Australian Government
Department of Health
Therapeutic Goods Administration

# AusPAR Attachment 2

# Extract from the Clinical Evaluation Report for Enzalutamide

Proprietary Product Name: Xtandi

Sponsor: Astellas Pharma Australia Pty Ltd

**Date of CER**
**First round: 27 November 2013**
**Second round: 5 March 2014**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

# About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

# Contents

# List of abbreviations

| Abbreviation | Meaning |
|---|---|
| ALT | Alanine transaminase |
| ARSI | Androgen receptor signalling inhibitor |
| AST | Aspartate transaminase |
| $AUC_{0-t}$ | Area under plasma concentration-time curve from zero to time t of the last measured concentration above the limit of quantification |
| $AUC_{0-inf}$ | Area under plasma concentration-time curve from zero to infinity |
| %AUC | Percentage of the AUC that is due to extrapolation |
| BCS | Biopharmaceutics Classification System |
| BP | Blood pressure |
| bpm | Beats per minute |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence interval |
| CL/F | Apparent clearance, calculated as dose/$AUC_{0-inf}$ |
| CRF | Clinical report form |
| CRPC | Castration-resistant prostate cancer |
| CSR | Clinical Study Report |
| DBP | Diastolic blood pressure |
| DDI | Drug-drug interaction |
| EOS | End-of-study |
| EU | European Union |
| e.g. | Exempli gratia; for example |
| FDA | Food and Drug Administration |
| g | Gram |
| GCP | Good Clinical Practice |
| GM | Geometric mean |

| Abbreviation | Meaning |
|---|---|
| GnRH | Gonadotropin-releasing hormone |
| i.e. | Id est; that is |
| IVRS | Interactive voice response system |
| ka | First-order absorption rate constant |
| L | Litre |
| m | Metre |
| MDV3100 | Xtandi, enzalutamide |
| mg | Milligram |
| mL | Millilitre |
| ms | Millisecond |
| PD | Pharmacodynamics |
| PI | Product Information |
| PK | Pharmacokinetics |
| PSA | Prostate specific antigen |
| Q/F | Inter-compartmental clearance |
| SBP | Systolic blood pressure |
| SD | Standard Deviation |
| SOC | System Organ Class |
| t½ | Half-life associated with the terminal slope |
| TGA | Therapeutic Goods Administration |
| $t_{lag}$ | Time to reach quantifiable concentrations; absorption lag time |
| US | United States |
| µg | Microgram |
| ≥ | At or greater than |
| ≤ | At or lesser than |

| Abbreviation | Meaning |
|---|---|
| > | Greater than |
| < | Less than |
| vs. | Versus |
| Vz/F | Apparent volume of distribution at terminal phase, calculated as dose/$AUC_{0\text{-}inf}$* λz |
| V/F | Apparent volume of distribution |
| $V_2$/F | Central volume of distribution |
| $V_3$/F | Peripheral volume of distribution |
| λz | Terminal elimination rate constant |

# 1. Introduction

Enzalutamide is a potent androgen receptor signalling inhibitor (ARSI) that blocks several steps in the androgen receptor signalling pathway. The proposed indication is:

> *"for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel".*

The proposed dose of enzalutamide is 160 mg (four 40 mg capsules) as a single oral daily dose with or without food. The capsules are to be swallowed whole with water.

# 2. Clinical rationale

Prostate cancer is known to be androgen sensitive. Hormonal therapies for prostate cancer include surgical castration or medical therapy with gonadotropin-releasing hormone (GnRH) analogues, anti-androgens (e.g. bicalutamide, flutamide, and nilutamide), androgen synthesis blockers (e.g. ketoconazole), and/or oestrogenic compounds. Tumours that progress despite castrate levels of testosterone in the blood are considered castration-resistant prostate cancer (CRPC). Castration-resistant progression generally represents a transition to the lethal state of the disease condition. The median survival of patients with CRPC is approximately 1–2 years.

According to the sponsor, results of studies on the molecular profiles of these progressing CRPCs showed that the androgen receptor remains functional, and that despite low or even undetectable levels of androgens, androgen receptor signalling continues to promote disease progression. This leads to the hypothesis that these tumours would respond to therapies directed at the androgen receptor signalling axis.

Clinical treatment of advanced prostate cancer is also limited by the development of resistance to currently available anti-androgen therapies. In addition, overexpression of the androgen receptor has been documented in upwards of 50% of CRPC specimens and is believed to contribute to tumour progression. Currently approved anti-androgens, including bicalutamide and flutamide, have been found to stimulate androgen receptor signalling in the setting of androgen receptor overexpression, thereby potentially exacerbating or accelerating castration-resistant tumour growth. In clinical practice, most patients receive 2 or more hormonal

manipulations and are then offered chemotherapy (e.g. with docetaxel or cabazitaxel) as their disease continues to progress.

Three pharmaceutical agents have demonstrated a survival advantage and are approved for the treatment of CRPC: docetaxel with prednisone as front-line chemotherapy; cabazitaxel with prednisone as second-line chemotherapy following docetaxel; and abiraterone acetate (an oral inhibitor of androgen biosynthesis) with prednisone following docetaxel. Once patients progress on docetaxel and require second-line therapy, the options included cabazitaxel plus prednisone or abiraterone plus prednisone. Cabazitaxel is an anti-neoplastic agent and needs to be administered by intravenous infusion, and treatment is complicated by febrile neutropenia, neutropenic deaths, and serious gastrointestinal side effects including diarrhoea. Abiraterone is an oral inhibitor of androgen biosynthesis and treatment requires the co-administration of prednisone, and is complicated by the side effects of mineralocorticoid excess (hypertension, hypokalemia, and fluid overload), hepatotoxicity, and adrenal insufficiency. The sponsor is therefore of the opinion that there is still a medical need for pharmaceutical agents to treat CRPC, and that enzalutamide, in having a mechanism of action (inhibition of the androgen receptor signalling pathway) that is distinct from those of currently approved drugs for CRPC, can be a therapeutic option for these patients.

> **Comments:** The clinical rationale is sound. Abiraterone (Zytiga) is currently approved in Australia and is *"indicated with prednisone or prednisolone for the treatment of metastatic advanced prostate cancer (castration resistant prostate cancer) in patients who have received prior chemotherapy containing a taxane"*[1]. It has a recommended dosing regimen of 1 g (four 250 mg tablets) as a single daily dose, and should not be taken with food. It is to be taken at least two hours after eating and no food should be eaten for at least one hour after taking Zytiga.

### 2.1. Guidance

The sponsor had stated that the specific issues identified as requiring sponsor action in the TGA Planning Letter has been addressed in the dossier submission.

# 3. Contents of the clinical dossier

### 3.1. Scope of the clinical dossier

The submission contained the following clinical information:

Module 5:

- 5 clinical pharmacology studies, including 5 that provided pharmacokinetic data.
- 5 population pharmacokinetic analyses.
- 1 pivotal efficacy/safety studies (AFFIRM study [CRPC2]).
- 1 dose-finding study (Study S-3100-1-01).
- 2 other efficacy/safety studies (Study S-3100-1-01 and Study CRPC-MDA-1).
- Statistical Analysis Plan for the Summary of Clinical Safety (SCS; which includes integrated safety results across studies), Table of Content for tables, figures and listings used in the SCS.

Module 1

[1] Australian Product Information for Zytiga, March 2012

- Application letter, application form, draft Australian PI and CMI, FDA-approved product label, proposed European Summary of Product Characteristics

Module 2

- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

In this evaluation report, Study CRPC2 will be evaluated as the pivotal efficacy/safety study, and studies S-3100-1-01 and CRPC-MDA-1 as supportive efficacy/safety studies. Study S-3100-1-01, a first-in-human, Phase I, single- and multiple-dose escalation study in patients with CRPC, was submitted as a supportive efficacy/safety study. It contains single- and multiple-dose PK results in CRPC patients, results pertaining to dose selection for the pivotal Phase III study, as well as supportive efficacy and safety results. In this evaluation report, the study design will be presented in Section 7 together with the supportive efficacy results. Supportive safety results will be described in the safety section (Section 8) of this report. Results pertaining to dose selection for the pivotal Phase III study will be described in Section 6.

### 3.2. Paediatric data

The submission did not include paediatric data. The sponsor has also stated that there have been no studies conducted with enzalutamide in the paediatric population as the main indication for enzalutamide is limited to prostate cancer and hence not relevant to the paediatric population.

### 3.3. Good clinical practice

The clinical studies reviewed in this evaluation were in compliance with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice.

## 4. Pharmacokinetics

### 4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic.

**Table 1. Submitted pharmacokinetic studies.**

| PK topic | Subtopic | Study ID | * |
|---|---|---|---|
| PK in healthy adults | General PK<br>- Single dose | 9785-CL-0001 | To evaluate the PK, metabolism, and excretion of MDV3100 in plasma, urine, and faeces after a single oral 160 mg (100 µCi) dose of $^{14}$C-MDV3100. |
| | Bioequivalence †<br>- Single dose | MDV3100-05 | To evaluate the bioequivalence of two oral formulations of MDV3100 ( following a single 160 mg dose in healthy male subjects under fasted and fed conditions; and to assess the effects of food on the rate and extent of absorption of the two oral formulations following a single 160 |

| PK topic | Subtopic | Study ID | * |
|---|---|---|---|
| | | | mg dose in healthy male subjects. |
| | Food effect | MDV3100-05 | See above |
| PK in special populations | Target population§<br>- Single dose and multi-dose | S-3100-1-01 | To determine the safety and tolerability profile of MDV3100 (30, 60, 150, 240, 360, 480, and 600 mg), including the dose-limiting toxicities, and the maximum tolerated dose when administered orally to patients with CRPC. |
| | Hepatic impairment | 9785-CL-0009 | To compare the single-dose PK of MDV3100 (160mg; four 40 mg capsules) in subjects with mild and moderate hepatic impairment to matched control subjects with normal hepatic function |
| PK interactions | Gemfibrozil; itraconazole | 9785-CL-0006 | To investigate the effect of multiple oral doses of 600 mg gemfibrozil twice daily on the PK of a single oral dose of 160 mg MDV3100; and to investigate the effect of multiple oral doses of 200 mg itraconazole once daily on the PK of a single oral dose of 160 mg MDV3100. |
| | Pioglitazone;<br>drug cocktail of S-warfarin, omeprazole and midazolam | 9785-CL-0007 | To determine the effect of multiple once daily administration of MDV3100 (160mg; four 40 mg capsules) on the PK of a single dose of pioglitazone (CYP2C8 substrate), S-warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate) and midazolam (CYP3A4 substrate) in patients with CRPC. |
| Population PK analyses | Healthy subjects | Study report 9785-PK-0002 | To assess the extent of drug-drug interaction of gemfibrozil and itraconazole on single dose MDV3100 PK, using data from study 9785-CL-0006. |
| | Target population | Study report 9785-PK-0001 | To develop a population PK model of MDV3100, and population PK-PD models for its effect on prostate-specific antigen (PSA) concentration (a biomarker for prostate cancer progression) and spontaneously reported fatigue (the most frequently |

| PK topic | Subtopic | Study ID | * |
|---|---|---|---|
| | | | reported adverse event), using data from Study S-3100-1-01. |
| | | Study report icon2147020 | To investigate potential factors that may cause increases in plasma concentrations of MDV3100 metabolite M1 (also referred to as MDCP0001) in CRPC patients in Study CRPC2. |
| | | Study report icon2147016 | To document the relationship(s) of MDV3100 and its major active metabolite M2 (also referred to as MDPC0002) steady-state pre-dose plasma concentrations (Cmin) with study efficacy and safety outcomes in Study CRPC2. |
| | Both healthy and target population | Study report icon2147014 | To build a population PK model of MDV3100 after oral administration of MDV3100 liquid-filled capsules in healthy male subjects and in patients with CRPC, including cofactors that contribute to inter-individual variability in MDV3100 PK, using PK data from studies S-3100-1-01, MDV3100-05, and CRPC2. |

* Indicates the primary aim of the study.
† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication. MDV3100: enzalutamide

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

## 4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic (PK) studies unless otherwise stated. In the PK studies, plasma concentrations of MDV3100 were measured using validated bioanalytical methods based on high-performance liquid chromatography with tandem mass spectrometry (LC-MS/MS). According to the sponsor, 2 validated LC-MS/MS methods were used for MDV3100 concentration determinations in human plasma. The first method (PRO3100NC33) measured only MDV3100 and used calibration standards that spanned from 0.002 to 5.0 µg/mL. The standard curve was described by a linear function with 1/y weighting. Six replicates of quality control (QC) samples were performed at each of the lower limit of quantification (LLOQ), low QC, medium QC, and high QC concentrations for MDV3100. Intra- and inter-assay results demonstrated a relative standard deviation (RSD) for QC samples to be ≤ 15% (≤ 20% at the LLOQ). Tests for dilution integrity demonstrated that MDV3100 measurements were accurate with sample dilutions up to 50-fold. The second method (PRO3100NC86) measured MDV3100, M1 (inactive metabolite) and M2 (active metabolite), and used calibration standards that spanned from 0.02 to 50 µg/mL. Six

replicates of QC samples were performed at each of the LLOQ, low QC, medium QC, and high QC concentrations for MDV3100, M1, and M2. Intra- and inter-assay results demonstrated an RSD for QC samples to be ≤ 15% (≤ 20% at the LLOQ). The standard curves were described by a linear function with 1/x2 weighting. Tests for dilution integrity demonstrated that MDV3100, M1, and M2 measurements were accurate with sample dilutions up to 50-fold.

### 4.2.1. Pharmacokinetics in healthy subjects

#### *4.2.1.1. Absorption*

##### *4.2.1.1.1. Sites and mechanisms of absorption*

In the radiolabel mass balance study in healthy subjects (Study 9785-CL-0001), MDV3100 was absorbed rapidly after oral administration, with a median time to maximum plasma concentration (tmax) of 1.75 hours post-dose (single dose of 160 mg).

#### *4.2.1.2. Bioavailability*

##### *4.2.1.2.1. Absolute bioavailability*

The sponsor had provided justification for not submitting absolute bioavailability data in this application. An absolute oral bioavailability study was not conducted as an intravenous formulation of enzalutamide for humans was not available because of its limited aqueous solubility. Due to this limited aqueous solubility, preparation of an intravenous formulation would likely involve toxic compounds such as cremophor, which would pose unacceptable risks to subjects. PK data from animals (rats and dogs) showed that enzalutamide as a Labrasol solution was well absorbed after oral dosing (absolute oral bioavailability of enzalutamide was 97% and 73% in rats and dogs, respectively). The high oral bioavailability in rats and dogs was consistent with the estimated absorption of enzalutamide in the $^{14}C$ human mass balance study (≥ 84.2%; Study 9785-CL-0001)[2].

In addition, according to the sponsor, the necessity of an absolute oral bioavailability study had been discussed with the CHMP, and the CHMP had agreed that an absolute oral bioavailability study was not considered necessary as data derived from the $^{14}C$ human mass balance study (Study 9785-CL-0001) could support the lack of absolute bioavailability study.

##### *4.2.1.2.2. Bioequivalence of different dosage forms and strengths*

Study MDV3100-05 was conducted to explore the bioequivalence of two oral formulations of MDV3100 following a single 160 mg dose in healthy male subjects under fasted and fed conditions. The soft gelatin capsule formulation was the formulation used in the pivotal Phase III study, and is the proposed to-be-marketed formulation. The rationale for this study was that, with the current proposed formulation (40 mg soft gelatin capsules), a patient would have to take four of these capsules each day to receive the recommended clinical dose of 160 mg/day. The results from this study were to help inform and guide future formulation development efforts, and are not directly relevant to this submission, which is for the registration of the 40 mg soft gelatin capsule formulations. Results of this study with regards to formulations comparison are presented in the dossier.

##### *4.2.1.2.3. Influence of food*

Study MDV3100-05 was conducted to assess the effects of food on the rate and extent of absorption of MDV3100 following a single 160 mg dose in healthy male subjects. Results showed that a high fat meal reduced the rate of MDV3100 absorption (manifesting as a Cmax that was 30% lower and a tmax that occurred 1 hour later than under fasted conditions) but that the extent of absorption was unaffected (adjusted geometric mean ratios for $AUC_{0-t}$ and

[2] Results in study 9785-CL-0001 showed that the overall radioactive recovery in excreta was 84.6% of radioactive dose, and that in the faeces, 0.39% of the radioactive dose was recovered as unchanged parent MDV3100, leading to the conclusion that at least 84.2% of the dose was absorbed.

$AUC_{0\text{-}inf}$ for fed conditions relative to fasted conditions of 99.61% and 98.98%, respectively). The sponsor considered this observed food effect on the rate of absorption not to be clinically significant, and therefore concluded that MDV3100 liquid-filled capsules could be taken with or without food. MDV3100 were administered without regard to meals in clinical trials in patients, including the pivotal phase III study CRPC2, and similar guidance has been included in the proposed prescribing information.

*4.2.1.2.4. Dose proportionality*

In Study S-3100-1-01, dose-proportionality during the single-dose and multiple-dose periods was assessed. Results showed that there was no major deviation from dose proportionality or linearity after single- or multiple-dose administration over the dose range of 30 to 600 mg.

### *4.2.1.3. Distribution*

*4.2.1.3.1. Volume of distribution*

The mean apparent volume of distribution (V/F) in healthy subjects ranged between 62.7 to 117 L.

*4.2.1.3.2. Plasma protein binding*

Results of the hepatic impairment study (9785-CL-0009) indicated that MDV3100 and its metabolites M1 and M2 were highly bound to plasma proteins. The protein binding, irrespective of hepatic function, was 98%, 98%, and 96% for MDV3100, M1, and M2, respectively.

*4.2.1.3.3. Erythrocyte distribution*

Red blood cell partitioning was indirectly measured using whole blood and plasma radioactivity from a mass balance study in healthy subjects (Study 9785-CL-0001). Results showed that following oral administration of $^{14}C$ -MDV3100, the overall blood-to-plasma radioactivity ratio (based on mean $^{14}C$ -$AUC_{0\text{-}inf}$ values for blood and plasma) was approximately 0.55, indicating that the radioactivity was preferentially retained in the plasma component of blood.

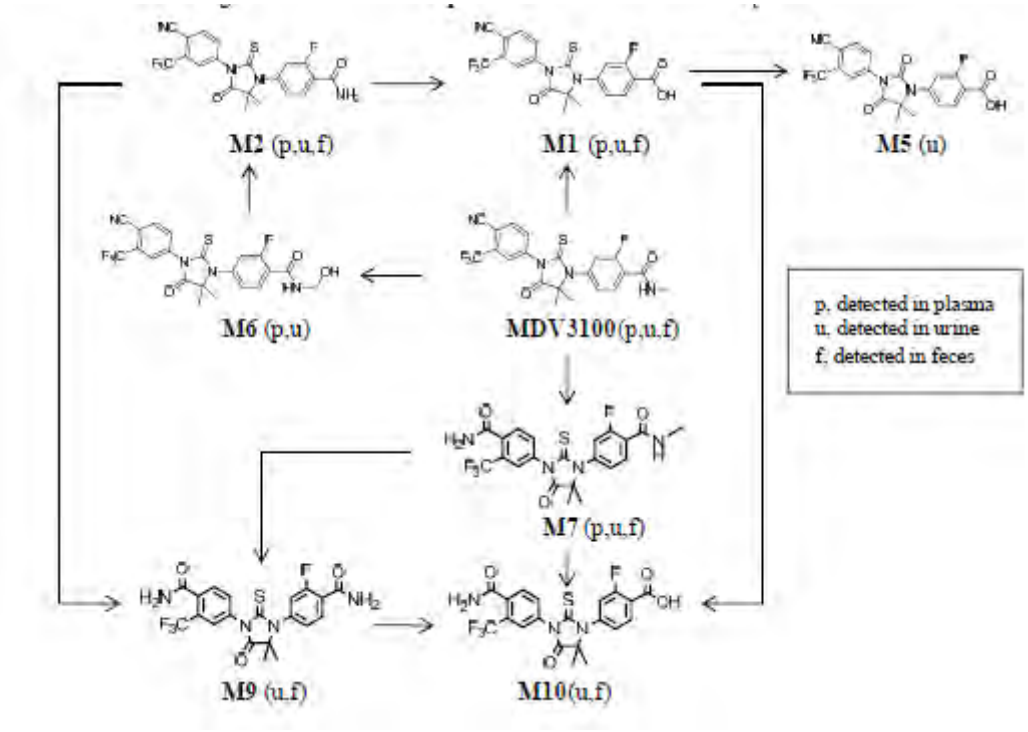
### *4.2.1.4. Metabolism*

*4.2.1.4.1. Sites of metabolism and mechanisms / enzyme systems involved*

In Study 9785-CL-0001, a single dose of 160 mg (100 µCi) $^{14}C$-MDV3100 was administered orally to healthy subjects to assess mass balance and to obtain metabolic profiles. A total of seven Phase I metabolites were identified in plasma, urine, and faeces by comparison with reference standards and liquid chromatography with multiple stage mass spectrometry methods. These metabolites were formed via demethylation, oxidation, and hydrolysis reactions. No Phase II conjugation products were observed. Metabolites M1 (inactive; a carboxylic acid derivative) and M2 (active; N-desmethyl enzalutamide) were the major metabolites in plasma.

