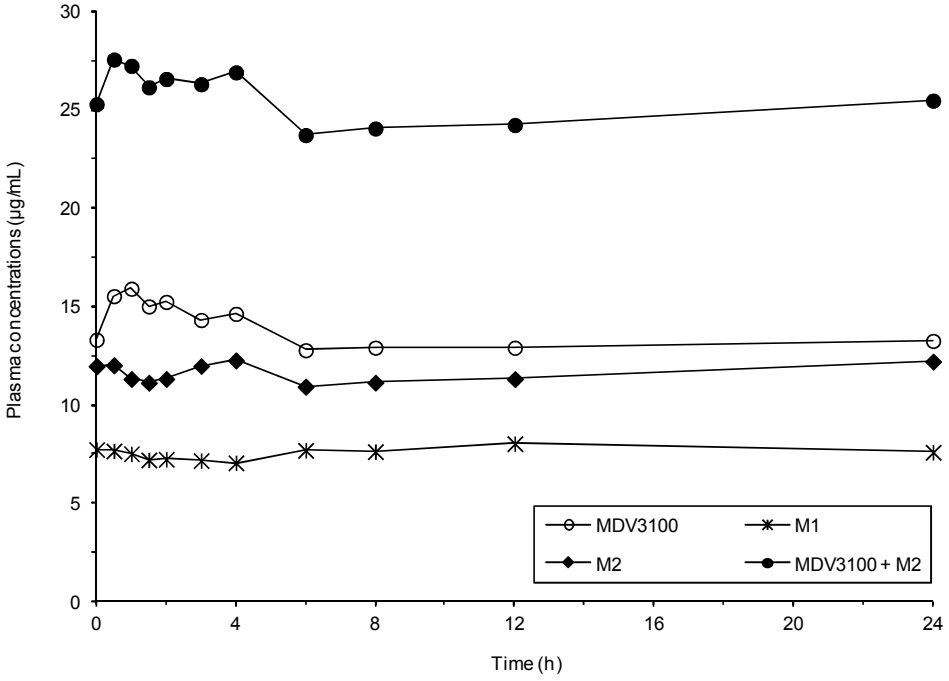
Source: [End-of-Text Table 12.4.2.4, End-of-Text Table 12.4.2.6, End-of-Text Table 12.4.2.8, End-of-text Table 12.4.3.1, End-of-text Table 12.4.3.2, End-of-text Table 12.4.3.3, End-of-text Table 12.4.3.4].

Figure 2 **Mean Plasma Concentration-time Curves After Single Dose Administration of CYP-Substrate Alone or in the Presence of Once Daily 160 mg MDV3100**



Note: Placebo to match MDV3100 (MDV3100 PTM) was coadministered with pioglitazone on day 1 and with S-warfarin, omeprazole and midazolam on day 5.
qd: once daily.
Source: [End-of-text Table 12.4.1.4, End-of -text Table 12.4.1.6, End-of-text Table 12.4.1.8, End-of-text Table 12.4.1.10]

Figure 3 **Mean Plasma Concentrations (µg/mL) of MDV3100, M1, M2 and the Sum of MDV3100 + M2 after 49 Days of Once Daily Dosing of 160 mg MDV3100**



Source: [End-of-Text Table 12.4.1.1, End-of-Text Table 12.4.1.2, End-of-Text Table 12.4.1.3, End-of-text Table 12.4.1.13]

Table 7 Overview of Treatment Emergent Adverse Events (Safety Analysis Set)

	Patients with TEAEs starting on or after day 1 (N = 14) n (%)	Patients with TEAEs starting on or after day 13 (N = 14) n (%)
Number (%) of patients who had a TEAE	14 (100)	13 (92.9)
Relationship† to MDV3100		
Not related	6 (42.9)	5 (35.7)
Possible	5 (35.7)	5 (35.7)
Probable	3 (21.4)	3 (21.4)
Relationship to pioglitazone		
Not related	14 (100)	13 (92.9)
Relationship to warfarin		
Not related	14 (100)	13 (92.9)
Relationship to omeprazole		
Not related	14 (100)	13 (92.9)
Relationship to midazolam		
Not related	14 (100)	13 (92.9)
Number (%) of patients who had a serious TEAE ‡	2 (14.3)	2 (14.3)
Relationship to MDV3100		
Possible	0	0
Probable	1 (7.1)	1 (7.1)
Deaths	0	0
Number (%) of patients who discontinued due to a TEAE	1 (7.1)	1 (7.1)
Relationship to MDV3100		
Probable	1 (7.1)	1 (7.1)

Note: A treatment-emergent adverse event (TEAE) was defined as an AE observed after starting administration of any of the study drugs (MDV3100 160 mg, placebo to match MDV3100 [MDV3100 PTM], pioglitazone, warfarin, omeprazole, and midazolam).
† Relationship to study drug was assessed as not related, possible, or probable, by the investigator; a missing relationship was handled as the maximum relationship.
‡ One patient ([redacted]) experienced a serious adverse event (retinal detachment) during screening and did not receive any study medication. This patient was not included in the Safety Analysis Set (i.e., is not shown on this table).
Source: [End-of-Text Table 12.6.1.1.1, End-of-Text Table 12.6.1.1.2]

Table 8 Number (%) of Patients Who Experienced Treatment Emergent Adverse Events, by System Organ Class and Preferred Term (MedDRA v.12.0) (Safety Analysis Set)