Five of the 7 metabolites identified were M1, M2, M5 (MDV3105), M6 (MDV3106), and M7 (MDPC196). Two additional components were deduced by their mass spectra to be N-desmethyl and carboxylic acid analogues of M7, and these were assigned metabolite identification numbers of M9 and M10, respectively. The major $^{14}C$ components in plasma were MDV3100, M1, and M2. Metabolites M6 and M7 were trace components in plasma. The main component in urine was M1 (62.7% of radioactive dose), followed by M7 (9.45% of the radioactive dose). Minor components in urine were M5, M9, and M10. In addition, trace amounts of MDV3100, M2, M6, and an unknown $^{14}C$ component were observed in urine. In faeces, the most abundant $^{14}C$ components were M1 and M10 (accounting for 3.34% and 4.26% of the radioactive dose, respectively). Minor components were M2 and M7. In addition, trace amounts of MDV3100 was observed in faeces. Based on these results, the sponsor had provided a proposed biotransformation pathways in humans for MDV3100 (Figure 1, below).

**Figure 1: Proposed Biotransformation Pathways of MDV3100 in Humans**




According to the sponsor, in-vitro studies showed that MDV3100 was metabolised by CYP2C8 and CYP3A4/5, both of which played a role in the formation of the active metabolite. A clinical drug-drug interaction study in healthy volunteers (Study 9785-CL-0006) showed that CYP2C8 played an important role in the metabolism of MDV3100 and the formation of M2. In the presence of a strong CYP2C8 inhibitor (gemfibrozil), plasma exposure to MDV3100 increased by 4.26-fold, while M2 exposure decreased by 25%. The same study also showed that CYP3A4 played a minor role in the metabolism of MDV3100. The exposure of MDV3100 and its metabolites (M1 and M2) were increased by no more than 41% in the presence of a strong CYP3A4 inhibitor (itraconazole). MDV3100 was not metabolised in-vitro by CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C18, CYP2C19, CYP2D6, or CYP2E1.

*4.2.1.4.2. Pharmacokinetics of metabolites*

In the radiolabel mass balance study in healthy subjects (Study 9785-CL-0001), after a single 160 mg dose of MDV3100 in healthy subjects, metabolites M1 and M2 were formed slowly (median Tmax of 96 and 132 hours post-dose for M1 and M2, respectively) and eliminated with a mean t½ of 223 and 186 hours, respectively. There were no significant changes in exposures to M1 and M2 when MDV3100 was administered with food.

### *4.2.1.5. Excretion*

*4.2.1.5.1. Routes and mechanisms of excretion*

In the radiolabel mass balance study (study 9785-CL-0001), following oral administration of $^{14}C$ -MDV3100 to healthy subjects, 84.6% of the administered dose (75.4% to 92.0% in individual subjects) was recovered through Day 77 post-dose: 71.0% was recovered in urine (primarily as M1, with trace amount of MDV3100 and M2), and 13.6% was recovered in faeces (0.39% of dose as unchanged parent MDV3100). Based on this result, renal excretion is a minor elimination pathway for unchanged parent MDV3100 and the active metabolite M2.

The averaged mean apparent clearance (CL/F) of MDV3100 was between 0.596 to 0.753 L/h in healthy subjects. The mean t½ of MDV3100 in healthy subjects was 2.9 to 4.8 days. The mean

t½ for M1 in healthy subjects ranged from 7.8 to 9.3 days, and that for M2 in healthy subjects ranged from 7.5 to 8.8 days.

#### *4.2.1.6. Intra- and inter-individual variability of pharmacokinetics*

In Study 9785-CL-0001 (healthy subjects; single dose), when measuring the exposure expressed as $AUC_{0\text{-}inf}$, the coefficient of variability (CV%) was 21% for MDV3100, 18% for M1 and 25% for M2, indicating a relatively low inter-subject variability. In Study 9785-CL-0007 (CRPC patients; multiple dose) inter-subject variability, expressed as CV%, on MDV3100 PK parameters at steady-state ($AUC_{tau}$, Cmin and Cmax) was also low, ranging from 23.0% to 29.3%.

### 4.2.2. Pharmacokinetics in the target population

Results in Study S-3100-1-01 showed that oral absorption of MDV3100 in patients with CRPC was rapid across dose range of 30mg to 600mg, when administered as single or multiple doses, with peak concentrations of MDV3100 achieved in about 1 to 2 hours post-dose (Table 2).

**Table 2: Summary of Plasma MDV3100 Pharmacokinetic Parameters for the Multiple-Dose Period, Study S-3100-1-01**

| Parameter (units) | 30 mg | 60 mg | 150/160 mg | 240 mg | 360 mg | 480 mg[a] |
|---|---|---|---|---|---|---|
| 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] $t_{max}$ 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.
NOTE: Reported values are the arithmetic mean ± SD, for $t_{max}$, the median (range) is reported.

ND, not determined; PTR, peak-to-trough ratio.

The mean V/F of MDV3100 in CRPC patients was 110 L or approximately 2.6-fold greater than total body water (42 L), indicating extensive extravascular distribution. The mean CL/F of MDV3100 in CRPC patients across combined doses of 30mg to 600mg was 0.564 L/h after single dose and 0.614 L/h after multiple dosing, or approximately 1% of the liver plasma flow rate (48.7 L/h), suggesting that MDV3100 is a low extraction ratio drug. The mean t½ of MDV3100 in CRPC patients was 139.6 hours (i.e. 5.8 days) after a single dose. The t½ did not appear to be affected by dose.

Due to its slow clearance from plasma, the daily fluctuations in steady-state MDV3100 concentrations after multiple dosing were low, with a mean peak-to-trough ratio (PTR) of 1.25 (range: 1.00 to 1.72), indicating that the average difference between the peak and trough concentrations was ≤ 25%. In accordance with the long t½, it took approximately 1 month to reach steady state, with daily administration.

### 4.2.3. Pharmacokinetics in other special populations

#### *4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function*

The PK of MDV3100 were examined in subjects with baseline mild (n=6) or moderate (n=8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 14 matched control subjects with normal hepatic function in Study 9785-CL-0009. Following a single oral 160 mg dose of MDV3100, exposure parameters for MDV3100 increased by up to 1.24- and 1.29-fold in subjects

with mild and moderate hepatic impairment, respectively, compared to healthy control subjects. Exposure parameters for M1, M2, and the sum of MDV3100 plus M2 increased by up to 1.30- and 1.18-fold in subjects with mild and moderate hepatic impairment, respectively, compared to healthy control subjects. Based upon the above findings, the sponsor drew the conclusion that no dose adjustment would be necessary for patients with baseline mild or moderate hepatic impairment.

> **Comments**: Study design of Study 9785-CL-0009 was consistent with the TGA-adopted EMA guidelines on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function[3]. The proposed dosing recommendation with regards to hepatic impairment was reasonable.

### 4.2.4. Pharmacokinetic interactions

#### *4.2.4.1. Pharmacokinetic interactions demonstrated in human studies*

##### *4.2.4.1.1. Gemfibrozil (potent CYP2C8 inhibitor) and itraconazole (potent CYP3A4 inhibitor)*

The effects of multiple oral doses of gemfibrozil (600mg twice daily to steady state) and of multiple oral doses of itraconazole (200 mg once daily to steady state) on the PK of a single oral dose of 160 mg MDV3100 was investigated in Study 9785-CL-0006. Results showed that the potent CYP2C8 inhibitor gemfibrozil resulted in 2.53-fold increase in the exposure ($AUC_{0\text{-}432h}$) of MDV3100, a 1.38-fold increase in $AUC_{0\text{-}432h}$ of M1, a 67% decrease in $AUC_{0\text{-}432h}$ of M2, and a 1.39-fold increase in $AUC_{0\text{-}432h}$ of the sum of MDV3100 and M2. The potent CYP3A4 inhibitor itraconazole resulted in 41%, 6%, 21% and 28% increases in the exposure ($AUC_{0\text{-}inf}$) of MDV3100, M1, M2, and the sum of MDV3100 and M2, respectively.

Overall, results in this clinical study showed that the effect of CYP2C8 inhibition by gemfibrozil was more pronounced than the effect of CYP3A4 inhibition by itraconazole, suggesting that CYP2C8 plays a more important role in the metabolism of MDV3100 and the formation of M2, compared to CYP3A4.

Results of Study 9785-CL-0006 also showed that the inhibitory effects of steady-state itraconazole on the PK of MDV3100, M1 and M2 were well characterised by non-compartmental methods. However, the full inhibitory effects of steady-state gemfibrozil on the PK of MDV3100, M1 and M2 could not be sufficiently addressed by non-compartmental methods alone[4], and therefore, the inhibitory effects of gemfibrozil were further explored by modelling and simulation in a population PK study (Study 9785-PK-0002). This population PK study showed that concomitant gemfibrozil was associated with a 4.26-fold increase in $AUC_{0\text{-}inf}$ of MDV3100, a 2.70-fold increase in $AUC_{0\text{-}inf}$ of M1, a 25% decrease in the $AUC_{0\text{-}inf}$ of M2, and a 2.17-fold increase in the $AUC_{0\text{-}inf}$ of the sum of MDV3100 plus M2. These results generally corroborated the previous non-compartmental PK analysis of data from Study 9785-CL-0006 in showing that the strong CYP2C8 inhibitor gemfibrozil had a moderate effect on MDV3100 exposure.

> **Comments**: The drug interactions recommendations in the proposed Product Information (PI) for enzalutamide state that "Strong inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin) of CYP2C8 are to be avoided or used with caution during enzalutamide treatment. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily" and that "No dose

[3] European Medicines Agency. Guidelines on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function. February 2005

[4] In Study 9785-CL-0006, plasma concentration-time profiles indicated a change in the elimination ($t_{½}$) for MDV3100 and its metabolites after discontinuation of gemfibrozil on day 21 (432h), indicating that the inhibitory effect of gemfibrozil had quickly stopped after discontinuation. As a result, $AUC_{0\text{-}inf}$ values were not reported for the treatment investigating the effects of gemfibrozil, and $AUC_{0\text{-}432h}$ was used instead. In addition, this change in the $t_{½}$ suggested that the reported effect on $AUC_{0\text{-}432h}$ based on non-compartmental PK assessments could be underestimating the effect of CYP2C8 inhibition on the PK of MDV3100.

adjustment is necessary when enzalutamide is co-administered with inhibitors or inducers of CYP3A4". Based on the study results, the sponsor's recommendations are appropriate.

*4.2.4.1.2. Pioglitazone (CYP2C8 substrate), S-warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate) and midazolam (CYP3A4 substrate)*

The effect of multiple, oral doses of MDV3100 (160mg once daily) on the PK of a single dose of pioglitazone (CYP2C8 substrate), S-warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate) and midazolam (CYP3A4 substrate) in patients with CRPC was investigated in Study 9785-CL-0007.

Overall, study results showed that MDV3100 had no clinically relevant effect on CYP2C8, was a moderate inducer of CYP2C9 and CYP2C19, and a strong inducer of CYP3A4. After a single dose of 30 mg pioglitazone in the presence of 160 mg MDV3100 at steady state, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ of CYP2C8 substrate pioglitazone increased by 30% and 20% , respectively, while Cmax of pioglitazone decreased by 18%, compared to administration of 30 mg pioglitazone alone. After a single oral dose of 10 mg warfarin in the presence of 160 mg MDV3100 at steady state, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ of CYP2C9 substrate S-warfarin decreased by 55% and 56%, respectively, compared to administration of 10 mg warfarin alone, while Cmax of S-warfarin was comparable between both treatments. After a single oral dose of 20 mg omeprazole in the presence of 160 mg MDV3100 at steady state, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and Cmax of CYP2C19 substrate omeprazole decreased by 72% and 70%, and 62%, respectively, compared to administration of 20 mg omeprazole alone. After a single oral dose of 2 mg midazolam in the presence of 160 mg MDV3100 at steady state, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and Cmax of CYP3A4 substrate midazolam decreased by 86%, 86% and 77%, respectively, compared to administration of 2 mg midazolam alone.

**Comments**: The drug interactions recommendations in the proposed PI for enzalutamide include mention of the potential interactions with drugs which are substrates of CYP3A4, CYP2C9, and CYP2C19. This is considered appropriate.

### *4.2.4.2. Clinical implications of in vitro findings*

According to the sponsor, in-vitro metabolism of $^{14}$C-MDV3100 was investigated with 12 human recombinant CYP isoforms (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5), and results indicated that CYP3A4/5 and CYP2C8 played an important role in the metabolism of MDV3100. In addition an in-vitro study was conducted to evaluate the potential of MDV3100 to induce enzymatic activity and messenger ribonucleic acid (mRNA) levels of CYP1A2, CYP2B6, and CYP3A4. The results showed no clear trend to suggest that MDV3100 induced CYP1A2 or CYP2B6, but suggested induction of CYP3A4. The potential for MDV3100 and its metabolites, M1 and M2, to inhibit 7 major CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) was also investigated. These in-vitro studies showed that MDV3100, M1, and/or M2 were inhibitors of CYP2C8 and CYP2C19 (50% inhibitory concentration [IC50] ≥ 10 μM), with lesser inhibitory effects on CYP2B6 and CYP2C9 (IC50 ≥ 42 μM).

**Comments**: Based on these reported in-vitro findings, the selection of drug-drug interactions (DDI) studies investigating potential DDI of MDV3100 with potent CYP2C8 and CYP3A4 inhibitors, and with substrates of CYP2C8, CYP2C9, CYP2C19, and CYP3A4 substrate were appropriate.

## 4.3. Evaluator's overall conclusions on pharmacokinetics

Overall, the PK data is adequate with respect to evaluation of this application. MDV3100 was absorbed rapidly after oral administration in patients, with maximum plasma concentrations (Cmax) observed 1 to 2 hours after administration. Based on a mass balance study in healthy human subjects, oral absorption of MDV3100 was estimated to be at least 84.2%. Food effect

study showed that food had no clinically significant effect on the extent of absorption. The mean apparent volume of distribution (V/F) of MDV3100 in patients after a single oral dose was 110 L (29% CV). MDV3100 and its metabolites M1 and M2 were found to be highly bound to plasma proteins (96% to 98%). MDV3100 was found to be extensively metabolised. There were two major metabolites in human plasma: M2 (N-desmethyl enzalutamide; active metabolite) and M1 (a carboxylic acid derivative; inactive metabolite). Drug interaction studies showed that CYP2C8 played an important role in the metabolism of MDV3100 and the formation of M2, while CYP3A4 played a more minor role. The mean apparent clearance (CL/F) of MDV3100 in CRPC patients was 0.564 L/h after single dose and 0.614 L/h after multiple dosing. Following oral administration of $^{14}$C-MDV3100, 84.6% of the radioactivity was recovered by 77 days post dose: 71.0% was recovered in urine (primarily as M1, with trace amount of MDV3100 and M2), and 13.6% was recovered in faeces (0.39% of dose as unchanged parent MDV3100). Based on this result, renal excretion appeared to be a minor elimination pathway for unchanged parent MDV3100 and the active metabolite M2.

The PK of MDV3100 were examined in subjects with baseline mild (n=6) or moderate (n=8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 14 matched control subjects with normal hepatic function. Results showed that following a single oral 160 mg dose of MDV3100, exposure parameters for MDV3100 increased by up to 1.24- and 1.29-fold in subjects with mild and moderate hepatic impairment, respectively, compared to healthy control subjects. Based on the study results, no dose adjustment was considered necessary for patients with baseline mild or moderate hepatic impairment.

No formal renal impairment study for MDV3100 had been conducted. Based on the results of a population PK analysis (icon2147014) which showed that creatinine clearance (≥ 30 mL/min; estimated by the Cockcroft and Gault formula) did not have clinically meaningful influence on the exposures to MDV3100, no dose adjustment was considered necessary for patients with creatinine clearance values ≥ 30 mL/min.

Drug interaction studies showed that CYP2C8 played an important role in the metabolism of MDV3100, while CYP3A4 played a more minor role. Hence strong inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin) of CYP2C8 are to be avoided or used with caution during treatment with MDV3100, but no dose adjustment is considered necessary when MDV3100 is co-administered with inhibitors or inducers of CYP3A4. Drug interaction studies looking at the effects of MDV3100 on other medicines showed that MDV3100 was a strong inducer of CYP3A4, a moderate inducer of CYP2C9 and CYP2C19, but had no clinically relevant effect on CYP2C8.

The sponsor had provided justification for not submitting absolute bioavailability data in this application, that an intravenous formulation of MDV3100 for humans was not available because of its limited aqueous solubility, but that non-clinical and clinical studies showed that MDV3100 had a high oral bioavailability. The evaluator considered this justification reasonable.

# 5. Pharmacodynamics

## 5.1. Studies providing pharmacodynamic data

Table 3 below shows the studies relating to each pharmacodynamic topic.

**Table 3: Submitted pharmacodynamic studies.**

| PD Topic | Subtopic | Study ID | * |
|---|---|---|---|
| Population PD and PK-PD analyses | Target population§ | Study report 9785-PK-0001 | To develop a population PK model of MDV3100, and population PK-PD models for its effect on prostate-specific antigen (PSA) concentration (a biomarker for prostate cancer progression) and spontaneously reported fatigue (the most frequently reported adverse event), using data from Study S-3100-1-01. |

* Indicates the primary aim of the study. ‡ And adolescents if applicable.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

## 5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

### 5.2.1. Mechanism of action

Prostate cancer is known to be androgen sensitive and responds to inhibition of androgen receptor signalling. In patients who had surgical or medical castration, it has been found that despite low or even undetectable levels of androgens, androgen receptor signalling continues to promote disease progression. This stimulation of tumour cell growth via the androgen receptor requires nuclear localisation and DNA binding. According to the sponsor, MDV3100 is a potent androgen receptor signalling inhibitor that targets several steps in the androgen receptor signalling pathway. MDV3100 competitively inhibits binding of androgen to the androgen receptor, inhibits nuclear translocation of activated receptors, and inhibits the association of the activated androgen receptor with DNA, even in the setting of androgen receptor overexpression and in prostate cancer cells resistant to anti-androgens. In non-clinical studies, MDV3100 treatment decreased the growth of prostate cancer cells. MDV3100 has been found to lack androgen receptor agonist activity.

### 5.2.2. Pharmacodynamic effects

#### *5.2.2.1. Primary pharmacodynamic effects*

In Study CRPC-MDA-1, a single-centre (the US), single arm, open-label study of patients with metastatic progressive CRPC treated with oral MDV3100 (160 mg/day), immunohistochemistry for androgen receptor in bone marrow samples was performed and subcellular distribution of androgen receptor was recorded (membranous, cytosolic, nuclear, or combination).

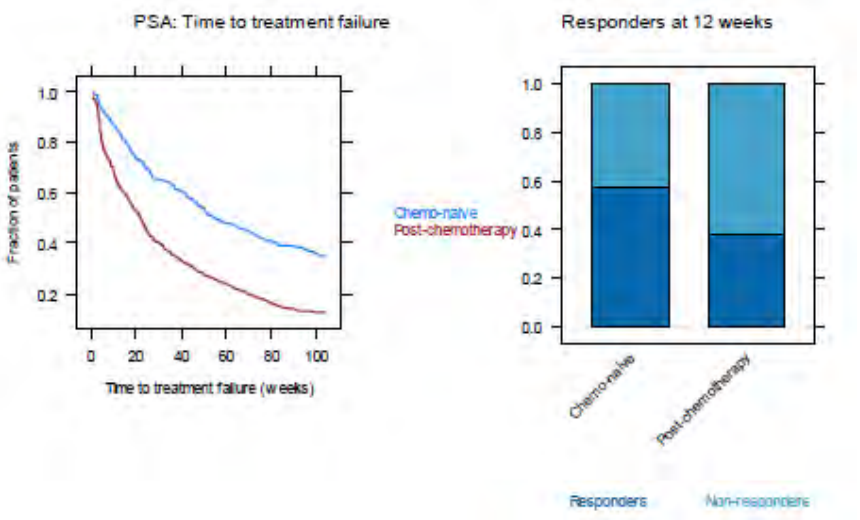
Bone marrow samples were considered eligible for assessment of androgen receptor expression by immunohistochemistry if paired bone marrow samples were obtained at both the baseline and Week 9 visits and both paired baseline and Week 9 bone marrow samples had prostate cancer cells observed. The paired specimens also had to have adequate immunohistochemistry results. Overall, 16 out of 60 patients (26.7%) met these criteria. Of these 16 patients who were evaluable for assessment of bone marrow androgen receptor expression by

immunohistochemistry, 5 were prostate specific antigen (PSA) responders (defined by a ≥ 50% reduction from baseline in PSA at Week 9) and 11 were PSA non-responders. Of the evaluable 5 PSA responders, all 5 showed reduction in nuclear androgen receptor localisation. Of the evaluable 11 PSA non-responders, 2 showed reduction in nuclear androgen receptor localisation and 9 showed no change or increase in nuclear androgen receptor localisation. Statistical correlation was not assessed due to low numbers of evaluable patients.

#### *5.2.2.2. Secondary pharmacodynamic effects*

A population PK/PD model (Study report 9785-PK-0001) was developed to examine the effect of MDV3100 exposures on PSA concentrations (a biomarker for prostate cancer progression), using data from Study S-3100-1-01. Results showed that at the start of treatment, MDV3100 administration induced a decrease in PSA concentrations, and that during treatment, MDV3100 slowed the rate of PSA concentration increase. In the cell-growth model, the 50% effective concentration (EC50) was estimated to be much lower than MDV3100 concentrations attained even for the lowest doses tested (30mg), suggesting that the effect of MDV3100 on PSA was already at a maximum at the lowest dose tested in this study. Simulation results showed that the 2 patient populations in this study (chemo-naïve patients and post-chemotherapy patients) appeared to respond differently to MDV3100 treatment, with a greater treatment benefit in the chemo-naïve patients (Figure 2).

**Figure 2: Kaplan-Meier survival curve for time until treatment failure (weeks) and bar chart for distribution of the fraction responders by patient population for the simulated data set using a dose of 160 mg/day, Study 9785-PK-0001**




Treatment failure = increase in PSA to 25% above baseline; responders = subjects showing a decrease in PSA of more than 50% from baseline.

### 5.3. Evaluator's overall conclusions on pharmacodynamics

Overall, the PD data is adequate with respect to evaluation of this application.

# 6. Dosage selection for the pivotal studies

Dose selection of MDV3100 for the pivotal study was based on the results of a Phase I dose-escalation study, S-3100-1-01. The study design is described in Section 7.1.2.1. With regards to dose selection for the pivotal study, the maximum tolerated dose in this study was determined to be 240 mg daily, based upon the occurrence of dose-limiting toxicities as well as adverse events of fatigue leading to dose reductions at higher doses. There were 5 dose-limiting

toxicities reported in Study S-3100-1-01, all occurring at doses of 360 mg daily or higher (3 events of seizure, and 1 each of rash and confusion). There was also a dose-dependent increase in adverse events of fatigue leading to dose reduction, with a 2.9% incidence at 240 mg daily, 7.5% incidence at 360 mg daily, and 20.0% incidence at 480 mg daily.

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

Given the comparable efficacy of doses ≥ 150 mg/day, and the increasing safety issues at doses ≥ 240 mg/day, a dose of 160 mg/day was selected for the CRPC2 study. According to the sponsor, a dose of 160 mg/day was selected rather than 150 mg/day because the dosage strength of the capsules had been changed from 30 mg to 40 mg per capsule in order to reduce the total number of capsules required.

**Comments**: The rationale for the dose selection in the Phase III study is sound.

# 7. Clinical efficacy

## 7.1. For the indication of the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxe

### 7.1.1. Pivotal efficacy study

#### *7.1.1.1. Study CRPC2 (AFFIRM)*

##### *7.1.1.1.1. Study design, objectives, locations and dates*

Study CRPC2 was a multi-centre, randomised, double-blind, placebo-controlled, Phase III study evaluating the efficacy and safety of MDV3100 in patients with progressive CRPC who had been previously treated with 1 or 2 chemotherapy regimens, at least 1 of which was docetaxel-based. The primary objective was to determine the benefit of MDV3100 compared to placebo as assessed by overall survival. The secondary objectives were to determine the benefit of MDV3100 compared to placebo as assessed by other efficacy outcomes (radiographic progression-free survival, time to first skeletal-related event, quality of life, time to PSA progression, pain palliation, and circulating tumour cell count conversion rate), to determine the safety of treatment with MDV3100 as compared to placebo, to determine the effects of MDV3100 on electrocardiographic (ECG) changes as compared to placebo, to establish the covariates that may affect variability in PK parameters, and to develop a PK model linking MDV3100 exposure with efficacy and safety outcomes[5].

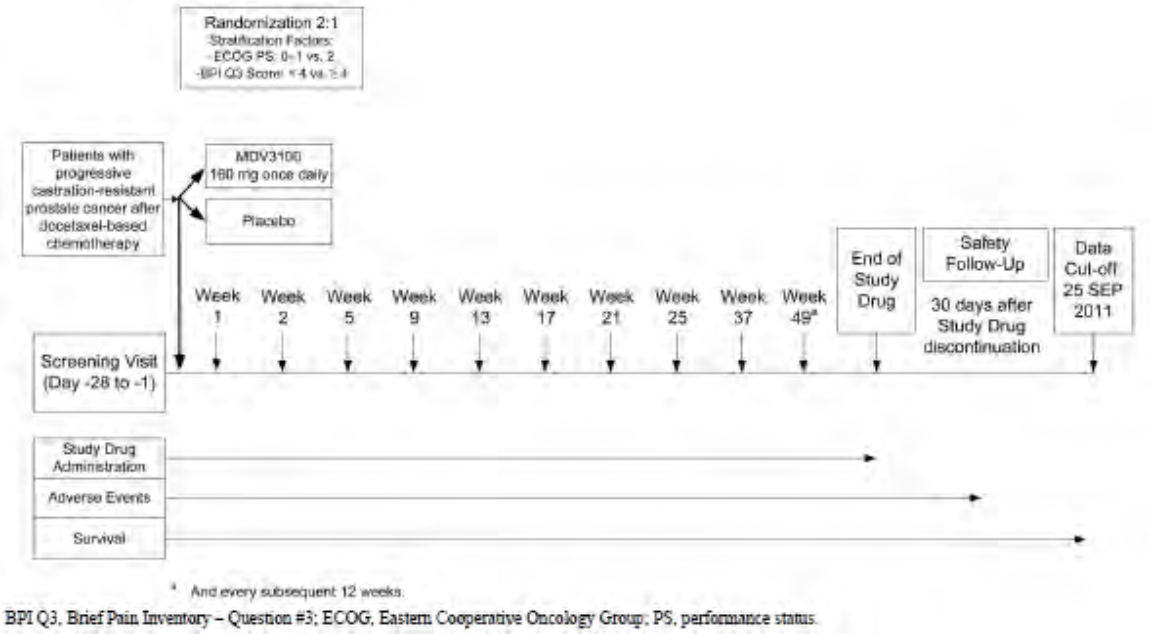
CRPC2 was an international, multi-centre study where subjects were enrolled in a total of 156 study sites across 15 countries in North America, South America, Europe, Australia, and South Africa.

[5] PK data collected in this study for the purpose of the last 2 study objectives were used in population PK analyses (studies icon2147020, icon2147016 and icon2147014), and were reported separately. The results of these population PK analyses are presented in an Appendix to this report [not included as part of the CER extract] and will not be described in this Efficacy Section.

The study start date (first patient enrolled) was 22 September 2009. The study was ongoing at the time of this submission. The last-patient-enrolled date was 15 November 2010, and the data cut-off date for the clinical study report (CSR) submitted was 25 September 2011.

After a screening period of up to 28 days, patients who met eligibility criteria were randomised in a 2:1 ratio to receive either MDV3100 (160 mg daily) or placebo (Figure 3).

**Figure 3: Study Schema: Study Design of Study CRPC2**




Treatment continued until unacceptable toxicity, confirmed disease progression and the patient was scheduled to initiate a new systemic antineoplastic therapy, death, or withdrawal. Patients had a safety follow-up visit 30 days after their last dose of study drug or prior to the initiation of another systemic antineoplastic therapy, whichever occurred first. An independent, external Data Monitoring Committee (DMC) had been formed prior to initiation of the study and monitored safety data on an ongoing basis, as well as efficacy results at the time of protocol-specified interim analysis. A thorough QT/QTc evaluation was embedded into the study, in which all electrocardiograms (ECGs) were read centrally at an ECG laboratory.

A formal interim analysis for overall survival was performed at 520 primary endpoint events (80% of the 650 targeted number of events for final analysis). This interim analysis was prepared by an independent statistical unit and presented to the independent DMC on 02 November 2011. The DMC considered the safety profile of MDV3100 along with the overall survival results and made the recommendation to the sponsor that the interim overall survival results were clinically significant for the patient population under study, and that the overall survival risk-to-benefit ratio favoured the MDV3100 arm. Based on the interim analysis results, the DMC recommended that the study be halted and that patients in the control group be crossed over to MDV3100. The study blind was maintained by the sponsor, sites, and patients until after database lock on 16 December 2011. The date of the 520$^{th}$ death (25 September 2011) was used as the analysis data cut-off date for all analyses in the submitted CSR.

*7.1.1.1.2. Inclusion and exclusion criteria*

Subjects enrolled in the study were men with CRPC who had received docetaxel therapy. Inclusion criteria included subjects with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features, who had ongoing androgen deprivation therapy with a GnRH analogue or orchiectomy (i.e. surgical or medical castration), with serum testosterone level < 1.7 nmol/L (50 ng/dL) at

screening, who had progressive disease[6] by PSA or imaging after docetaxel-based chemotherapy in the setting of medical or surgical castration, and who had no more than 2 prior chemotherapy regimens with at least 1 regimen containing docetaxel.

Patients were excluded if they had a previous history of seizures or any condition that might predispose to seizures (e.g. brain metastases, active epidural disease, stroke, or head trauma), or who were taking medications known to lower the seizure threshold, as seizure had been identified as a potential MDV3100-associated safety signal in the Phase I study S-3100-1-01. Patients were also excluded if they received prior ketoconazole, sipuleucel-T, concurrent anti-androgen therapy, or herbal products known to affect PSA levels as these had the potential to confound some or all of the efficacy analyses of this study. A full list of inclusion and exclusion criteria is presented in the study report.

> **Comments**: The inclusion and exclusion criteria were appropriate and generally in line with the EMA *Guidelines on the evaluation of anticancer medicinal products in man*[7]. Overall, the inclusion and exclusion criteria aimed to recruit men with castration-resistant prostate cancer who have received prior docetaxel therapy. The sponsor had provided the rationale that this patient population had been chosen as an initial indication to test MDV3100 as there is an urgent need for new active therapies in this setting, given that patients with CRPC who have been previously treated with docetaxel-based chemotherapy suffer from a disease that is usually fatal within 12–16 months.

*7.1.1.1.3. Study treatments*

Patients received daily oral dose of four 40 mg soft gelatin capsules of MDV3100 (i.e. 160 mg per day) or matching placebo. Patients received their assigned therapy until unacceptable toxicity, confirmed disease progression and the patient was scheduled to initiate another systemic antineoplastic therapy, death, or withdrawal.

Definitions of disease progression in this study are presented as follows:

- Bone disease: appearance of 2 or more new lesions on bone scan. New lesions at the first scheduled tumor assessment at Week 13 had to be confirmed by a second scan 6 or more weeks later. Confirmatory scans were required to show at least 2 additional new lesions compared to the Week 13 scan.
- Soft tissue disease: as documented on CT or MRI scan and defined by RECIST v1.1. Progression at the first scheduled tumor assessment at Week 13 had to be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans had to show progressively worsening disease compared to the Week 13 scan.
- Skeletal-related event, defined by 1 of the following:
  - Radiation therapy or surgery to bone;
  - Pathologic bone fractures;
  - Spinal cord compression;
  - Change of antineoplastic therapy to treat bone pain.

Increases in PSA, especially during the first 12 weeks of therapy, were not considered disease progression. An alteration of analgesic medication for bone pain was not considered a skeletal-

[6] Disease progression for study entry was defined as 1 or more of the following 3 criteria: PSA progression, as defined by a minimum of 3 rising PSA levels with an interval of ≥ 1 week between each determination (PSA value at the screening visit was to have been ≥ 2 µg/L [2 ng/mL]); soft tissue disease progression, as defined by the Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST, v1.1); bone disease progression as defined by 2 or more new lesions on bone scan

[7] European Medicines Agency, Guidelines on the evaluation of anticancer medicinal products in man. 14 December 2005.

related event. An increase in pain within the first 12 weeks of therapy, in the absence of other evidence of disease progression, was not considered progressive disease.

Prohibited or approved concomitant medications are presented in the study report.

> **Comments**: The study dose selection is appropriate and has been previously discussed in Section 6 of this evaluation report. The study design involving a placebo control is appropriate. The definitions of disease progression were appropriate and in line with the recommendations of the Prostate Cancer Clinical Trials Working Group 2[8, 9].

*7.1.1.1.4. Efficacy variables and outcomes*

The primary efficacy outcome was a comparison of overall survival between the MDV3100 and placebo-treated groups. Overall survival was defined as time from randomisation to death from any cause. Survival status was determined by the site via contact with the patient, patient's family, or other physician, at time of regular study visits, the safety follow-up visit, DMC meetings, and protocol-specified analyses. Once a patient had discontinued treatment and completed the safety follow-up visit, the investigator or study coordinator contacted the patient, patient's family, or patient's regular physician every 12 (± 1) weeks to assess survival status and cause of death.

Key secondary efficacy endpoints were time to PSA progression, radiographic progression-free survival, and time to first skeletal-related event.

Other secondary efficacy endpoints were:

· quality of life (Functional Assessment of Cancer Therapy–Prostate [FACT-P]):

The FACT-P questionnaire is a 39-item questionnaire consisting of 5 domains (physical well-being, social/family well-being, emotional well-being, functional well-being, and "additional concerns" [consisting of items relating to prostate cancer and its treatment]). Each item can be answered on a scale of 0–4. The sum of the score on the first 4 domains is the FACT-G (General) score. The sum of scores on all 5 domains constitutes the FACT-P score. Patients were defined as having a positive quality of life response for this endpoint if they had a 10-point improvement in their FACT-P score, compared with baseline, on 2 consecutive measurements obtained at least 3 weeks apart.

· PSA response rate

PSA response was defined as ≥ 50% or ≥ 90% reductions in PSA from baseline to lowest post-baseline PSA result, and was calculated by treatment group for patients with PSA values at the baseline assessment and at least 1 post-baseline assessment. A consecutive assessment that was conducted at least 3 weeks later was required to confirm PSA response.

· rate of pain palliation

In order to be included in the pain palliation analysis, patients must have had a stable and sufficient pain burden at study entry. Pain burden was measured by Question #3 of the Brief Pain Inventory–Short Form ("On a scale of 0 to 10, please rate your pain at its worst in the last 24 hours") averaged over the 7 days prior to randomisation. To be eligible for this analysis, patients must have had metastatic bone disease at baseline, provided answers to the above for a minimum of 4 out of 7 days in the baseline run-in period, had stable baseline pain (≤ 2-point variation in daily pain scores), had stable analgesic use (≤ 30% variation in analgesic use), and had an average pain score during the baseline run-in period of ≥ 4. Pain palliation was defined

8 Scher, H.I. et al., End Points and Outcomes in Castration-Resistant Prostate Cancer: From Clinical Trials to Clinical Practice. Journal of Clinical Oncology 2011; 29:3695-3704.
9 Scher, H.I. et al., Design and End Points of Clinical Trials for Patients With Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. Journal of Clinical Oncology 2008; 26:1148-1159.

as a ≥ 30% reduction in average pain score at Week 13 compared to baseline with a ≤ 30% increase in analgesic use.

Exploratory efficacy endpoints included:

- best overall soft tissue radiographic response,

In order to be eligible for the radiographic response analysis, patients must have had measurable disease at screening and at least 1 target lesion. The best overall radiographic response was assessed using RECIST v1.1 (Table 4). The same imaging studies used to determine time to radiographic progression were used to determine the best radiographic response. The best overall radiographic response was first assessed at Week 13, again at Week 25, and then every 12 weeks until death.

**Table 4: Time Point Response: Patients with Target (± Non-Target) Disease, Study CRPC2**

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|---|
| Complete response | Complete response | No | Complete response |
| Complete response | Not evaluated | No | Partial response |
| Complete response | Non-complete response/<br>Non-progressive disease | No | Partial response |
| Partial response | Not evaluated | No | Partial response |
| Stable disease | Non-progressive disease<br>or not all evaluated | No | Stable disease |
| Not all evaluated | Non-progressive disease<br>or not all evaluated | No | Inevaluable |
| Progressive disease | Any | Yes or no | Progressive disease |
| Any | Progressive disease | Yes or no | Progressive disease |
| Any | Any | Yes | Progressive disease |

From: Eisenhauer EA et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45(2):228-247.

- quality of life (European Quality of Life Five-Domain Scale [EQ-5D]),

The EQ-5D is a standardised instrument for use as a measure of health outcome. Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each assessed on 3-point categorical scales ranging from “no problem” to “severe problem”. Higher scores reflect worse quality of life. The EQ-5D was administered only at selected sites in Europe (France, United Kingdom, Germany, Italy, and Spain).

- the Eastern Cooperative Oncology Group (ECOG) Performance Status,

The ECOG performance status has 6 grades. 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.

- pain progression rate,

In order to be included in the pain progression rate analysis, patients must have had valid responses to Question #3 of the Brief Pain Inventory – Short Form ("On a scale of 0 to 10, please rate your pain at its worst in the last 24 hours") on at least 4 of the 7 days prior to randomisation, and during the 7 days preceding the Week 13 visit. Pain progression was defined as any increase in the average pain score at Week 13 compared to the baseline average pain score.

- time to pain progression,

For the endpoint of time to pain progression, pain progression was defined as an increase above baseline in the FACT-P pain assessment, which had to be confirmed by a second consecutive assessment 3 or more weeks later. The FACT-P pain assessment asks patients to respond to the statement, "I have pain," using the following scale: 0-Not at all; 1-A little bit; 2-Somewhat; 3-Quite a bit; and 4-Very much.

- circulating tumour cell count conversion rate.

According to the sponsor, the analysis plan and the report for circulating tumour cell counts, molecular profiling, and markers of bone turnover were not included in the clinical study report submitted for this application.

Assessments of endpoints were performed according the schedule provided in the study report.

For the end point of time to PSA progression, PSA progression was defined as ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir, with confirmation by a second consecutive value obtained ≥ 3 weeks later. For patients with no PSA decline at Week 13, the PSA progression date was defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the baseline was documented, which was confirmed by a second consecutive value ≥ 3 weeks later. For the endpoint of radiographic progression-free survival, the criteria for determining and confirming radiographic disease progression is presented in Table 5:

**Table 5: Criteria for Determining and Confirming Disease Progression**

| Evidence of Progression | Confirmation (6 Weeks Later) |
|---|---|
| Bone Disease<br>Appearance of 2 or more new bone lesions on bone scan | New lesions at the first scheduled reassessment at Week 13 must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should show additional new lesions compared to the Week 13 scan. |

| Evidence of Progression | Confirmation (6 Weeks Later) |
|---|---|
| Soft Tissue Disease<br>As defined by RECIST v1.1 on CT/MRI | Progression at the first scheduled reassessment at Week 13 must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should show progressively worsening disease compared to the Week 13 scan. |

Unless warranted sooner, disease progression was first assessed at Week 13 and if deemed present then to be confirmed at least 6 weeks later. Disease progression was assessed again at Week 25 and then every 12 weeks until death. This endpoint of radiographic progression-free survival was defined as the time from randomisation to radiographic progression (included both radiographic progression and death from any cause). For the endpoint of time to first skeletal-related event, a skeletal-related event was defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. An alteration of analgesic medication for bone pain was not considered a skeletal-related event.

> **Comments**: Overall, the primary and secondary endpoints are appropriate and consistent with the recommendations of the Prostate Cancer Clinical Trials Working Group 2 (PCWG2). The study primary and key secondary endpoints allowed evaluations of effect on survival (primary endpoint), changes in PSA (secondary endpoint of time to PSA progression), and bone and soft-tissue disease (secondary endpoints of radiographic progression-free survival, and time to first skeletal-related event), while the other endpoints allowed further characterisations of potential effects on symptoms (pain palliation, pain progression rate, time to pain progression), quality of life (FACT-P and EQ-5D) and functional status (ECOG performance status).

*7.1.1.1.5. Randomisation and blinding methods*

Patients were randomised to MDV3100 or placebo treatment groups in a 2:1 ratio, using a centrally administered, randomised, permuted block method and stratified by baseline ECOG performance status score (0-1 vs. 2) and baseline mean Brief Pain Inventory-Short Form Question #3 score (Brief Pain Inventory-Short Form Question #3: "On a scale of 0 to 10, please rate your pain at its worst in the last 24 hours") averaged over the 7 days prior to randomisation (< 4 vs. ≥ 4). Randomisation was done centrally using an Interactive Voice/Web Response System (IVRS/IWRS) on Study Day 1. The IVRS/IWRS assigned the patient a study drug bottle number available at the study site according to the randomisation code. The study was double-blind. Placebo capsules appeared identical to the MDV3100 capsules. All patients, investigators, site personnel, and the sponsor staff involved in the conduct of the study were blinded to treatment assignment.

*7.1.1.1.6. Analysis populations*

There were 3 main analysis population sets in the study. The Intent-To Treat (ITT) Population was defined as all randomised patients regardless of whether they received study drug. The Safety Population was defined as all randomised patients who had received at least 1 dose of study drug. The PK Population was defined as all randomised patients who had received at least 1 dose of MDV3100 and had at least one MDV3100, M1, or M2 plasma concentration result.

The primary efficacy endpoint and the key secondary efficacy endpoints were analysed using the ITT Population. The Safety Population and the PK Population were used for safety and PK analyses, respectively.

**Comments**: The definitions of the analysis populations and the efficacy analyses on the ITT population are in keeping with the TGA-adopted ICH E 9 Statistical Principles for Clinical Trials.

*7.1.1.1.7. Sample size*

It was estimated that an observed 650 deaths would provide approximately 90% power to detect a 3.7 month difference in median survival between MDV3100 and placebo (based on an estimated median survival for placebo of 12 months; estimated median survival for MDV3100 of 15.7 months; target hazard ratio of 0.76), using a 2-sided log-rank test with a 0.05 level of significance. Assuming all patients were followed for survival, it was calculated that the study would require approximately 1080 patients (720 MDV3100-treated patients, 360 placebo-treated patients) to achieve the targeted 650 deaths. To allow for up to 8% lost to follow-up, the sample size was set at 1170 patients (780 MDV3100- treated patients, 390 placebo-treated patients).

*7.1.1.1.8. Statistical methods*

The primary efficacy endpoint for this study was overall survival, defined as time from randomisation to death from any cause. The duration of overall survival was right-censored for patients who were lost to follow-up since randomisation (date of censoring was to be date of randomisation), or who were not known to have died at the data analysis cut-off date (this included patients who were known to have died after the data analysis cut-off date; date of censoring was to be the date last known alive or data analysis cut-off date, whichever occurred first). Analysis of overall survival results was planned at 2 major milestones. The first analysis was to occur when 520 death events were reported. If this interim analysis did not result in the halting of the study, another overall survival analysis was planned when 650 death events were reported.