System organ class Preferred term	Patients with TEAEs starting on day 1 or later (N = 14) n (%)	Patients with TEAEs starting on day 13 or later (N = 14) n (%)	Patients with TEAEs considered drug-related† to MDV3100 (N = 14) n (%)
Overall	**14 (100.0)**	**13 (92.9)**	**8 (57.1)**
Blood and lymphatic system disorders	**1 (7.1)**	**0**	**0**
Anaemia	1 (7.1)	0	0
Cardiac disorders	**1 (7.1)**	**1 (7.1)**	**1 (7.1)**
Palpitations	1 (7.1)	1 (7.1)	1 (7.1)
Eye disorders	**2 (14.3)**	**2 (14.3)**	**1 (7.1)**
Asthenopia	1 (7.1)	1 (7.1)	1 (7.1)
Conjunctivitis	1 (7.1)	1 (7.1)	0
Gastrointestinal disorders	**10 (71.4)**	**10 (71.4)**	**5 (35.7)**
Nausea	5 (35.7)	5 (35.7)	2 (14.3)
Constipation	4 (28.6)	3 (21.4)	2 (14.3)
Diarrhoea	1 (7.1%)	1 (7.1)	0
Dyspepsia	1 (7.1)	1 (7.1)	1 (7.1)
Flatulence	1 (7.1)	1 (7.1)	1 (7.1)
Gingivitis	1 (7.1)	1 (7.1)	0
Hypoaesthesia oral	1 (7.1)	1 (7.1)	1 (7.1)
Odynophagia	1 (7.1)	1 (7.1)	0
Vomiting	1 (7.1)	1 (7.1)	1 (7.1)
General disorders and administration site conditions	**4 (28.6)**	**4 (28.6)**	**3 (21.4)**
Fatigue	3 (21.4)	3 (21.4)	3 (21.4)
Chest pain	1 (7.1)	1 (7.1)	0
Infections and infestations	**6 (42.9)**	**4 (28.6)**	**1 (7.1)**
Gastroenteritis	2 (14.3)	0	0
Diverticulitis	1 (7.1)	1 (7.1)	1 (7.1)
Otitis externa	1 (7.1)	1 (7.1)	0
Tonsillitis	1 (7.1)	1 (7.1)	0
Trichomoniasis	1 (7.1)	1 (7.1)	0
Injury, poisoning and procedural complications	**3 (21.4)**	**3 (21.4)**	**0**
Arthropod bite	3 (21.4)	3 (21.4)	0
Investigations	**2 (14.3)**	**2 (14.3)**	**0**
Blood alkaline phosphatase increased	1 (7.1)	1 (7.1)	0
Blood bilirubin increased	1 (7.1)	1 (7.1)	0
Metabolism and nutrition disorders	**2 (14.3)**	**1 (7.1)**	**1 (7.1)**
Anorexia	1 (7.1)	1 (7.1)	1 (7.1)
Decreased appetite	1 (7.1)	0	0
Musculoskeletal and connective tissue disorders	**4 (28.6)**	**3 (21.4)**	**1 (7.1)**
Arthralgia	1 (7.1)	1 (7.1)	1 (7.1)
Arthritis	1 (7.1)	0	0
Back pain	1 (7.1)	1 (7.1)	0
Muscle spasms	1 (7.1)	1 (7.1)	0

Table continued on next page

System organ class Preferred term	Patients with TEAEs starting on day 1 or later (N = 14) n (%)	Patients with TEAEs starting on day 13 or later (N = 14) n (%)	Patients with TEAEs considered drug-related† to MDV3100 (N = 14) n (%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**1 (7.1)**	**1 (7.1)**	**0**
Metastatic pain	1 (7.1)	1 (7.1)	0
Nervous system disorders	**6 (42.9)**	**6 (42.9)**	**3 (21.4)**
Dizziness	4 (28.6)	4 (28.6)	2 (14.3)
Dysgeusia	1 (7.1)	1 (7.1)	1 (7.1)
Grand mal convulsion	1 (7.1)	1 (7.1)	1 (7.1)
Headache	1 (7.1)	1 (7.1)	0
Paraesthesia	1 (7.1)	1 (7.1)	0
Psychiatric disorders	**1 (7.1)**	**0**	**0**
Delirium	1 (7.1)	0	0
Renal and urinary disorders	**1 (7.1)**	**1 (7.1)**	**0**
Pollakiuria	1 (7.1)	1 (7.1)	0
Respiratory, thoracic and mediastinal disorders	**3 (21.4)**	**3 (21.4)**	**1 (7.1)**
Dyspnoea	2 (14.3)	2 (14.3)	1 (7.1)
Oropharyngeal pain	1 (7.1)	1 (7.1)	0
Skin and subcutaneous tissue disorders	**3 (21.4)**	**3 (21.4)**	**1 (7.1)**
Pruritus	2 (14.3)	2 (14.3)	1 (7.1)
Eczema	1 (7.1)	1 (7.1)	0
Vascular disorders	**3 (21.4)**	**2 (14.3)**	**2 (14.3)**
Hot flush	3 (21.4)	2 (14.3)	2 (14.3)

Notes: 1. A treatment-emergent adverse event (TEAE) was defined as an adverse event observed after starting administration of any of the study drugs (MDV3100 160 mg, placebo to match MDV3100 [MDV3100 PTM], pioglitazone, warfarin, omeprazole, and midazolam)

2. Sorted by alphabetical order of MedDRA system organ class and decreasing order of frequency of preferred terms within each individual system organ class.

3. Within a system organ class, patients may have reported more than 1 type of adverse event.

† Possible or Probable, as assessed by the investigator, or records where relationship is missing. 'Missing' relationship was handled as the maximum relationship.

Source: [End-of-text Table 12.6.1.2.1, End-of-text Table 12.6.1.2.2, End-of-text Table 12.6.1.3.1]