A log-rank test, stratified by baseline ECOG performance status and mean Brief Pain Inventory-Short Form score (Question #3), was used as the primary analysis to compare the MDV3100 and the placebo groups, with a 2-sided test at the 0.05 level of significance. Kaplan-Meier median survival times and their 95% confidence intervals (CI) as well as survival curves were used for statistical description. In addition, the benefit of MDV3100 compared to placebo was evaluated by a single hazard ratio (MDV3100/placebo) with its 95% CI based on a stratified Cox regression model. A sensitivity analysis for overall survival was also conducted using an unstratified log-rank test. A single hazard ratio (MDV3100/placebo) with its 95% CI based on an unstratified Cox regression model was also provided. Pre-specified subgroup analyses of overall survival were performed to determine whether the treatment effect was concordant among subgroups[10].

The key secondary analyses in this study were the comparison between treatment arms of time to PSA progression, of radiographic progression-free survival, and of time to first skeletal-related event between treatment arms. These key secondary analyses were to be performed only if MDV3100 therapy had resulted in a statistically significant prolongation of overall survival (i.e. a statistically significant primary efficacy analysis in favour of MDV3100) at the time of the interim analysis (2-sided $p < 0.0244$) or at the final analysis (2-sided $p < 0.0429$). The testing of the key secondary endpoints was conducted in the fixed sequence listed above

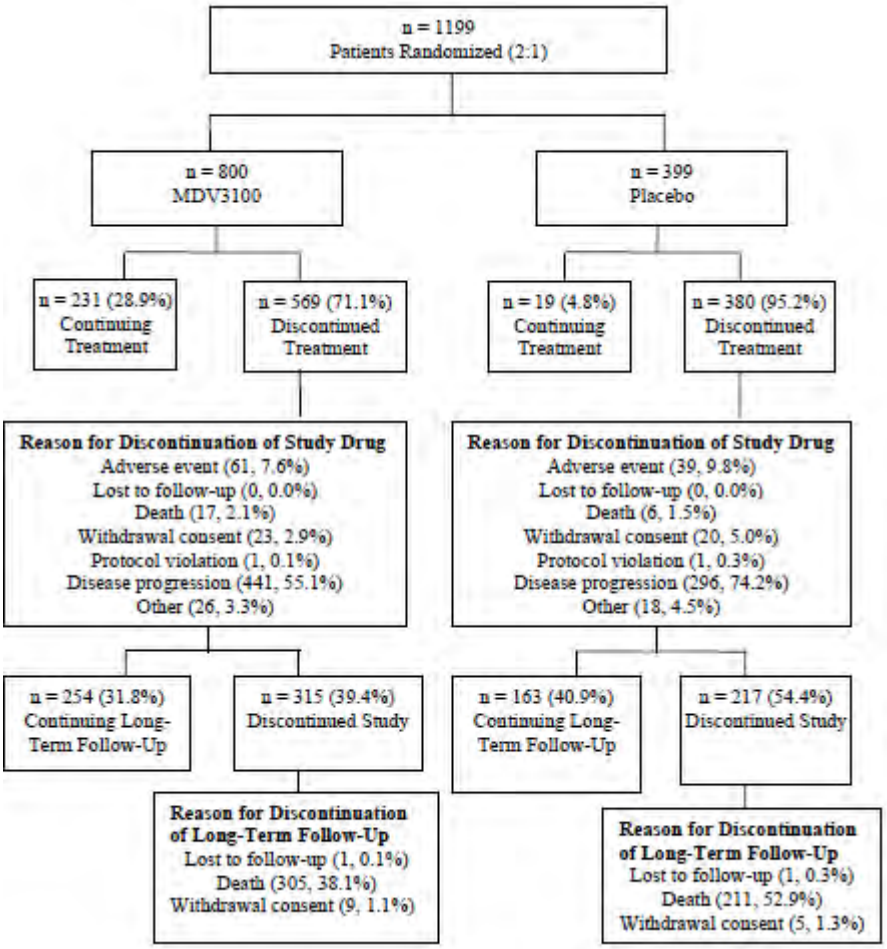
[10] The subgroups were ECOG performance status at study entry (0 or 1 vs. 2); average pain score based on Question 3 of the Brief Pain Inventory-Short Form at study entry (< 4 vs. ≥ 4); age (< 65 vs. ≥ 65); geographic region (North America vs. Europe vs. rest of the world); gleason score at diagnosis (≤ 7 vs. ≥ 8); number of prior chemotherapy regimens (1 vs. ≥ 2); type of progression at study entry (PSA progression only vs. radiographic progression with or without PSA progression); visceral disease at study entry (yes vs. no); baseline PSA value (≤ median vs. > median); baseline lactacte dehydrogenase value (≤ median vs. > median); and baseline haemoglobin value (≤ median vs. > median). According to the sponsor, these subgroups were selected because they were prognostic factors for prostate cancer, demographic features of interest, or represented different regional practice patterns.

such that if statistical significance (2-sided $p < 0.05$) was not achieved for 1 of the endpoints, all key secondary endpoints following in the sequence were not to be considered statistically significant for purposes of regulatory evaluation. For each of the 3 key secondary analyses, a log-rank test, stratified by baseline ECOG performance status and mean Brief Pain Inventory-Short Form score (Question #3), with a 2-sided test at the 0.05 level of significance, was used to compare the MDV3100 treatment group and the placebo group.

*7.1.1.1.9. Participant flow*

Between 22 September 2009 (study start date) and 15 November 2010 (last-patient-enrolled date), 1199 patients were randomised into the study: 800 into the MDV3100 arm, and 399 into the placebo arm (Figure 4 below).

**Figure 4: Patient Disposition Flow Chart as of 25 September 2011, ITT Population, Study CRPC2**




A summary of the analysis population datasets is presented in the study report.

*7.1.1.1.10. Major protocol violations/deviations*

Overall, the proportion of patients with protocol deviations was comparable between treatment groups (14.6% and 12.5% in the MDV3100 and placebo groups, respectively). The most common types of protocol deviations reported were not meeting an eligibility or exclusion criteria (7.5% in each treatment group), and receiving an excluded concomitant medication (7.0% and 5.5% in the MDV3100 and placebo groups, respectively). The most common types of deviations related to eligibility or exclusion criteria were clinically significant cardiovascular disease (1.8% and 1.3% in the MDV3100 and placebo groups, respectively), received a medication known to lower the seizure threshold or prolong the QT interval (1.3% and 1.0%,

respectively), more than 2 prior chemotherapy regimens (0.9% and 0.8%, respectively) and history of another malignancy (0.6% and 0.5%, respectively).

In the study, patients were asked to bring back all remaining study drug and all study drug packaging at each study visit. Treatment compliance was defined as the number of capsules taken during the study divided by the expected number of capsules, multiplied by 100%. Capsules that were not returned were considered to have been taken, unless otherwise specified in the comments section of the Case Report Form. Overall compliance with protocol-defined therapy was high. The percentage of patients with < 80% compliance was low in both treatment groups (0.9% and 1.3% in the MDV3100 and placebo groups, respectively).

*7.1.1.1.11. Baseline data*

Baseline demographic characteristics were comparable between treatment groups. The majority of subjects in each treatment group were White (93.1% and 91.7% in the MDV3100 and placebo groups, respectively). The median age was 69.0 years in both groups, with 24.9% and 26.1% of patients in the MDV3100 and placebo groups, respectively, being ≥ 75 years old. Baseline mean weight was similar between treatment groups (mean [SD] weight of 84.2 [14.51] and 85.0 [15.56] kg, respectively).

Baseline disease characteristics were also comparable between treatment groups. Overall, the median time from initial diagnosis of prostate cancer to randomisation was 70.9 months, 51.1% of patients had a Gleason score[11] of 8–10 at the time of diagnosis, 98.3% of patients had a Gleason score of 5–10 at the time of diagnosis, 62.2% of patients entered the study with both bone and soft tissue metastases, and 91.2% of patients entered the study with bone metastases. Prior therapy for prostate cancer was similar between treatment groups. Overall, the median number of cycles of prior docetaxel received was 8.0, and the median time from last docetaxel exposure to randomisation was 6.0 months.

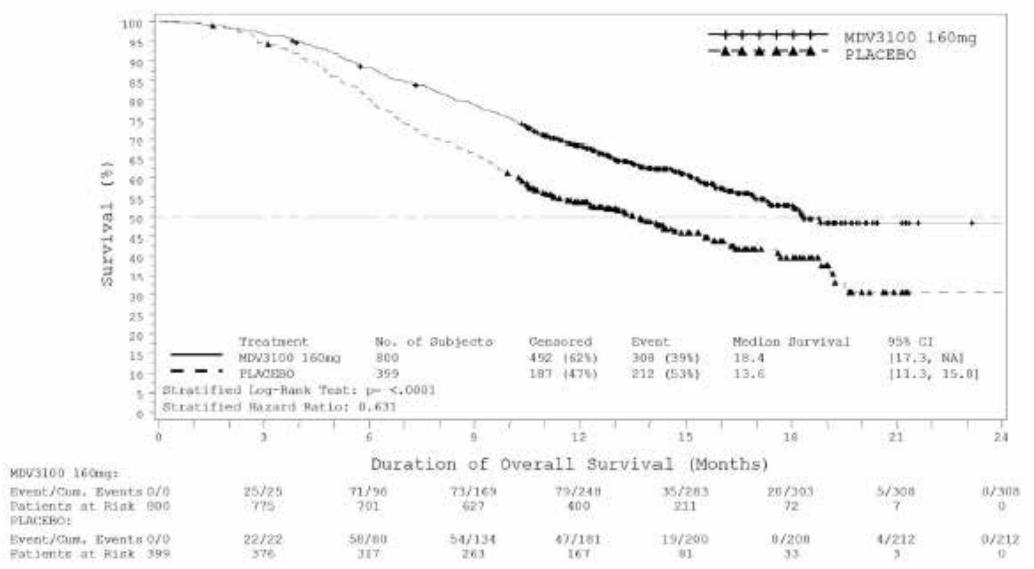
> **Comments**: Overall, the baseline demographic and disease characteristics were comparable between treatment groups. The study population was representative of the target population of patients with advanced CRPC, with an overall median age of 69.0 years, and where 98.3% had a Gleason score of 5–10 at the time of diagnosis, and 91.2% had entered the study with bone metastases.

*7.1.1.1.12. Results for the primary efficacy outcome*

At the time of the data cut-off (25 September 2011), 308 deaths (38.5%) had occurred among patients in the MDV3100 group and 212 deaths (53.1%) had occurred among patients in the placebo group. Stratified analysis of overall survival showed a statistically significant increase in the duration of survival among patients treated with MDV3100 compared with patients treated with placebo ($p < 0.0001$). Median survival was 18.4 months in the MDV3100 group, compared with 13.6 months in the placebo group. The stratified hazard ratio for death for MDV3100-treated patients relative to placebo was 0.631 (95% CI: 0.529, 0.752), indicating a 37% decrease in the risk of death for patients receiving MDV3100 compared to those receiving placebo. Unstratified results for both the log-rank test and the hazard ratio were consistent with the primary stratified results. Kaplan-Meier curves for duration of survival are shown in Figure 5:

[11] Gleason score on aggressiveness of prostate cancer. Score of 2-4: low; score of 5-6: moderate; score of 7: intermediate; score of 8-10: high

**Figure 5: Duration of Survival: Intent-to-Treat Population, Study CRPC2**




*7.1.1.1.13. Results for other efficacy outcomes*

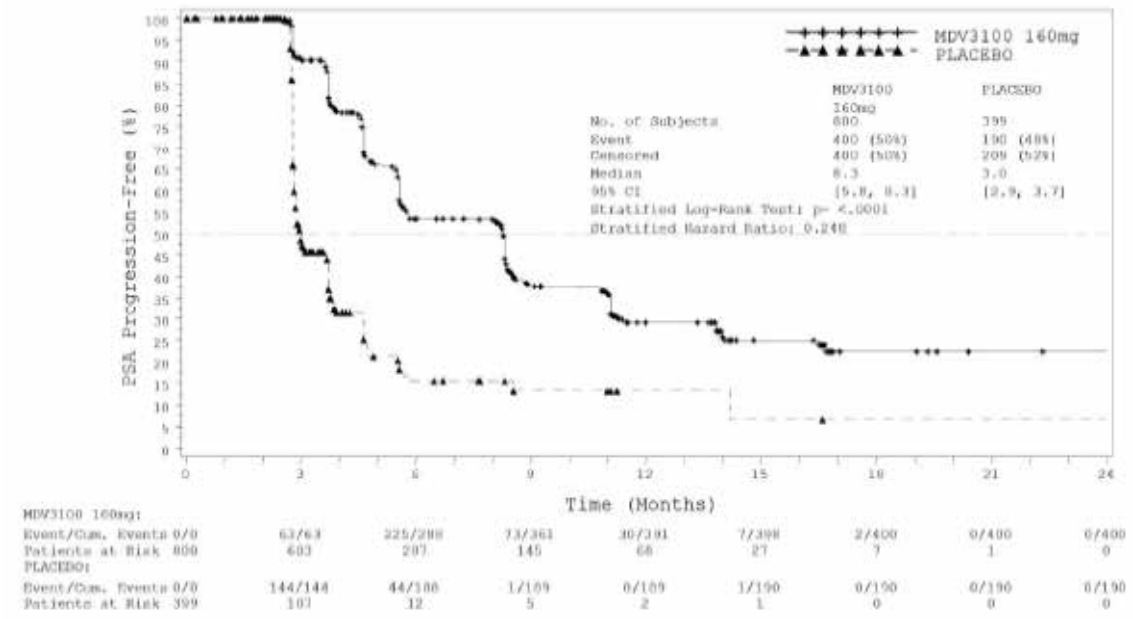
· Subgroup analyses on the primary efficacy endpoint

Subgroup analyses of overall survival yielded results that were consistent with the primary efficacy analysis in the overall study population, with survival benefit of MDV3100 over placebo seen in all pre-specified patient subgroups.

· Key secondary endpoints

A total of 400 (50.0%) patients in the MDV3100 group and 190 (47.6%) patients in the placebo group experienced PSA progression. Stratified analysis showed a statistically significant increase in time to PSA progression among MDV3100 treated patients compared with placebo-treated patients ($p < 0.0001$). Median time to PSA progression was 8.3 months in the MDV3100 group, compared with 3.0 months in the placebo group. The stratified hazard ratio for time to PSA progression in the MDV3100 group relative to the placebo group was 0.248 (95% CI: 0.204, 0.303). Kaplan-Meier curves for time to PSA progression are presented in Figure 6:

**Figure 6: Time to PSA Progression: Intent-to-Treat Population, Study CRPC2**



A total of 524 (65.5%) patients in the MDV3100 group and 337 (84.5%) patients in the placebo group experienced radiographic progression or death. Stratified analysis showed a statistically significant increase in time to radiographic progression among MDV3100-treated patients compared with placebo-treated patients ($p < 0.0001$). Median duration of radiographic progression-free survival was 8.3 months in the MDV3100 group, compared with 2.9 months in the placebo group. The stratified hazard ratio for time to radiographic progression in the MDV3100 group relative to the placebo group was 0.404 (95% CI: 0.350, 0.466). Kaplan-Meier curves for radiographic progression-free survival are presented in the clinical study report.

A total of 287 (35.9%) patients in the MDV3100 group and 161 (40.4%) patients in the placebo group experienced skeletal-related events. Stratified analysis showed a statistically significant increase in time to first skeletal-related events among MDV3100-treated patients compared with placebo-treated patients ($p = 0.0001$). Median time to first skeletal-related events was 16.7 months in the MDV3100 group, compared with 13.3 months in the placebo group. The stratified hazard ratio for time to first skeletal-related event in the MDV3100 group relative to the placebo group was 0.688 (95% CI: 0.566, 0.835). Kaplan-Meier curves for time to first skeletal-related event are presented in the clinical study report.

- Other secondary endpoints

For the endpoint of response rate for quality of life (FACT-P), patients were defined as having a quality of life response if they had a 10-point improvement in their global FACT-P score compared with baseline, on 2 consecutive measurements obtained at least 3 weeks apart. The response rate for quality of life (FACT-P) among MDV3100-treated patients was 43.2%, compared to 18.3% among placebo treated patients. The difference in response rate of 24.9% was found to be statistically significant ($p < 0.0001$).

For the endpoint of PSA response rate, the 50% PSA response rate[12] among MDV3100-treated patients was 54.0%, compared to 1.5% among placebo-treated patients. The difference in response rate of 52.5% was found to be statistically significant ($p < 0.0001$). The 90% PSA response rate[13] among MDV3100-treated patients was 24.8%, compared to 0.9% among placebo-treated patients. The difference in response rate of 23.9% was also found to be statistically significant ($p < 0.0001$).

Analysis of pain palliation[14] showed that the rate of pain palliation among MDV3100-treated patients was 44.9% compared to 6.7% among placebo-treated patients. The difference in rate of pain palliation of 38.2% was found to be statistically significant ($p = 0.0079$). It is noted that the sample size for this analysis was small (N=49 in MDV3100 group; N=15 in placebo group), affecting the ability to draw definitive conclusions. The sponsor had provided the reasons for the small sample size, that the pre-specified requirements to be evaluable for this analysis were that a patient had to have metastatic bone disease at baseline, provided answers to Question #3 of the Brief Pain Inventory-Short Form for a minimum of 4 out of 7 days in the baseline run-in period, had stable baseline pain (no greater than a 2-point variation in daily pain scores), had stable analgesic use (no greater than 30% variation in analgesic use), and had an average pain score during the baseline run-in period of ≥ 4. While there were 228 patients (28.5%) in the MDV3100 group and 104 patients (26.1%) in the placebo group who met the second and fifth criteria for this analysis, there were eventually only 49 patients (6.1%) in the MDV3100 group and 15 patients (3.8%) in the placebo arm who met all 5 criteria. The sponsor had observed that the main reason for this discrepancy was unusable analgesic dose information recorded in the pain diary making it impossible to strictly evaluate many patients for stable analgesic use over time.

[12] i.e. patients with ≥ 50% reduction in PSA from baseline to lowest post-baseline PSA result
[13] i.e. patients with ≥ 90% reduction in PSA from baseline to lowest post-baseline PSA result
[14] Palliation was defined as ≥ 30% reduction in average pain score at Week 13 compared to baseline without a ≥ 30% increase in analgesic use.

· Exploratory endpoints

The analysis of best overall soft tissue radiographic response showed that the investigator-assessed objective radiographic response rate among MDV3100-treated patients was 28.9%, compared with 3.8% for placebo-treated patients. The difference in radiographic response rate of 25.08% was found to be statistically significant ($p < 0.0001$).

Analyses on the quality of life over time using the EQ-5D were difficult to interpret due to the small sample size of evaluable patients and the large decrease in the number of patients completing the questionnaire over time. The EQ-5D scores were generally comparable between both treatment groups. As pre-specified in the statistical analysis plan (SAP), no statistical tests were performed on these analyses.

Analyses on the ECOG performance status over time showed that the mean ECOG performance status deterioration from baseline was greater in the placebo group compared with the MDV3100 group, across all assessed time points (Weeks 9, 17, 25, 37 and 49). As pre-specified in the SAP, no statistical tests were performed on these analyses.

Analyses on pain progression rate showed that the proportion of patients with pain progression[15] at Week 13 was 27.8% in the MDV3100 group compared 39.0% in the placebo group. The difference in pain progression rate of 11.2% in favour of MDV3100 was found to be statistically significant ($p = 0.0018$).

In the analyses on time to pain progression, a total of 141 (17.6%) patients in the MDV3100 group and 57 (14.3%) patients in the placebo group experienced pain progression[16]. Stratified analysis showed a statistically significant increase in time to pain progression among MDV3100-treated patients compared with placebo-treated patients ($p=0.0004$). The stratified hazard ratio for time to pain progression in the MDV3100 group relative to the placebo group was 0.564 (95% CI: 0.409, 0.777).

### 7.1.2. Other efficacy studies

#### *7.1.2.1. Study S-3100-1-01*

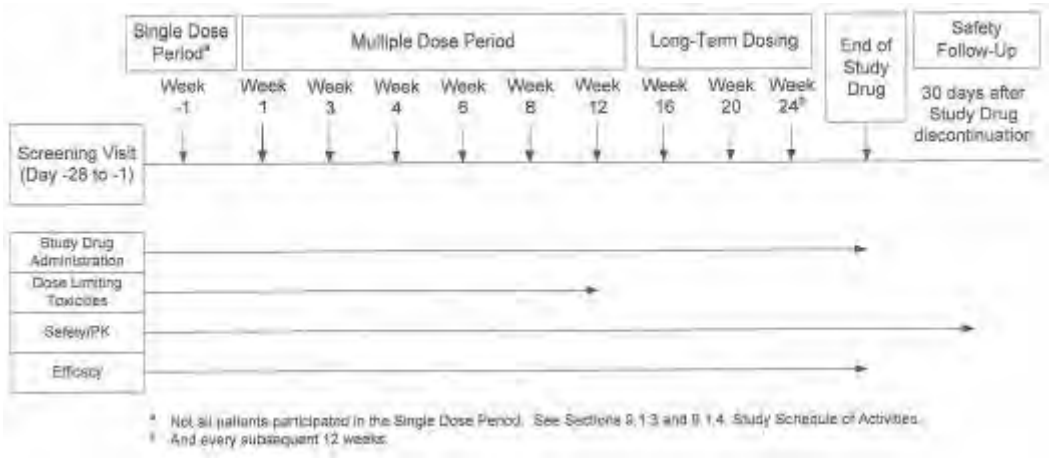
Study S-3100-1-01 was a multi-centre (5 centres in the US), Phase I, open-label, uncontrolled, dose-escalation safety and PK study of MDV3100 with dose-expansion at the tolerated doses, in patients with CRPC. The primary objective was to determine the safety and tolerability profile of MDV3100, including the dose-limiting toxicities, and the maximum tolerated dose when administered orally to patients with CRPC. The study start date (first patient enrolled) was 23 July 2007 and the last- patient-enrolled date was 08 December 2008. The study was ongoing at the time of this submission. Data cut-off date for the CSR submitted was 01 September 2010.

The study consisted of 4 periods: the Single-Dose Period, the Multiple-Dose Period, the Long-Term Dosing Period, and the Safety Follow-Up Period (Figure 7).

[15] Pain progression for this analysis was defined as any increase in the average pain score at Week 13 compared to the baseline average pain score. The pain score used for this analysis was the average of responses to Question #3 from the Brief Pain Inventory-Short Form ("On a scale of 0 to 10, please rate your pain at its worst in the last 24 hours").

[16] Pain progression for this analysis was defined as an increase above baseline in the FACT-P pain assessment, which must have been confirmed by a second consecutive assessment obtained 3 or more weeks later.

**Figure 7: Study Periods, Study S-3100-1-01**




At the initiation of each cohort, patients received a single-dose of the study drug, MDV3100, and were then followed for 6 days (Single-Dose Period). Patients then entered the Multiple-Dose Period where they received the same dose of MDV3100 as they received in the Single-Dose Period for 84 days. The Multiple-Dose Period was then followed by the Long-Term Dosing Period. In the actual study conduct, during the Long-Term Dosing Period, at the time when the maximum tolerated dose was determined to be 240 mg daily, patients taking doses higher than the maximum tolerated dose had their doses decreased to this maximum tolerated dose (i.e. 240 mg/day). Patients taking doses lower than the maximum tolerated dose were allowed to have their doses increased. Once the optimal dose for Phase III was selected (160mg/day), all patients had their doses lowered to this dose (i.e. 160 mg/day).

There were 2 different study cohorts: the dose-escalation cohort, which included a minimum of 3 patients per dose evaluated for dose-limiting toxicities prior to dose-escalation, and the dose-expansion cohort, which allowed enrolment of up to 24 additional patients at each dose to obtain further safety and efficacy data. In the dose-escalation cohorts, doses of 30, 60, 150, 240, 360, 480, and 600 mg daily were studied in 7 cohorts of patients (each cohort were to comprise of 3 to 6 patients). A minimum of 3 patients were enrolled per dose-escalation cohort. If 1 of the first 3 patients within a dose-escalation cohort experienced a protocol-defined dose-limiting toxicity, an additional 3 patients were enrolled at the same dose prior to escalating to the next dose. Subsequent doses were determined by safety and PK data from prior cohort(s). A decision to dose-escalate was made after the previous dose was proven tolerable in the previous dose-escalation cohort, following completion of at least 28 days in the Multiple-Dose Period. Dose escalation was to continue until the tentative maximum tolerated dose was determined or until a dose of 600 mg/day was evaluated.

With regards to the dose-expansion cohorts, once dose escalation had occurred, the previous cohort was expanded to further define safety, as well as PSA response and PSA response duration.

Patients in the dose-expansion cohorts did not participate in the Single-Dose Period, but initiated treatment in the Multiple-Dose Period. Dose-expansion cohorts occurred for doses of 60 mg/day and higher. For doses of 60 to 360 mg/day, up to 24 additional patients were added at each dose level, of which 12 were chemotherapy-naïve and 12 were previously treated with chemotherapy (1 or 2 regimens, which must have included docetaxel). For doses higher than 360 mg/day, up to 24 additional patients previously treated with chemotherapy only were to be enrolled.

The final maximum tolerated dose was defined as the dose below the intolerable dose determined from the dose-escalation phase of the study. For doses of 60 to 360 mg/day, the final maximum tolerated dose was required to have been evaluated and found tolerable in a

dose-expansion cohort of 12 chemotherapy-naïve patients and 12 patients previously treated with chemotherapy followed through at least 28 days of the Multiple-Dose Period. Tolerability was defined as less than 4 out of12 chemotherapy-naïve and less than 4 out of 12 post-chemotherapy patients reporting a dose-limiting toxicity within the first 28 days of treatment. For doses higher than 360 mg/day, tolerability was defined as less than 8 out of 24 patients previously treated with chemotherapy experiencing a dose-limiting toxicity within the first 35 days of treatment.

Study inclusion and exclusion criteria were generally similar to those of Study CRPC2, except that previous docetaxel therapy was not part of the inclusion criteria for all patients. The study enrolled men with CRPC and the main inclusion criteria were subjects with histologically or cytologically confirmed adenocarcinoma of the prostate, who had ongoing androgen deprivation therapy with a GnRH analogue or inhibitor, or orchiectomy (i.e. surgical or medical castration), with serum testosterone level < 50 ng/dL at screening, who had progressive disease[17] after medical or surgical castration, with or without a trial of anti-androgen therapy and withdrawal. Patients previously treated with chemotherapy must have had no more than 2 prior chemotherapy regimens with at least 1 regimen containing docetaxel. A full list of inclusion and exclusion criteria is presented in the study report.

MDV3100 was initially supplied as 30 mg hard gelatin capsules. Over the course of the study, the capsule presentation was changed to 40 mg soft gelatin capsules. All patients enrolled in the study received treatment with MDV3100 orally. The doses evaluated were 30, 60, 150, 240, 360, 480, and 600 mg/day. All patients took their MDV3100 dose as a single administration, except for patients in the 480 and 600 mg/day groups who were instructed to take the dose in 2 divided doses. Capsules were to be taken in the morning with breakfast at approximately the same time each day, with the second dose taken with dinner for those patients assigned to the 480 and 600 mg/day groups. Patients were considered to have completed the study if they completed the Multiple-Dose Period, however, they continued to receive therapy on an ongoing basis in the Long-Term Dosing Period, provided they did not experience disease progression or unacceptable drug-related toxicity. For patients who experienced a Grade 3 or 4 toxicity that was not a dose-limiting toxicity, treatment was temporarily held until the severity of toxicity decreased to Grade 1 or lower. Study drug could then be restarted at a lower dose. Patients with evidence of disease progression were allowed to initiate re-treatment with MDV3100 at a higher dose, but only if the patient continued to meet the study eligibility criteria and only after agreement by the Medical Monitor and the Investigator.

Efficacy analyses included a description of the changes in PSA, disease progression on imaging, circulating tumour cell counts, and bone turnover markers (serum bone-specific alkaline phosphatase [ALP] and urinary N-telopeptide). Efficacy analyses were performed on the Safety Population, which consisted of all enrolled patients who received at least 1 dose of study drug.

Overall, 140 patients were enrolled and analysed. The majority were White (96.4%), with an overall median age of 68 years, and 84% had Gleason score of ≥ 7 at diagnosis.

The percentage of patients who experienced any PSA decrease from baseline, ≥ 30%, ≥ 50%, and ≥ 90% decreases at 12 weeks (i.e. end of Multiple-Dose Period) and at time of PSA nadir is presented in the study report. Results showed that at 12 weeks, 69.8% of patients without previous chemotherapy, and 54.0% of patients with previous chemotherapy had a ≥ 50% decrease in PSA levels as compared with baseline. The median time to PSA progression was not reached in patients without previous chemotherapy. The median time to PSA progression was 316 days (10.4 months) in patients with previous chemotherapy. In patients with measurable

[17] Disease progression for study entry was defined as 1 or more of the following 3 criteria: PSA progression, defined by a minimum of 3 rising PSA levels with an interval of ≥ 1 week between each determination (PSA value at the Screening visit was to have been ≥ 2 ng/mL); soft tissue disease progression, defined by RECIST, v1.1; bone disease progression, defined by 2 or more new lesions on bone scan

disease at study entry, 71.0% of those without previous chemotherapy had partial responses or stable disease in radiographically-evident soft tissue and bone lesions as their best radiographic response. In patients with previous chemotherapy, 54.8% had partial responses or stable disease as their best radiographic response. Overall, of the 121 patients who were evaluable for the effect on circulating tumour cell counts, 72 patients (60%) had favourable circulating tumour cell counts at baseline (< 5 circulating tumour cells per 7.5 mL blood), and of these, 56 (77.8%; 56/72) maintained favourable circulating tumour cell counts post-baseline. Of the 49 patients who had unfavourable circulating tumour cell counts at baseline (≥ 5 circulating tumour cells per 7.5 mL of blood), 21 (42.9%; 21/49) converted on study to favourable circulating tumour cell counts. With regards to effect on bone turnover markers, 74.8% of patients (86.8% without previous chemotherapy and 65.7% with previous chemotherapy) had some reduction in bone-specific ALP after initiation of MDV3100 treatment, while 54.9% of patients (70.8% without previous chemotherapy and 43.1% with previous chemotherapy) had some reduction in urinary N-telopeptide.

#### *7.1.2.2. Study CRPC-MDA-1*

This was a single-centre (the US), single arm, open-label study of patients with metastatic progressive CRPC treated with oral MDV3100 (160 mg/day) evaluating the tumour micro-environment. The primary objective was to explore the effect of treatment with MDV3100 on androgen receptor signalling and expression of survival/resistance pathways in the bone marrow metastases of CRPC patients in correlation with measures of antitumour activity to identify predictors of response or resistance to therapy. Secondary objectives were to explore the antitumour activity of treatment with MDV3100 as assessed by serum PSA levels, imaging of soft tissue and bone metastases, and markers of bone metabolism, and to determine the safety and tolerability of treatment with MDV3100. The study start date (first patient enrolled) was 18 February 2010 and the last-patient-enrolled date was 01 July 2011. The study was ongoing at the time of this submission. Data cut-off date for the CSR submitted was 26 August 2011.

Study inclusion and exclusion criteria were generally similar to those of Study CRPC2, except that previous docetaxel therapy was not part of the inclusion criteria. The study enrolled men with CRPC who had metastatic bone disease and the main inclusion criteria were subjects with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features, who had metastatic disease to the bone, who had ongoing androgen deprivation therapy with a GnRH analogue or orchiectomy (i.e. surgical or medical castration), with serum testosterone level < 50 ng/dL at screening, and who had progressive disease[18]. Patients previously treated with chemotherapy must have had no more than 2 prior chemotherapy regimens. A full list of inclusion and exclusion criteria is presented in the clinical study report.

In this study, patients took oral doses of MDV3100 (160 mg; four 40 mg capsules) once daily.

MDV3100 could be taken with or without food. In the absence of unacceptable toxicities, patients were treated until disease progression.

Efficacy endpoints were PSA levels, time to treatment discontinuation, and plasma and urine markers of bone turnover (urinary N-telopeptide and bone-specific ALP). In addition, blood and bone marrow samples (bone marrow biopsies were performed on Day 1 [baseline] and Week 9 [Day 57]) were assessed for testosterone and dihydrotestosterone levels and these were correlated with PSA response. Immunohistochemistry for androgen receptor in the bone marrow samples was also performed and subcellular distribution of androgen receptor was recorded (membranous, cytosolic, nuclear, or combination). The sponsor had stated that the

[18] Disease progression for study entry was defined as 1 or more of the following 3 criteria: PSA progression, as defined by a minimum of 3 rising PSA levels with an interval of ≥ 1 week between each determination (PSA value at the Screening visit was to have been ≥ 2 ng/mL); soft tissue disease progression, as defined by RECIST, v1.1; bone disease progression, as defined by 2 or more new lesions on bone scan

sampling of plasma and bone marrow testosterone and dihydrotestosterone levels and the subcellular localisation of androgen receptor in the bone marrow samples were considered experimental and exploratory.

Overall, 60 patients were enrolled and treated. Thirteen of the 60 patients were still enrolled on study and continued to receive MDV3100 therapy as of the data cut-off date (26 August 2011) for the CSR submitted. Fifty-six of the 60 patients (93.3%) were on study drug and participated in the study through the Week 9 visit assessments. The majority of the study population were White (88.3%). Overall median age was 69.5 years, 58.3% had Gleason score of ≥ 8 at diagnosis, and 77.3% had prior therapy with docetaxel.

The percentage of patients who experienced any PSA decrease from baseline, ≥ 50%, and ≥ 90% decreases from baseline at Week 9 and at time of PSA nadir is presented in the clinical study report. Results showed that 41.1% and 21.4% of patients had ≥ 50%, and ≥ 90% decreases from baseline at Week 9, respectively. Out of the 58 patients treated with MDV3100 who had a baseline and at least 1 post-baseline PSA, 74.1% had a reduction from baseline in PSA levels, 46.6% had a ≥ 50% and 22.4% had a ≥ 90% maximum reduction from baseline in PSA levels. Among patients in this study who had not received previous docetaxel and had a baseline and at least 1 post-baseline PSA (n = 16), 43.8% had a ≥ 50% and 31.3% had a ≥ 90% maximum reduction from baseline in PSA levels. Among patients in this study who received previous docetaxel chemotherapy and had a baseline and at least 1 post-baseline PSA (n = 42), 47.6% had a ≥ 50% and 19.0% had a ≥ 90% maximum reduction from baseline in PSA levels.

The median time to treatment discontinuation for the 60 patients with CRPC in this study was 5.0 months. There were no significant changes in mean levels of urinary N-telopeptide with MDV3100 therapy over time. Serum bone-specific ALP levels decreased from Week 33 through Week 57.

Plasma and bone marrow testosterone and dihydrotestosterone analyses showed that both mean plasma testosterone and dihydrotestosterone levels increased from baseline to Week 9 (0.15 ng/mL at baseline vs. 0.24 ng/mL at Week 9 for testosterone, $p < 0.0001$; 0.01 vs. 0.02 ng/mL for dihydrotestosterone, $p = 0.0140$). Mean bone marrow testosterone levels also increased from baseline to Week 9 (0.09 vs. 0.14 ng/mL, $p = 0.0010$), but no difference was seen in the mean bone marrow dihydrotestosterone level, likely due to the large number of samples below the lower limit of quantitation. The sponsor had offered a hypothesis that the observed increase in testosterone could be an adaptive biologic response to effective androgen receptor signalling inhibition.

There was no statistically significant difference observed in plasma testosterone and dihydrotestosterone levels at Week 9 in PSA responders (defined by a ≥ 50% reduction from baseline in PSA at Week 9) compared with PSA non-responders (testosterone: mean change from baseline of 0.12 ng/ml in PSA responders vs. 0.07 ng/ml in PSA non-responders [$p = 0.168$]; dihydrotestosterone: mean change from baseline of 0.02 vs. 0.01 ng/ml [$p = 0.221$]). There was also no statistically significant difference observed in bone marrow testosterone and dihydrotestosterone levels at Week 9 in PSA responders as compared with PSA non-responders (testosterone: mean change from baseline of 0.05 vs. 0.05 ng/ml [$p = 0.9427$]; dihydrotestosterone: mean change from baseline of -0.01 vs. 0.00 ng/ml [$p = 0.3370$]).

Bone marrow samples were considered eligible for assessment of androgen receptor expression by immunohistochemistry if paired bone marrow samples were obtained at both the baseline and Week 9 visits (55/60 [91.7%]) and both paired baseline and Week 9 bone marrow samples had prostate cancer cells observed (23/60 [38.3%]). The paired specimens also had to have adequate immunohistochemistry results (16/60 [26.7%]). Of these 16 patients who were evaluable for assessment of bone marrow androgen receptor expression by immunohistochemistry, 5 were PSA responders and 11 were PSA non-responders. Of the evaluable 5 PSA responders, all 5 showed reduction in nuclear androgen receptor localisation.

Of the evaluable 11 PSA non-responders, 2 showed reduction in nuclear androgen receptor localisation and 9 showed no change or increase in nuclear androgen receptor localisation. Statistical correlation was not assessed due to low numbers of evaluable patients.

### 7.2. Analyses performed across trials (pooled analyses and meta-analyses)

Not applicable.

### 7.3. Evaluator's conclusions on clinical efficacy for the indication of treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel

Overall, the study design, study inclusion and exclusion criteria, and study endpoints of the pivotal Phase III study (CRPC2) were appropriate. The study primary endpoint allowed evaluation of the effect of MDV3100 on survival, while the key secondary endpoints allowed evaluations of effect on changes in PSA and on bone and soft-tissue disease. Other study endpoints allowed further characterisations of potential effects on pain, quality of life and functional status. Baseline demographic and disease characteristics were comparable between treatment groups, and were generally consistent with the target patient population.

Primary efficacy analysis showed that there was a statistically significant increase in the duration of overall survival among patients treated with MDV3100 compared with patients treated with placebo (median survival duration of 18.4 months with MDV3100 vs. 13.6 months with placebo; $p < 0.0001$). The stratified hazard ratio for death for MDV3100-treated patients relative to placebo was 0.631, indicating a 37% decrease in the risk of death for patients receiving MDV3100 compared to those receiving placebo. There was also a statistically significant increase in time to PSA progression among MDV3100 treated patients compared with placebo-treated patients (median time to PSA progression of 8.3 months with MDV3100 vs. 3.0 months with placebo; $p < 0.0001$). The stratified hazard ratio for time to PSA progression in the MDV3100 group relative to the placebo group was 0.248, indicating a 75% decrease in the risk of PSA progression for patients receiving MDV3100 compared to those receiving placebo.

In terms of effect on bone and soft tissue disease, study results showed that the time to radiographic progression was statistically significantly longer in MDV3100-treated patients compared with placebo-treated patients (median duration of radiographic progression-free survival of 8.3 months with MDV3100 vs. 2.9 months with placebo; $p < 0.0001$). The stratified hazard ratio for time to radiographic progression in the MDV3100 group relative to the placebo group was 0.404, indicating a 60% decrease in the risk of radiographic progression with MDV3100 compared to placebo. The time to first skeletal-related events was also statistically significantly longer among MDV3100-treated patients compared with placebo-treated patients (median time to first skeletal-related events of 6.7 months with MDV3100 vs. 13.3 months with placebo; $p = 0.0001$). The stratified hazard ratio for time to first skeletal-related event in the MDV3100 group relative to the placebo group was 0.688, indicating a 31% decrease in the risk of skeletal-related events with MDV3100 compared to placebo. The proportion of patients whose best overall soft tissue radiographic response was complete or partial response was 28.9% in the MDV3100 group compared with 3.8% in the placebo group (difference of 25.08%; $p < 0.0001$).

With regards to the effect on pain, the rate of pain palliation at Week 13 was 44.9% among MDV3100-treated patients, compared to 6.7% among placebo-treated patients (difference of 38.2%; $p = 0.0079$). The proportion of patients with pain progression at Week 13 was 27.8% in the MDV3100 group compared to 39.0% in the placebo group (difference of 11.2%; $p = 0.0018$). In terms of effect on quality of life, the FACT-P response rate was 43.2% with MDV3100 compared to 18.3% with placebo (difference of 24.9%; $p < 0.0001$). However, the EQ-5D scores were generally comparable between both treatment groups, although analyses on the quality of

life over time using the EQ-5D were difficult to interpret due to the small sample size of evaluable patients and the large decrease in the number of patients completing the questionnaire over time. In terms of effect on functional status, analyses on the ECOG performance status over time showed that the mean ECOG performance status deterioration from baseline was greater in the placebo group compared with the MDV3100 group, across all assessed time points (Weeks 9, 17, 25, 37 and 49).

Results of the supportive efficacy studies (S-3100-1-01 and CRPC-MDA-1) were generally supportive of the results in the pivotal study. Results in Study S-3100-1-01 showed that 62.1% of the overall study population had a ≥ 50% decrease in PSA levels from baseline. This effect was seen in patients with and without previous chemotherapy (69.8% of patients without previous chemotherapy and 54.0% of patients with previous chemotherapy had a ≥ 50% decrease in PSA levels from baseline). Results in Study CRPC-MDA-1 showed that 41.1% of overall study population had ≥ 50% decrease from baseline at Week 9. In Study S-3100-1-01, the proportion of patients whose best overall radiographic response was partial or stable response was 61.6% in the overall study population. This proportion was 71.0% in patients without previous chemotherapy, and 54.8% in patients with previous chemotherapy.

# 8. Clinical safety

## 8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

### 8.1.1. Pivotal efficacy study

In the pivotal efficacy study (CRPC2), the following safety data were collected:

- General adverse events (AEs) were assessed by the investigator obtaining and recording all AEs at each scheduled visit. AEs were collected for 30 days after the patient's last dose of study drug or prior to the initiation of another systemic antineoplastic therapy, whichever occurred first.
- AEs of special interest were not pre-specified in the protocol. Based on analyses of AEs in Study CRPC2, additional analyses were performed by the sponsor looking at AEs in study CRPC2 of fatigue, diarrhoea, hot flush, musculoskeletal pain, and spinal cord compression.
- Laboratory tests performed included haematology, and routine blood chemistry (alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, total protein, albumin, lactate dehydrogenase [LDH], serum potassium, sodium, chloride, bicarbonate, magnesium, creatinine, blood urea nitrogen [BUN], glucose, calcium, phosphorus, uric acid, creatine phosphokinase [CK]). Laboratory tests were performed according to the schedule presented in the study report.
- Other safety endpoints included vital signs and 12-lead electrocardiogram (ECG) performed according to the schedule presented in in the study report. A thorough QT/QTc evaluation was embedded into the study, in which all ECGs were read centrally at an independent and blinded ECG laboratory.

### 8.1.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

### 8.1.3. Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies provided safety data, as follows:

- Study S-3100-1-01 provided data on adverse events, vital signs, routine laboratory evaluations and 12-lead ECG.
- Study CPRC-MDA-1 provided data on adverse events, vital signs, routine laboratory evaluations and 12-lead ECG.

#### 8.1.4. Other studies evaluable for safety only

Not applicable.

**Comments**: The sponsor had provided within the Summary of Clinical Safety (SCS;) safety results in 3 safety populations: the safety population from the pivotal Phase III study CRPC2, the integrated safety populations of 3 open-label uncontrolled studies (S3100-1-01, CRPC-MDA-1, and 9785-CL-0111[19]), and the integrated safety populations of all 4 studies (i.e. studies CRPC2, S3100-1-01, CRPC-MDA-1, and 9785-CL-0111). In addition, the SCS contains the individual presentation of the safety results of 5 Phase I PK studies (9785-CL-0007, 9785-CL-0009, 9785-CL-0001, MDV3100-05, and 9785-CL-0006), as well as updated safety information (serious adverse events and deaths) for 2 ongoing Phase II open-label studies (9785-CL-0121 [open-label extension of the DDI study 9785-CL-0007] and 9785-CL-0321 [open-label single-arm, efficacy and safety study in patients with hormone-naïve prostate cancer]).

In this evaluation report, the safety results in the pivotal Phase III study (CRPC2) and the integrated results of the 3 open-label uncontrolled studies (S3100-1-01, CRPC-MDA-1, and 9785-CL-0111) will be presented. The individual safety results of studies S3100-1-01 and CRPC-MDA-1, the integrated safety results of CRPC2 and the 3 open-label uncontrolled studies, the individual safety results of the 5 Phase I PK studies stated above and the updated safety information of the 2 ongoing Phase II open-label studies stated above, were evaluated for the purpose of this submission and no major safety concerns were raised, and hence will not be elaborated in the following sections.

### 8.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

### 8.3. Patient exposure

In study CRPC2, the overall median duration of exposure was 8.3 and 3.0 months in the MDV3100 and placebo groups, respectively (Table 6). Overall, 61.1% (489/800) and 17.8% (71/399) of patients in the MDV3100 and placebo groups, respectively, had an exposure of ≥ 6 months, while 24.8% (198/800) and 4.5% (18/399), respectively, had an exposure of ≥ 12 months.

[19] The CSR of study 9785-CL-0111 has not been submitted in this application dossier. According to the sponsor, study 9785-CL-0111 was an ongoing Phase I-II multi-centre, open-label, uncontrolled, dose-escalation study in Japanese patients with CRPC. At the time of the 07 October 2011 cut-off date for safety analyses, 27 of the anticipated 46 patients (9 patients in dose escalation cohorts and 37 patients in dose expansion cohorts) were enrolled into the study. Study objectives include a determination of the safety and PK of single doses of 80, 160, and 240 mg of MDV3100 in Japanese patients, safety and PK of multiple daily doses of 160 mg MDV3100 in Japanese patients, and efficacy measures such as PSA response, circulating tumour cell counts, disease progression, and markers of bone turnover.

**Table 6: Extent of Exposure to Study Drug, Study CRPC2**

| | MDV3100 160 mg (n = 800) | Placebo (n = 399) |
|---|---|---|
| Time on Study Drug (months)[a] | | |
| Mean (SD) | 8.5 (5.08) | 4.3 (3.44) |
| Median | 8.3 | 3.0 |
| Min, Max | 0.0, 23.2 | 0.2, 20.7 |
| Time on Study Drug Category | | |
| ≤ 2 Months | 73 (9.1%) | 74 (18.5%) |
| > 2–< 6 Months | 238 (29.8%) | 254 (63.7%) |
| ≥ 6–< 12 Months | 291 (36.4%) | 53 (13.3%) |
| ≥ 12 Months | 198 (24.8%) | 18 (4.5%) |
| Number of Dose Interruptions | | |
| 0 | 703 (87.9%) | 338 (84.7%) |
| 1 | 74 (9.3%) | 47 (11.8%) |
| 2 | 13 (1.6%) | 10 (2.5%) |
| ≥ 3 | 10 (1.3%) | 4 (1.0%) |
| Number of Dose Reductions | | |
| 0 | 782 (97.8%) | 388 (97.2%) |
| 1 | 14 (1.8%) | 7 (1.8%) |
| 2 | 3 (0.4%) | 1 (0.3%) |
| ≥ 3 | 1 (0.1%) | 3 (0.8%) |

[a] Time on study drug is defined as (date of last dose − date of first dose + 1) / 30.4375. If patient was still on study drug at the analysis data cutoff then time on study drug was censored at date of data cutoff.
mg, milligrams; SD, standard deviation.

In the integrated safety data of the 3 open-label uncontrolled studies, the overall median exposure to MDV3100 was 4.6 months (Table 7). Overall, 37.0% (84/227) of patients had an exposure of ≥ 6 months and 23.3% (53/227) had an exposure of ≥ 12 months.

**Table 7: Extent of Exposure to Study Drug in the Open-Label Studies**

| | MDV3100 < 150 mg (n = 33) | MDV3100 150–160 mg (n = 109) | MDV3100 > 160 mg (n = 85) | Total MDV3100 (n = 227) |
|---|---|---|---|---|
| Time on Study Drug (months)[a] | | | | |
| Mean (SD) | 11.6 (11.51) | 7.6 (9.36) | 9.9 (12.43) | 9.0 (10.97) |
| Median | 5.9 | 4.5 | 4.3 | 4.6 |
| Min, Max | 1.7, 50.1 | 0.0, 45.3 | 0.1, 43.9 | 0.0, 50.1 |
| Time on Study Drug Category | | | | |
| ≤ 2 Months | 1 (3.0%) | 22 (20.2%) | 22 (25.9%) | 45 (19.8%) |
| > 2–< 6 Months | 17 (51.5%) | 50 (45.9%) | 31 (36.5%) | 98 (43.2%) |
| ≥ 6–<12 Months | 4 (12.1%) | 15 (13.8%) | 12 (14.1%) | 31 (13.7%) |
| ≥ 12 Months | 11 (33.3%) | 22 (20.2%) | 20 (23.5%) | 53 (23.3%) |
| Number of Dose Interruptions | | | | |
| 0 | 29 (87.9%) | 91 (83.5%) | 49 (57.6%) | 169 (74.4%) |
| 1 | 1 (3.0%) | 10 (9.2%) | 21 (24.7%) | 32 (14.1%) |
| 2 | 3 (9.1%) | 3 (2.8%) | 9 (10.6%) | 15 (6.6%) |
| ≥ 3 | 0 (0.0%) | 5 (4.6%) | 6 (7.1%) | 11 (4.8%) |
| Number of Dose Reductions | | | | |
| 0 | 30 (90.9%) | 105 (96.3%) | 46 (54.1%) | 181 (79.7%) |
| 1 | 1 (3.0%) | 1 (0.9%) | 5 (5.9%) | 7 (3.1%) |
| 2 | 0 (0.0%) | 1 (0.9%) | 3 (3.5%) | 4 (1.8%) |
| ≥ 3 | 2 (6.0%) | 2 (1.8%) | 31 (36.5%) | 35 (15.4%) |

[a] Time on study drug is defined as (date of last dose − date of first dose + 1) / 30.4375. If a patient is still on study drug at the analysis data cutoff the time on study drug is censored at the date of the data cutoff.
mg, milligrams; SD, standard deviation.

**Comments**: Overall, the study drug exposure is adequate to assess the safety profile of MDV3100.

## 8.4. Adverse events

### 8.4.1. All adverse events (irrespective of relationship to study treatment)

#### *8.4.1.1. Pivotal study*

The percentages of subjects with any AEs were comparable among between treatment groups (98.1% [785/800] and 97.7% [390/399] in the MDV3100 and placebo groups, respectively). AEs that occurred in ≥5% of patients in either treatment group are presented in the study report. The most commonly reported AE by preferred term in the MDV3100 group was fatigue (33.6% vs. 29.1% in placebo group), nausea (33.1% vs. 41.9%) and decreased appetite (28.1% vs. 30.3%). AEs more common in the MDV3100 treatment group with at least a 2% absolute increase in incidence from placebo are noted: Among these, the largest imbalances between groups as represented by the greatest absolute increase in frequency were in the events of hot flush (20.3% with MDV3100 vs. 10.3% with placebo), headache (11.6% vs. 5.5%), fatigue (33.6% vs. 29.1%), diarrhoea (21.4% vs. 17.5%), hypertension (6.1% vs. 2.8%) and musculoskeletal pain (14.5% vs. 11.5%). As the median duration of treatment in the MDV3100 treatment group was more than 5 months longer than in the placebo group (8.3 months vs. 3.0 months), the sponsor had performed additional analyses looking at the incidences of these AEs starting within the first 60 days of treatment and the event rates/100 patient-years. In these 2 additional analyses, the higher incidences with MDV3100 compared to placebo remained for the AEs of hot flush, headache, and hypertension.

All AEs that occurred more frequently in MDV3100-treated patients than in placebo-treated patients (≥ 2% absolute difference in event frequency) in Study CRPC2 are presented in Table 8 and included (in order of largest to smallest imbalances between groups as represented by the absolute increase in frequency in MDV3100 vs. placebo) hot flush, headache, fatigue, diarrhoea, hypertension, musculoskeletal pain, fall (4.0% vs. 1.3%), insomnia (8.6% vs. 6.0%), anxiety (6.4% vs. 4.0%), pruritus (3.6% vs. 1.3%), dry skin (3.5% vs. 1.3%), musculoskeletal stiffness (2.5% vs. 0.3%), nasopharyngitis (5.1% vs. 3.0%), pollakiuria (4.6% vs. 2.5%), paresthesia (6.5% vs. 4.5%), and haematuria (6.5% vs. 4.5%).

**Table 8: All Adverse Events Occurring at a ≥ 2% Absolute Difference in Event Frequency between Treatment Groups by Preferred Term: Safety Population, Study CRPC2**

| Preferred Term[a] | MDV3100 (n = 800) | Placebo (n = 399) |
|---|---|---|
| Number of Patients Reporting at Least 1 Adverse Event[b] | 785 (98.1%) | 390 (97.7%) |
| MDV3100 > Placebo | | |
| Fatigue | 269 (33.6%) | 116 (29.1%) |
| Diarrhea | 171 (21.4%) | 70 (17.5%) |
| Hot flush | 162 (20.3%) | 41 (10.3%) |
| Musculoskeletal pain | 109 (13.6%) | 40 (10.0%) |
| Headache | 93 (11.6%) | 22 (5.5%) |
| Insomnia | 69 (8.6%) | 24 (6.0%) |
| Paresthesia | 52 (6.5%) | 18 (4.5%) |
| Hematuria | 52 (6.5%) | 18 (4.5%) |
| Anxiety | 51 (6.4%) | 16 (4.0%) |
| Hypertension | 49 (6.1%) | 11 (2.8%) |
| Nasopharyngitis | 41 (5.1%) | 12 (3.0%) |
| Pollakiuria | 37 (4.6%) | 10 (2.5%) |
| Fall | 32 (4.0%) | 5 (1.3%) |
| Pruritus | 29 (3.6%) | 5 (1.3%) |
| Dry skin | 28 (3.5%) | 5 (1.3%) |
| Musculoskeletal stiffness | 20 (2.5%) | 1 (0.3%) |
| Placebo > MDV3100 | | |
| Nausea | 265 (33.1%) | 167 (41.9%) |
| Constipation | 188 (23.5%) | 110 (27.6%) |
| Vomiting | 130 (16.3%) | 88 (22.1%) |
| Bone Pain | 111 (13.9%) | 68 (17.0%) |
| Anemia | 115 (14.4%) | 76 (19.0%) |
| Urinary retention | 16 (2.0%) | 17 (4.3%) |

[a] Adverse events were assigned to preferred term based on MedDRA (version 12.0).
[b] Patients with multiple events for a given preferred term, system organ class, or overall are counted only once for each preferred term and overall.

#### *8.4.1.2. Other studies (Integrated studies S3100-1-01, CRPC-MDA-1, and 9785-CL-0111)*

Overall, the percentages of subjects with any AEs were 96.5% (219/227). The incidence of AEs was 100% (33/33), 95.4% (104/109) and 96.5 % (82/85) in the combined MDV3100 <150mg, 150-160mg and >160mg dose groups, respectively. AEs that occurred in ≥5% of the combined open-label study population (N = 227) are presented in the study report. Overall, the most commonly reported AE by preferred term was fatigue (63.9%), nausea (31.3%), decreased appetite (30.4%) and constipation (29.5%).

The sponsor had noted that it would be difficult to draw conclusions about dose response from these integrated results due to the heterogeneity of the patients included in the dose groups and the method used to assign patients to each dose group[20].

Safety results of Study S-3100-1-01 were evaluated with regards to dose-dependent trends. Overall, there was no obvious dose-dependent trend in the incidence of AEs or serious adverse events (SAEs). There appeared to be a possible dose-dependent relationship in the incidence of AEs leading to study drug discontinuation (incidence of 0%, 3.6%, 9.8%, 8.7%, 9.4%, 12.0% and 66.7% in the 30mg, 60mg, 150/160mg, 240mg, 360mg, 480mg and 600mg/day dose groups,

[20] In the dose-escalation Study S-3100-01-1, dosing could be increased or decreased based on patient response and tolerability. In addition, all patients were switched to a dose of 160 mg after this dose was chosen as the Phase III dose. For the purposes of the safety analyses in the clinical study report, AEs were attributed to the dose the patient was taking at the time of the event (or prior to the event if the study drug was being temporarily withheld). However, in the integrated analyses in the SCS, patients were assigned to dose groups according to the dose that they were treated with at the initiation of the study. Therefore, the integrated analyses of AEs by dose group in the SCS might not reflect the dose received at the time of the event and this would limit the interpretations that could be made with respect to dose response.

respectively) and AEs leading to dose reduction (incidence of 0%, 0%, 3.9%, 8.7%, 13.2%, 20.0%, 0%, respectively).

Overall, the most commonly reported AE by preferred term was fatigue (70.0%), nausea (40.0%) and constipation (32.1%). A possible dose-dependent increase in nausea was observed in the most commonly reported AEs (incidence of 33.3%, 14.3%, 19.6%, 21.7%, 45.3%, 36.0% and 33.3% in the 30mg, 60mg, 150/160mg, 240mg, 360mg, 480mg and 600mg/day dose groups respectively).

Overall, the most commonly reported AE leading to study drug discontinuation was fatigue (2.9%). There was no obvious dose-dependent trends in the AEs (preferred term) leading to study drug discontinuation. The overall most commonly reported AE leading to dose reduction was also fatigue (7.9%). Among the AEs (preferred term) leading to dose reduction, there appeared to be a dose-dependent increase in the AE of fatigue with a 2.9% incidence at 240 mg daily, 7.5% incidence at 360 mg daily, and 20.0% incidence at 480 mg daily.

There were 5 dose-limiting toxicities[21] reported in 4 patients, all occurring at doses of 360 mg daily and above. In this study, the maximum tolerated dose of 240 mg/day was defined, based upon the occurrence of 2 dose-limiting toxicity at the 600 mg daily dose (seizure, rash), 1 dose-limiting toxicity at 480 mg daily (possible seizure), and 1 dose-limiting toxicity at 360 mg daily (seizure), as well as the above-mentioned dose-dependent occurrence of fatigue leading to dose reductions at doses of 240 mg daily and above. Overall, the most commonly reported SAE was fatigue (2.9%). There was no obvious dose-dependent trend in the incidences of the SAEs by preferred term.

### 8.4.2. Treatment-related adverse events (adverse drug reactions)

#### *8.4.2.1. Pivotal study*

The percentages of subjects with any treatment-related AEs were comparable between treatment groups (69.3% [554/800] and 66.7% [266/399] in the MDV3100 and placebo groups, respectively). Treatment-related AEs that occurred in ≥1% of patients in either treatment group are presented in Table 9 and Table 10.

**Table 9: All Study Drug-Related Adverse Events Occurring at a ≥ 10% Frequency in Either MDV3100 or Placebo Arms by Preferred Term: Safety Population, Study CRPC2**

| | MDV3100 (n = 800) | | Placebo (n = 399) | |
|---|---|---|---|---|
| Preferred Term[a] | Grade 3/4/5 | All | Grade 3/4/5 | All |
| Number of Patients Reporting at Least 1 Study Drug-Related Adverse Event[b] | 93 (11.6%) | 554 (69.3%) | 48 (12.0%) | 266 (66.7%) |
| Nausea | 5 (0.6%) | 161 (20.1%) | 6 (1.5%) | 99 (24.8%) |
| Fatigue | 25 (3.1%) | 172 (21.5%) | 12 (3.0%) | 71 (17.8%) |
| Hot flush | 0 (0.0%) | 120 (15.0%) | 0 (0.0%) | 32 (8.0%) |
| Anorexia | 8 (1.0%) | 88 (11.0%) | 1 (0.3%) | 51 (12.8%) |
| Asthenia | 7 (0.9%) | 80 (10.0%) | 3 (0.8%) | 37 (9.3%) |

[a] Adverse events were assigned to preferred term based on MedDRA (version 12.0).
[b] Patients with multiple events for a given preferred term, system organ class, or overall are counted only once for each preferred term and overall.
MedDRA, Medical Dictionary for Regulatory Activities.

[21] Defined as Grade 3 or greater toxicity regardless of perceived causality that is not ameliorated by the use of adequate/maximal medical intervention. Grade 3 alopecia, fever without neutropenia, nausea, vomiting, fatigue, and self-limited or medically controllable adverse events were not considered dose-limiting toxicities in this study

**Table 10: All Study Drug-Related Adverse Events Occurring at ≥ 1% to < 10% frequency in Either MDV3100 or Placebo Arms by Preferred Term: Safety Population, Study CRPC2**

| | MDV3100 (n = 800) | | Placebo (n = 399) | |
|---|---|---|---|---|
| Preferred Term* | Grade 3/4/5 | All | Grade 3/4/5 | All |
| Diarrhea | 2 (0.3%) | 71 (8.9%) | 1 (0.3%) | 31 (7.8%) |
| Vomiting | 5 (0.6%) | 55 (6.9%) | 6 (1.5%) | 39 (9.8%) |
| Constipation | 1 (0.1%) | 37 (4.6%) | 0 (0.0%) | 20 (5.0%) |
| Headache | 1 (0.1%) | 36 (4.5%) | 0 (0.0%) | 9 (2.3%) |
| Anemia | 8 (1.0%) | 22 (2.8%) | 6 (1.5%) | 17 (4.3%) |
| Edema peripheral | 0 (0.0%) | 27 (3.4%) | 0 (0.0%) | 10 (2.5%) |
| Dysgeusia | 0 (0.0%) | 25 (3.1%) | 0 (0.0%) | 10 (2.5%) |
| Weight decreased | 1 (0.1%) | 22 (2.8%) | 0 (0.0%) | 13 (3.3%) |
| Dizziness | 1 (0.1%) | 27 (3.4%) | 0 (0.0%) | 6 (1.5%) |
| Myalgia | 2 (0.3%) | 17 (2.1%) | 3 (0.8%) | 10 (2.5%) |
| Insomnia | 0 (0.0%) | 22 (2.8%) | 0 (0.0%) | 4 (1.0%) |
| Arthralgia | 1 (0.1%) | 18 (2.3%) | 1 (0.3%) | 5 (1.3%) |
| Decreased appetite | 0 (0.0%) | 14 (1.8%) | 0 (0.0%) | 8 (2.0%) |
| Back pain | 2 (0.3%) | 12 (1.5%) | 1 (0.3%) | 9 (2.3%) |
| Abdominal pain upper | 0 (0.0%) | 12 (1.5%) | 0 (0.0%) | 8 (2.0%) |
| Hypertension | 5 (0.6%) | 15 (1.9%) | 2 (0.5%) | 3 (0.8%) |
| Abdominal distension | 0 (0.0%) | 12 (1.5%) | 0 (0.0%) | 5 (1.3%) |
| Dyspnea | 0 (0.0%) | 12 (1.5%) | 0 (0.0%) | 5 (1.3%) |
| Dry mouth | 0 (0.0%) | 12 (1.5%) | 0 (0.0%) | 4 (1.0%) |
| Dyspepsia | 0 (0.0%) | 11 (1.4%) | 0 (0.0%) | 5 (1.3%) |
| Hyperhidrosis | 0 (0.0%) | 9 (1.1%) | 0 (0.0%) | 6 (1.5%) |
| Lethargy | 0 (0.0%) | 8 (1.0%) | 0 (0.0%) | 7 (1.8%) |
| Muscular weakness | 1 (0.1%) | 10 (1.3%) | 2 (0.5%) | 6 (1.5%) |
| Rash | 1 (0.1%) | 10 (1.3%) | 0 (0.0%) | 6 (1.5%) |
| Abdominal pain | 0 (0.0%) | 9 (1.1%) | 0 (0.0%) | 5 (1.3%) |
| Dry skin | 0 (0.0%) | 14 (1.8%) | 0 (0.0%) | 0 (0.0%) |
| Cough | 0 (0.0%) | 10 (1.3%) | 0 (0.0%) | 3 (0.8%) |
| Flatulence | 0 (0.0%) | 9 (1.1%) | 0 (0.0%) | 4 (1.0%) |
| Muscle spasms | 0 (0.0%) | 7 (0.9%) | 2 (0.5%) | 6 (1.5%) |
| Pain in extremity | 0 (0.0%) | 7 (0.9%) | 2 (0.5%) | 5 (1.3%) |
| Night sweats | 0 (0.0%) | 9 (1.1%) | 0 (0.0%) | 3 (0.8%) |
| Paresthesia | 0 (0.0%) | 10 (1.3%) | 0 (0.0%) | 1 (0.3%) |
| Pruritus | 0 (0.0%) | 10 (1.3%) | 0 (0.0%) | 1 (0.3%) |
| Anxiety | 1 (0.1%) | 8 (1.0%) | 0 (0.0%) | 1 (0.3%) |
| Dehydration | 0 (0.0%) | 3 (0.4%) | 1 (0.3%) | 5 (1.3%) |
| Hypotension | 0 (0.0%) | 2 (0.3%) | 1 (0.3%) | 4 (1.0%) |
| Neck pain | 0 (0.0%) | 1 (0.1%) | 0 (0.0%) | 4 (1.0%) |

* Adverse events were assigned to preferred term based on MedDRA (version 12.0).

The most commonly reported treatment-related AE by preferred term in the MDV3100 group was fatigue (21.5% vs. 17.8% with placebo), nausea (20.1% vs. 24.8%), and hot flush (15.0% vs. 8%). Treatment- related AEs occurring at ≥ 1% frequency and with an incidence at least 2% higher in the MDV3100-treated group than the placebo-treated group were fatigue, hot flush, and headache (4.5% vs. 2.3%).

#### *8.4.2.2. Other studies (Integrated studies S3100-1-01, CRPC-MDA-1, and 9785-CL-0111)*

Incidences of treatment-related AEs were not presented for the integrated safety results of studies S3100-1-01, CRPC-MDA-1 and 9785-CL-0111.

In Study S3100-1-01, the percentages of subjects with any treatment-related AEs were generally comparable among treatment dose groups (69.7% [2/3], 75.0% [21/28], 62.7% [32/51], 69.6% [48/69], 81.1% [43/53], 80.0% [20/25], and 100.0% [3/3] in the 30mg, 60mg, 150/160mg, 240mg, 360mg, 480mg and 600mg/day dose groups, respectively). Overall, the most commonly reported treatment-related AEs by preferred term were fatigue (58.6%; 82/140), nausea (32.9%; 46/140) and anorexia (15.0%; 21/140). Among these, there appeared to be a possible dose-dependent trend for treatment-related fatigue, from doses of 30mg to 480 mg /day (incidences of 33.3%, 39.3%, 45.1%, 43.5%, 54.7%, and 60.0% in the 30mg, 60mg, 150/160mg, 240mg, 360mg, and 480mg dose groups, respectively).

In Study CRPC-MDA-1, the overall incidence of treatment-related AEs was 75.0% (45/60). The most commonly reported treatment-related AEs by preferred term were fatigue (40.0%; 24/60), constipation (15.0%; 9/60), anorexia (15.0%; 9/60), and hot flush (15.0%; 9/60).

### 8.4.3. Deaths and other serious adverse events

#### *8.4.3.1. Pivotal study*

The incidence of AEs leading to death was generally comparable between treatment groups (2.9% and 3.5% in the MDV3100 and placebo groups, respectively). The most common AE by preferred term leading to death in both treatment groups was general physical health deterioration (0.8% MDV3100 group vs. 1.3% placebo group).

The percentage of subjects with any SAEs was also generally comparable among between treatment groups (33.5% and 38.6% in the MDV3100 and placebo groups, respectively). The most commonly reported SAE by preferred term in the MDV3100 group was spinal cord compression (6.0% with MDV3100 vs. 3.8% with placebo) and anaemia (2.6% vs. 3.0%). SAEs with at least a 0.5% absolute higher incidence in MDV3100-treated patients than placebo patients were pathological fracture (1.5% vs. 0.5%), metastatic pain (1.5% vs. 0.8%), and spinal cord compression (6.0% vs. 3.8%).

#### *8.4.3.2. Other studies (Integrated studies S3100-1-01, CRPC-MDA-1, and 9785-CL-0111)*

There were no adverse events leading to death reported in any of the 3 open-label studies. The overall incidence of SAEs was 26.0% (59/227). There was no obvious dose-dependent trend in the incidence of SAEs (30.3%, 26.6% and 23.5% in the <150mg, 150-160mg and >160 mg dose groups, respectively). Overall, the most commonly reported SAEs were fatigue (overall 2.2%; 0%, 0.9% and 4.7% in the <150mg, 150-160mg and >160 mg dose groups, respectively) and spinal cord compression (overall 2.2%; 0%, 2.8% and 2.4% in the <150mg, 150-160mg and >160 mg dose groups, respectively).

Analyses of the safety results in Study S-3100-1-01 showed that there was no obvious dose-dependent trend in the incidence of SAEs, or in the incidences of the SAEs by preferred term. The most commonly reported SAE in the study was fatigue (overall 2.9% [4/140]; occurring only in the 240mg/day and 360mg/day dose groups with incidences of 2.9% [2/69] and 3.8% [2/53], respectively).

### 8.4.4. Discontinuation due to adverse events

#### *8.4.4.1. Pivotal study*

The percentage of subjects with any AEs leading to permanent study drug discontinuation was lower in the MDV3100 group compared to the placebo group (7.6% vs. 9.8%). The most commonly reported AE by preferred term leading to permanent study drug discontinuation in the MDV3100 group was fatigue (0.6% with MDV3100 vs. 0.5% with placebo).

#### *8.4.4.2. Other studies (Integrated studies S3100-1-01, CRPC-MDA-1, and 9785-CL-0111)*

The overall incidence of AEs leading to permanent study drug discontinuation was 9.3% (21/227). There appeared to be a dose relationship with higher dose being associated with an increased incidence of AEs leading to permanent study drug discontinuation (0.0%, 6.4% and 16.5%, in the <150mg, 150-160mg and >160 mg dose groups, respectively). Overall, the most common AEs leading to permanent study drug discontinuation were fatigue (1.3%) and convulsion (1.3%), and all of these events were restricted to patients within the >160 mg daily dose group.

## 8.5. Laboratory tests

### 8.5.1. Clinical laboratory tests

#### *8.5.1.1. Pivotal study*

Treatment with MDV3100 was not associated with any significant changes in liver function tests (LFTs). The overall incidences of Grade 3 or 4 abnormalities and the incidence of an increase by more than two grades post-baseline for LFTs were either comparable between treatment groups or lower in the MDV3100 group compared to placebo group.

Treatment with MDV3100 was also not associated with any significant changes in renal function tests. The overall incidences of Grade 3 or 4 abnormalities and the incidence of an increase by more than two grades post-baseline for potassium and creatinine were either comparable between treatment groups or lower in the MDV3100 group compared to placebo group.

In the haematological analyses, there appeared to be an association of MDV3100 treatment with decreased leukocyte and neutrophil counts. Analyses of the incidences of Grade 3 or 4 abnormalities and the incidence of an increase by more than two grades post-baseline for haematological parameters showed a higher incidence in MDV3100 compared to placebo for grade 3 or 4 low leucocytes (0.9% vs. 0.3%) and low neutrophils (1.1% vs. 0.0%). There was also a higher incidence with MDV3100 compared to placebo of an increase by more than two grades post-baseline for low leucocytes (4.6% vs. 1.5%) and low neutrophils (3.6% vs. 1.0%). Review of haematological parameters over time showed that there was a decline in mean white blood cell counts from baseline to Week 21 in the MDV3100 group, whereas mean white blood cell counts in the placebo group remained at around baseline level during this period of time. This change in leukocytes appeared to be driven by a change in neutrophil count as a similar pattern was seen in mean changes in absolute neutrophil count. The change from baseline was greatest at the Week 5 visit with a maximum mean decline of approximately 800/μL in leukocyte counts and approximately 700/μL in neutrophil counts.

According to the sponsor, the aetiology for the decrease in neutrophil counts (and corresponding leucocyte counts) associated with MDV3100 were not known but it was noted that neutropenia was not implicated in any SAEs in study CRPC2. The overall incidence of AEs of leucopenia and neutropenia in the MDV3100 group was low (AE by preferred term of "white blood cell count decreased": 0.3% vs. 0.3% in placebo group; AE by preferred term of "neutropenia" or "neutrophil count decreased": 1.3% vs. 0.8% in placebo group.

#### *8.5.1.2. Other studies (Integrated studies S3100-1-01, CRPC-MDA-1, and 9785-CL-0111)*

Overall, the incidence of Grade 3 or 4 abnormalities and the incidence of an increase by more than two grades post-baseline for LFT were low in the integrated safety population (0.4% to 1.3%), as was the incidence of Grade 3 or 4 abnormalities and the incidence of an increase by more than two grades post-baseline for potassium and creatinine (0.4% to 3.1%). In the haematological analyses, there was no obvious dose-related trend in the incidence of Grade 3 or 4 haematological abnormalities and the incidence of an increase by more than two grades post-baseline for haematological parameters. The overall incidence of grade 3 or 4 low leucocytes and low neutrophils was low (0.4% and 1.3%, respectively).

Analysis of the incidence of Grade 3 or 4 haematological abnormalities in Study S3100-1-01 also did not detect any obvious dose-related trend.

### 8.5.2. Electrocardiograph

#### *8.5.2.1. Pivotal study*

A thorough QT/QTc substudy, conducted in accordance with ICH E14 guidelines, was embedded within Study CRPC2, in which all ECGs were read centrally at an independent and blinded ECG laboratory. The sponsor had acknowledged that thorough QT/QTc studies of non-oncology

drugs were frequently done with healthy volunteers, but gave the reason for a thorough QT/QTc study being conducted in prostate cancer patients instead for MDV3100, that it would take 30 days for MDV3100 to reach steady-state, and hence it would not be appropriate to conduct the study in a healthy volunteer population.

The objectives of this independent review of ECGs were to determine the effects of MDV3100 on ECG changes as compared to placebo, and to exclude an effect of MDV3100 on the QTc interval exceeding 10 ms at the 1-sided upper 95% confidence limit. According to the sponsor, this threshold had been chosen in accordance with ICH E14 guidance, to provide reasonable assurance that the mean effect of the study drug on the QT/QTc interval was not greater than around 5 ms, because drugs that prolong the mean QT/QTc interval by around 5 ms or less do not appear to cause Torsades de Pointes. The independent review of ECGs in CRPC2 was a randomised, placebo controlled, triple-blind (site, Sponsor, and ECG readers) substudy, intended to be done on all randomised patients. ECGs were obtained in triplicates on Days 1 (pre-treatment), 8, 29, and 57. Single ECGs were also collected at Screening, Days 85, 113, 141, 169, and every subsequent 12 weeks, and at the Safety Follow-Up Visit. ECGs were analysed in a validated core ECG laboratory.

Results showed that, compared to placebo, MDV3100 (160 mg/day) resulted in no clinically relevant changes in heart rate, atrioventricular conduction as determined by the PR interval, or cardiac depolarisation as determined by the QRS duration (time-averaged placebo-corrected mean changes from baseline across all 57 days of MDV3100 for heart rate, PR interval, and QRS interval were -2 bpm, -2 ms and -1 ms, respectively).

The time-averaged, placebo-corrected mean change from baseline across all 57 days of MDV3100 for QTcF interval was +3 ms which was not considered a clinically relevant change. The time point analysis for the triplicate ECGs showed a maximum mean placebo-corrected change from baseline in QTcF of +4.8 ms at Day 57 (Week 9). The time point analysis across all days did not show any signal of clinically relevant effect.

#### *8.5.2.2. Other studies (Integrated studies S3100-1-01, CRPC-MDA-1, and 9785-CL-0111)*

Analyses of the ECGs in studies S-3100-1-01 and CRPC-MDA-1 did not raise any significant safety concerns.

### 8.5.3. Vital signs

#### *8.5.3.1. Pivotal study*

Analyses of vital signs did not raise any significant safety concerns. However, there appeared to be an association of MDV3100 treatment with increased blood pressure. Analyses of blood pressures across timepoints showed that at baseline, mean systolic blood pressures (SBP) were comparable between the MDV3100 and placebo groups (131.8 vs. 131.6 mmHg). In the MDV3100 group, mean SBPs were slightly higher than baseline at post-baseline time points up through the Week 49 visit, with a maximum mean increase of 2.1 mmHg from baseline observed at the Week 5 visit. By contrast, mean SBPs were slightly lower than baseline at all post-baseline time points in the placebo group, with a maximum mean decrease of 3.6 mmHg from baseline at the Week 37 visit. However, the difference between treatment groups in median SBPs were not greater than 3 mmHg at any post-baseline time point up through the Week 49 visit. Similar patterns were noted for diastolic blood pressure (DBP), with a maximum mean increase of 1.2 mmHg from baseline in the MDV3100 group at the Week 9 visit and a maximum mean decrease of 2.7 mmHg from baseline in the placebo group at the Week 21 visit.

Additional analyses performed to further evaluate the potential effect of MDV3100 on SBP and DBP at patients' final study visits as well as at their most extreme post-baseline measurement during Study CRPC2 showed that there was an increased proportion of MDV3100 patients demonstrating elevated SBP and increased change from baseline in SBP, compared to placebo

patients. The effect of MDV3100 on DBP measurements was less apparent and less consistent in this study.

#### *8.5.3.2. Other studies (Integrated studies S3100-1-01, CRPC-MDA-1, and 9785-CL-0111)*

Analyses of vital signs did not raise any significant safety concerns. Analyses looking at SBP and DBP and change from baseline at patients' final study visits and at their most extreme post-baseline measurement showed that there was no obvious dose relationship. However, as noted previously, the interpretation may be limited by the method of assigning patients to dose group in the SCS analyses[22]. SBP and DBP in different dose groups in study S3100-1-01 was not presented in the CSR of the study. This will be raised as a clinical question (below).

### 8.5.4. AEs of special interest

#### *8.5.4.1. Pivotal study*

Adverse events of special interest were not pre-specified in the protocol. Based on analyses of AEs in study CRPC2, additional analyses were performed by the sponsor looking at AEs in study CRPC2 of fatigue, diarrhoea, hot flush, musculoskeletal pain, and spinal cord compression, and presented in the SCS.

Adverse events of fatigue were reported for 33.6% of patients (269/800) in the MDV3100 group compared with 29.1% of patients (116/399) in the placebo group. Of the MDV3100-treated patients reporting AE of fatigue, the majority were of Grades 1 and 2 (14.1% [113/800], 13.3% [106/800] and 6.3% [50/800] with Grades 1, 2 and 3 severity of fatigue, respectively). The imbalance in the frequency of AE of fatigue seen between the MDV3100 and placebo groups primarily resulted from Grade 1 events. The proportion of patients with Grades 2 and 3 severity of fatigue was comparable between the MDV3100 and placebo groups (Grade 2: 13.3% with MDV3100 vs. 12.3% with placebo; Grade 3: 6.3% vs. 7.3%). The incidences of SAE of fatigue (0.3% with MDV3100 vs. 0.8% with placebo) and of AE of fatigue leading to discontinuation of study drug (0.6% vs. 0.5%) were low in the MDV3100 group, and were either comparable with or lower than those in the placebo group. A similar pattern was seen for the AE term of asthenia. When the event rates for the AEs of fatigue and asthenia were adjusted by adverse event reporting period, the event rates per 100 patient-years at risk were higher in the placebo-treated group than in the MDV3100-treated group for both AE terms (fatigue: 49.9 with MDV3100 vs. 72.0 with placebo; asthenia: 26.3 vs. 45.0).

Adverse events of diarrhoea were reported for 21.4% of patients (171/800) in the MDV3100 group compared with 17.5% of patients (70/399) in the placebo group. Of the MDV3100-treated patients reporting AE of diarrhoea, the majority were of Grade 1 (17.4% [139/800], 2.9% [23/800] and 1.1% [9/800] with Grades 1, 2 and 3 severity of diarrhoea, respectively). The incidences of SAE of diarrhoea (0.4% with MDV3100 vs. 0.0% with placebo) and of AE of diarrhoea leading to discontinuation of study drug (0.3% vs. 0.0%) were low in the MDV3100 group. When the event rates for the AE of diarrhoea were adjusted by adverse event reporting period, the event rates per 100 patient-years at risk were higher in the placebo-treated group than in the MDV3100-treated group (36.3 with MDV3100 vs. 47.4 with placebo).

Adverse events of hot flush were reported for 20.3% of patients (162/800) in the MDV3100 group compared with 10.3% of patients (41/399) in the placebo group. Of the MDV3100-

[22] In the dose-escalation Study S-3100-01-1, dosing could be increased or decreased based on patient response and tolerability. In addition, all patients were switched to a dose of 160 mg after this dose was chosen as the Phase III dose. For the purposes of the safety analyses in the clinical study report, AEs were attributed to the dose the patient was taking at the time of the event (or prior to the event if the study drug was being temporarily withheld). However, in the integrated analyses in the SCS, patients were assigned to dose groups according to the dose that they were treated with at the initiation of the study. Therefore, the integrated analyses of AEs by dose group in the SCS might not reflect the dose received at the time of the event and this would limit the interpretations that could be made with respect to dose response.

treated patients reporting AE of hot flush, the majority were of Grade 1 (14.6% [117/800] and 5.6% [45/800] with Grades 1 and 2 severity of hot flush, respectively). There was no incidence of SAE of hot flush or of AE of hot flush leading to discontinuation of study drug in the MDV3100 group. When the event rates for the AE of hot flush were adjusted by adverse event reporting period, the event rates per 100 patient-years at risk remained higher in the MDV3100 group compared to the placebo group (27.4 with MDV3100 vs. 24.6 with placebo).

Adverse events of musculoskeletal pain were reported for 14.5% of patients (116/800) in the MDV3100 group compared with 11.5% of patients (46/399) in the placebo group. Of the MDV3100-treated patients reporting AE of musculoskeletal pain, the majority were of Grade 1 (7.8% [62/800], 5.6% [45/800] and 1.1% [9/800] with Grades 1, 2 and 3 severity of musculoskeletal pain, respectively). There was no incidence of AE of musculoskeletal pain leading to discontinuation of study drug in the MDV3100 group. One (0.1%) patient in the MDV3100 group had an SAE of musculoskeletal pain (compared with 0 patients in the placebo group).

Adverse events of spinal cord compression were reported for 6.4% of patients (51/800) in the MDV3100 group compared with 4.5% of patients (18/399) in the placebo group. A similar imbalance was noted in AE term of pathological fracture, reported in 1.5% MDV3100-treated patients (12/800) compared to 0.8% placebo-treated patients (3/399). The sponsor had noted that in study CRPC2, skeletal-related events such as spinal cord compression and pathological fracture were not required to be reported as AEs unless they met the criteria for an SAE. Instead, they were required to be reported on the skeletal-related event case report form (CRF), although many investigators also included them as adverse events. This would mean that in only evaluating spinal cord compression and pathological fracture from the adverse event CRF, many non-serious AEs were not included. The sponsor did additional analyses looking at spinal cord compression and pathological fractures that occurred during the safety reporting period using data from the skeletal-related events CRF. Results showed that the imbalance between treatment groups was smaller (spinal cord compression: 8.3% with MDV3100 vs. 7.3% with placebo; pathological fracture: 3.5% vs. 3.8%). When the event rates for the AEs of spinal cord compression and pathological fracture were adjusted by adverse event reporting period, the event rates per 100 patient-years at risk were higher in the placebo-treated group than in the MDV3100-treated group (spinal cord compression: 11.9 with MDV3100 vs. 18.6 with placebo; pathological fracture: 6.8 vs. 9.1).

## 8.6. Post-marketing experience

Not applicable.

## 8.7. Safety issues with the potential for major regulatory impact

### 8.7.1. Haematological effect

The effect of MEV3100 on leucocyte and neutrophil counts has been presented above (section 8.5.1.1).

Haematological analyses in study CRPC2 showed that there appeared to be an association of MDV3100 treatment with decreased leukocyte and neutrophil counts. There was a decline in mean white blood cell counts and neutrophil counts from baseline to Week 21 in the MDV3100 group, whereas mean white blood cell counts and neutrophil counts in the placebo group remained at around baseline level during this period of time. The change from baseline was greatest at the Week 5 visit with a maximum mean decline of approximately 800/μL in leukocyte counts and a maximum mean decline of approximately 700/μL in neutrophil counts.

According to the sponsor, the aetiology for the decrease in neutrophil counts (and corresponding white blood cell counts) associated with MDV3100 were not known but it was

noted that neutropenia was not implicated in any SAEs in study CRPC2. The overall incidence of AEs of leucopenia and neutropenia in the MDV3100 group was low (AE by preferred term of "white blood cell count decreased": 0.3% vs. 0.3% in placebo group; AE by preferred term of "neutropenia" or "neutrophil count decreased": 1.3% vs. 0.8% in placebo group).

### 8.7.2. Neuropsychiatric effect

According to the sponsor, seizure was a known potential toxicity of MDV3100, based on non-clinical findings. In addition, in the dose-escalation study in patients with CRPC, Study S- 3100-1-01, seizures were reported in 3 patients (1 each at daily doses of 360, 480, and 600 mg MDV3100), and were identified as dose-limiting toxicities. No seizures were reported in patients receiving daily doses of 240 mg MDV3100 or below in this study. Analysis in Study CRPC2 of the incidence of seizures showed that 5 out of 800 patients (0.6%) treated with MDV3100 had reported an AE of seizure (preferred terms of convulsion [n=2], partial seizure [n=2], or status epilepticus [n=1]; all 5 were considered SAEs ) compared with no patients treated with placebo. The sponsor performed an additional review of the AEs relating to seizures, which identified an additional patient (MDV3100 group) with an event term of syncope but with several features suggestive of seizure. Therefore, in study CRPC2, the overall incidence of seizure was 6/800 (0.8%) in the MDV3100 group. The sponsor had observed that dose appeared to be an important predictor of the risk of seizure, based on findings of dose-dependent convulsions observed in mice, that seizure was a dose-limiting toxicity in Study S-3100-1-01, occurring at doses ≥ 360 mg, and that of the 5 patients who experienced a seizure in CRPC2, 4 patients had PK data available, and their MDV3100 Cmin plasma concentrations were in the upper two quartiles (Study icon2147016).

In addition, the sponsor noted that the overall incidence of adverse events of any grade in the Nervous System and the Psychiatric Disorders system organ classes (SOC) was higher in the MDV3100 group compared to the placebo group (Nervous System Disorders: 48.6% with MDV3100 vs. 37.3% with placebo; Psychiatric Disorders: 24.9% vs. 19.3%) in Study CRPC2. Additional analyses were done looking at AEs in these 2 SOCs reported by at least 1% of patients in either treatment group. In the Nervous System Disorders SOC, the greatest imbalance in AE incidence (in terms of absolute increase in frequency in MDV3100 vs. placebo) was in events of headache (11.6% with MDV3100 vs. 5.5% with placebo). In the Psychiatric Disorders SOC, the greatest imbalance in AE incidence (in terms of absolute increase in frequency in MDV3100 vs. placebo) was in the event of insomnia (8.8% with MDV3100 vs. 6.0% with placebo).

In Study CRPC2, AEs of headache were reported for 11.6 % of patients (93/800) in the MDV3100 group compared with 5.5% of patients (22/399) in the placebo group. Of the MDV3100-treated patients reporting AE of headache, the majority were of Grade 1 (9.4% [75/800], 1.5% [12/800] and 0.8% [6/800] with Grades 1, 2 and 3 severity of headache, respectively). The incidences of SAE of headache (0.1% with MDV3100 vs. 0.2% with placebo) and of AE of headache leading to discontinuation of study drug (0.0% vs. 0.3%) were low in the MDV3100 group. When the event rates for the AE of headache were adjusted by adverse event reporting period, the event rates per 100 patient-years at risk remained higher in the MDV3100 group compared to the placebo groups (17.7 with MDV3100 vs. 14.4 with placebo).

In Study CRPC2, AEs of insomnia were reported for 8.8 % of patients (70/800) in the MDV3100 group compared with 6.0% of patients (24/399) in the placebo group. Of the MDV3100-treated patients reporting AE of insomnia, the majority were of Grade 1 (5.8% [46/800] and 3.0% [24/800] with Grades 1 and 2 severity of insomnia, respectively). There were no incidences of SAE of insomnia or of AE of insomnia leading to discontinuation of study drug in the MDV3100 group. When the event rates for the AE of insomnia were adjusted by adverse event reporting period, the event rates per 100 patient-years at risk was lower in the MDV3100 group compared to the placebo groups (12.1 with MDV3100 vs. 14.4 with placebo).

### 8.7.3. Cardiovascular safety

Results of a thorough QT/QTc study embedded in study CRPC2 did not raise any safety concerns. However, there appeared to be an association of MDV3100 treatment with increased blood pressure (see above). Analyses of blood pressures across timepoints in Study CRPC2 showed that in the MDV3100 group, mean SBPs were slightly higher than baseline at post-baseline timepoints up through the Week 49 visit, with a maximum mean increase of 2.1 mmHg from baseline observed at the Week 5 visit. Similar patterns were noted for DBP, with a maximum mean increase of 1.2 mmHg from baseline in the MDV3100 group at the Week 9 visit. The proportion of patients with a most extreme post-baseline SBP measurement of ≥ 180 mmHg was low in the MDV3100 group, although it was higher compared to the placebo group (7.3% with MDV3100 vs. 5.5% with placebo). The proportion of patients with a most extreme post-baseline DBP measurement of ≥ 105 mmHg was also low in the MDV3100 group, although it was higher compared to the placebo group (2.9% with MDV3100 vs. 2.5% with placebo).

Additional analyses looking at the occurrence of adverse events of hypertension in Study CRPC2 showed that there was no incidence of AE of hypertensive crisis in the MDV3100 group vs. 0.3% (1/399) in the placebo group. Adverse events of hypertension were reported for 6.1 % of patients (49/800) in the MDV3100 group compared with 2.8% of patients (11/399) in the placebo group. Of the MDV3100-treated patients reporting AE of hypertension, the majority were of Grades 1 and 2 (2.5% [20/800], 1.6% [13/800] and 2.0% [16/800] with Grades 1, 2 and 3 severity of hypertension, respectively). There was no incidence of SAE of hypertension in the MDV3100 group versus 0.3% (1/399) in the placebo group. The incidence of AE of hypertension leading to discontinuation of study drug was low in the MDV3100 group (0.1% with MDV3100 vs. 0.0% with placebo). When the event rates for the AE of hypertension were adjusted by adverse event reporting period, the event rates per 100 patient-years at risk remained higher in the MDV3100 group compared to the placebo group (8.4 with MDV3100 vs. 7.2 with placebo).

## 8.8. Other safety issues

### 8.8.1. Safety in special populations

Results of a population PK study using PK data from studies S-3100-1-01, MDV3100-05, and CRPC2 (Study report icon2147014) showed that the medians of individual post-hoc estimates of CL/F of MDV3100 for subjects with normal renal function (creatinine clearance [CRCL] ≥ 90 mL/min; N = 512), mild renal impairment (CRCL 60 to < 90 mL/min; N = 332), and moderate renal impairment (CRCL 30 to < 60 mL/min; N = 88) were 0.550, 0.524, and 0.501 L/h, respectively[23]. Hence, the medians of individual estimates of CL/F in the mild and moderate renal impairment categories were 5% and 9% lower, respectively, than in the normal category, suggesting that no dose adjustment was necessary for patients with calculated CRCL values ≥ 30 mL/min, which was an expected finding for a drug that is not cleared renally. On the basis of this population PK analysis, dose adjustments were not considered necessary for patients with mild or moderate renal impairment. Caution is advised in patients with severe renal impairment.

A PK study (Study 9785-CL-0009) had been conducted to compare the single-dose PK of MDV3100 (160mg; four 40 mg capsules) in subjects with mild (N=6) or moderate (N=8) hepatic impairment (Child-Pugh Class A and B, respectively) to matched control subjects with normal hepatic function (N=14). Following a single oral 160 mg dose of MDV3100, exposure parameters for MDV3100 were increased by up to 1.24- and 1.29-fold in subjects with mild and moderate hepatic impairment, respectively, compared to healthy control subjects. Based upon these findings, the sponsor drew the conclusion that no dose adjustment would be necessary for

[23] As there was only one patient with CRCL < 30 mL/min, it was not possible to assess the severe impairment category.

patients with baseline mild or moderate hepatic impairment. Safety results in this study did not reveal any clinically significant trends with regards to use of MDV3100 in the setting of mild or moderate hepatic impairment. Overall 2 subjects each experienced 1 treatment-emergent AE (TEAE) during the study, 1 with moderate hepatic impairment (TEAE of gynaecomastia) and the other a healthy subject (TEAE of hypertensive crisis).

## 8.9. Evaluator's overall conclusions on clinical safety

Overall, safety results in the pivotal Phase III study (CRPC2) did not raise any major safety concerns. The incidences of all-causality AEs, treatment-related AEs, deaths, SAEs, and AEs leading to discontinuation of study drug were either comparable or lower in the MDV3100 group vs. the placebo group. The most commonly reported treatment-related AEs by preferred term in the MDV3100 group were fatigue (21.5% vs. 17.8% with placebo), nausea (20.1% vs. 24.8%), and hot flush (15.0% vs. 8%). Treatment-related AEs occurring at ≥ 1% frequency and with an incidence of at least 2% higher in the MDV3100-treated group than the placebo-treated group were fatigue, hot flush, and headache (4.5% vs. 2.3%).

Safety results in the 3 open-label studies (S3100-1-01, CRPC-MDA-1, and 9785-CL-0111) were generally consistent with those of the pivotal study. Safety results in Study S3100-1-01 showed that there was no obvious dose-dependent trend in the incidence of all-causality AEs, SAEs, or treatment-related AEs, but with a possible dose-dependent relationship in the incidence of AEs leading to study drug discontinuation and AEs leading to dose reduction. Among the most commonly reported all-causality AEs, a possible dose-dependent increase in nausea was observed (incidence of 33.3%, 14.3%, 19.6%, 21.7%, 45.3%, 36.0% and 33.3% in the 30mg, 60mg, 150/160mg, 240mg, 360mg, 480mg and 600mg/day dose groups respectively). Overall, the most commonly reported SAE was fatigue (2.9%), but there was no obvious dose-dependent trend in the incidences of the SAEs by preferred term. The most commonly reported treatment-related AE by preferred term was also fatigue (58.6%). Among the most commonly reported treatment-related AEs, there appeared to be a possible dose-dependant trend for treatment-related fatigue, from doses of 30mg to 480 mg /day (incidences of 33.3%, 39.3%, 45.1%, 43.5%, 54.7%, and 60.0% in the 30mg, 60mg, 150/160mg, 240mg, 360mg, and 480mg dose groups, respectively). The most commonly reported AE leading to study drug discontinuation was fatigue (2.9%), as was the most commonly reported AE leading to dose reduction (7.9%). There was no obvious dose-dependent trends in the AEs (preferred term) leading to study drug discontinuation, but among the AEs (preferred term) leading to dose reduction, there appeared to be a dose-dependent increase in the AE of fatigue with a 2.9% incidence at 240 mg daily, 7.5% incidence at 360 mg daily, and 20.0% incidence at 480 mg daily.

In Study CRPC2, among all-causality AEs with a higher incidence with MDV3100 vs. placebo, the largest imbalances between treatment groups (as represented by the greatest absolute increase in frequency) were in the events of hot flush (20.3% with MDV3100 vs. 10.3% with placebo), headache (11.6% vs. 5.5%), fatigue (33.6% vs. 29.1%), diarrhoea (21.4% vs. 17.5%), hypertension (6.1% vs. 2.8%), and musculoskeletal pain (14.5% vs. 11.5%). As the median duration of treatment in the MDV3100 treatment group was more than 5 months longer than in the placebo group (8.3 months vs. 3.0 months), the sponsor had performed additional analyses looking at the incidences of these AEs starting within the first 60 days of treatment and the event rates/100 patient-years. In these 2 additional analyses, the higher incidences with MDV3100 compared to placebo remained for the AEs of hot flush, headache, and hypertension.

With regards to AE of hot flush, the majority of AEs of hot flush among MDV3100-treated patients in Study CRPC2 were of Grade 1, and there was no incidence of SAE of hot flush or of AE of hot flush leading to discontinuation of study drug in the MDV3100 group. When the event rates for the AE of hot flush were adjusted by adverse event reporting period, the event rates per 100 patient-years at risk remained higher in the MDV3100 group compared to the placebo group (27.4 with MDV3100 vs. 24.6 with placebo).

With regards to AE of headache, the majority of AEs of headache among MDV3100-treated patients in Study CRPC2 were of Grade 1. The incidences of SAE of headache (0.1% with MDV3100 vs. 0.2% with placebo) and of AE of headache leading to discontinuation of study drug (0.0% vs. 0.3%) were low in the MDV3100 group. When the event rates for the AE of headache were adjusted by adverse event reporting period, the event rates per 100 patient-years at risk remained higher in the MDV3100 group compared to the placebo group (17.7 with MDV3100 vs. 14.4 with placebo).

With regards to effect on blood pressure, analyses of the vital signs in Study CRPC showed that there appeared to be an association of MDV3100 treatment with increased blood pressure. Analyses of blood pressure across timepoints in Study CRPC2 showed that in the MDV3100 group, mean SBPs and DBPs were slightly higher than baseline at post-baseline timepoints up through the Week 49 visit. However, the maximum mean increase from baseline was small (SBP: maximum mean increase of 2.1 mmHg from baseline [observed at Week 5]; DBP: maximum mean increase of 1.2 mmHg from baseline [observed at Week 9]). Additional analyses looking at the occurrence of adverse events of hypertension in Study CRPC2 showed that there was no incidence of AE of hypertensive crisis in the MDV3100 group vs. 0.3% (1/399) in the placebo group. The majority of AEs of hypertension among MDV3100-treated patients in Study CRPC2 were of Grades 1 and 2. There was no incidence of SAE of hypertension in the MDV3100 group vs. 0.3% (1/399) in the placebo group. The incidence of AE of hypertension leading to discontinuation of study drug was low in the MDV3100 group (0.1% with MDV3100 vs. 0.0% with placebo). When the event rates for the AE of hypertension were adjusted by adverse event reporting period, the event rates per 100 patient-years at risk remained higher in the MDV3100 group compared to the placebo group (8.4 with MDV3100 vs. 7.2 with placebo).

Haematological analyses in study CRPC2 also showed that there appeared to be an association of MDV3100 treatment with decreased leukocyte and neutrophil counts. There was a decline in mean white blood cell counts and neutrophil counts from baseline to Week 21 in the MDV3100 group, whereas mean white blood cell counts and neutrophil counts in the placebo group remained at around baseline level during this period of time. The change from baseline was greatest at the Week 5 visit with a maximum mean decline of approximately 800/μL in leukocyte counts and a maximum mean decline of approximately 700/μL in neutrophil counts. According to the sponsor, the aetiology for the decrease in neutrophil counts (and corresponding white blood cell counts) associated with MDV3100 were not known but it was noted that neutropenia was not implicated in any SAEs in study CRPC2. The overall incidence of AEs of leucopenia and neutropenia in the MDV3100 group was low (AE by preferred term of "white blood cell count decreased": 0.3% vs. 0.3% in placebo group; AE by preferred term of "neutropenia" or "neutrophil count decreased": 1.3% vs. 0.8% in placebo group).

# 9. First round benefit-risk assessment

## 9.1. First round assessment of benefits

The benefits of enzalutamide in the proposed usage are:

- treatment of patients with metastatic CRPC who have previously received docetaxel, in terms of potential benefits in improving overall survival, prolonging time to disease progression and symptom relief

Efficacy results in the pivotal study (CRPC2) showed that there was a statistically significant increase in the duration of overall survival among patients treated with MDV3100 compared with patients treated with placebo (median survival duration of 18.4 months with MDV3100 vs. 13.6 months with placebo; $p < 0.0001$), and a 37% decrease in the risk of death for patients receiving MDV3100 compared to those receiving placebo. There was also a statistically

significant increase in time to PSA progression among MDV3100 treated patients compared with placebo-treated patients (median time to PSA progression of 8.3 months with MDV3100 vs. 3.0 months with placebo; $p < 0.0001$). The time to radiographic progression was statistically significantly longer in MDV3100-treated patients compared with placebo-treated patients (median duration of radiographic progression-free survival of 8.3 months with MDV3100 vs. 2.9 months with placebo; $p < 0.0001$), as was the time to first skeletal-related events was also statistically significantly longer among MDV3100-treated patients compared with placebo-treated patients (median time to first skeletal-related events of 6.7 months with MDV3100 vs. 13.3 months with placebo; $p = 0.0001$). The proportion of patients whose best overall soft tissue radiographic response was complete or partial response was 28.9% in the MDV3100 group compared with 3.8% in the placebo group (difference of 25.08%; $p < 0.0001$).

With regards to the effect on pain, the rate of pain palliation at Week 13 was statistically significantly higher with MDV3100 compared to placebo (44.9% among MDV3100-treated patients, compared to 6.7% among placebo-treated patients; $p = 0.0079$). The proportion of patients with pain progression at Week 13 was statistically significantly lower with MDV3100 compared to placebo (27.8% in the MDV3100 group vs. 39.0% in the placebo group; $p = 0.0018$). Measurement of effect on quality of life using the FACT-P showed that there was a statistically significantly higher FACT-P response rate with MDV3100 compared to placebo (43.2% with MDV3100 vs. 18.3% with placebo; $p < 0.0001$).

## 9.2. First round assessment of risks

The risks of enzalutamide in the proposed usage are:

- fatigue
- hot flush
- headache
- increased in blood pressure
- decreased leukocyte and neutrophil counts
- seizures

Safety results in Study CRPC2 showed that treatment- related AEs occurring at ≥ 1% frequency and with an incidence at least 2% higher in the MDV3100-treated group than the placebo-treated group were fatigue (21.5% vs. 17.8% with placebo), hot flush (15.0% vs. 8%), and headache (4.5% vs. 2.3%).

With regards to AEs of fatigue, hot flush and headache, the majority of these all-causality AEs in Study CRPC2 were of Grades 1 or 2 in severity. The incidences of SAEs of these AE preferred terms, and of these AEs leading to discontinuation of study drug were low in the MDV3100 group in Study CRPC2.

With regards to effect on blood pressure, analyses of the vital signs in Study CRPC showed that there appeared to be an association of MDV3100 treatment with increased blood pressure, with mean SBPs and DBPs observed to be slightly higher than baseline at post-baseline timepoints up through the Week 49 visit. However, the maximum mean increase from baseline was small (SBP: maximum mean increase of 2.1 mmHg from baseline [observed at Week 5]; DBP: maximum mean increase of 1.2 mmHg from baseline [observed at Week 9]). There was also no incidence of AE of hypertensive crisis in the MDV3100 group vs. 0.3% (1/399) in the placebo group in Study CRPC2. In addition, the majority of AEs of hypertension among MDV3100-treated patients in Study CRPC2 were of Grades 1 and 2, there was no incidence of SAE of hypertension in the MDV3100 group, and the incidence of AE of hypertension leading to

discontinuation of study drug was low in the MDV3100 group (0.1%). It also needs to be taken into consideration that this AE is monitorable by routine BP measurements.

Haematological analyses in study CRPC2 also showed that there appeared to be an association of MDV3100 treatment with decreased leukocyte and neutrophil counts, with a decline in mean white blood cell counts and neutrophil counts from baseline to Week 21 observed in the MDV3100 group. However, the maximum mean decline from baseline was small (maximum mean decline of approximately 800/μL and 700/μL in leukocyte counts and neutrophil counts, respectively, at Week 5). In addition, neutropenia was not implicated in any SAEs in study CRPC2, and the overall incidence of AEs of leucopenia and neutropenia in the MDV3100 group was low (AE by preferred term of "white blood cell count decreased": 0.3% vs. 0.3% in placebo group; AE by preferred term of "neutropenia" or "neutrophil count decreased": 1.3% vs. 0.8% in placebo group). It also needs to be taken into consideration that this AE is monitorable by routine clinical laboratory tests.

Of clinical concern was the potential risk of seizures. Seizure was a known potential toxicity of MDV3100, based on non-clinical findings, and had been identified as a dose-limiting toxicity in the dose-escalation study, Study S- 3100-1-01. Analysis in Study CRPC2 of the incidence of seizures showed that the incidence in the MDV3100 group was low (0.8% [6/800] vs. 0% with placebo), although it is noted that Study CRPC2 excluded patients with medical conditions that could predispose them to seizures and medications known to decrease the seizure threshold. Five of these AEs of seizures were considered SAEs (preferred terms of convulsion [n=2], partial seizure [n=2], or status epilepticus [n=1])[24]. The sponsor had observed that dose appeared to be an important predictor of the risk of seizure, based on findings of dose-dependent convulsions observed in mice, that seizure was a dose-limiting toxicity in Study S-3100-1-01, occurring only at doses ≥ 360 mg, and that of the 5 patients who experienced a seizure in CRPC2, 4 patients had PK data available, and their MDV3100 Cmin plasma concentrations were in the upper two quartiles (Study icon2147016). It is noted that the potential risk of seizure has been clearly indicated in the proposed PI under the heading of "Precautions", that "Caution should be used in administering XTANDI to patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, stroke, primary brain tumours or brain metastases, or alcoholism. In addition, the risk of seizure may be increased in patients receiving concomitant medicines that lower the seizure threshold". This is considered appropriate.

## 9.3. First round assessment of benefit-risk balance

The benefit-risk balance of enzalutamide, given the proposed usage, is favourable.

Efficacy results showed that treatment with enzalutamide in CRPC patients led to a statistically significant increase in the duration of overall survival (median survival duration of 18.4 months with enzalutamide vs. 13.6 months with placebo), and a 37% decrease in the risk of death for CRPC patients receiving enzalutamide compared to those receiving placebo. There was also a statistically significant increase in time to PSA progression among enzalutamide-treated patients compared with placebo-treated patients (median time to PSA progression of 8.3 months with MDV3100 vs. 3.0 months with placebo), as well as in time to radiographic progression (median duration of radiographic progression-free survival of 8.3 months with MDV3100 vs. 2.9 months with placebo).

Safety result showed that common AEs associated with enzalutamide were fatigue, hot flush and headache. In Study CRPC2, these AEs were mostly of Grades 1 or 2 in severity, with low incidences of SAEs. Enzalutamide appeared to be associated with an increase in blood pressure

[24] The remaining AE was that of a patient in the MDV3100 group with an event term of syncope but with several features suggestive of seizure, and included in the incidence calculation by the sponsor following an additional review of the AEs of seizures.

and a decrease in leukocyte and neutrophil counts. However, the effect on blood pressure appeared to be small (maximum mean increase from baseline in SBP and DBP of 2.1 mmHg and 1.2 mmHg, respectively). The majority of AEs of hypertension among enzalutamide-treated patients in Study CRPC2 were of Grades 1 and 2 in severity, and there was no incidence of SAE of hypertension in the enzalutamide group. In addition, this effect on blood pressure is monitorable by routine BP measurements. The effect on leukocyte and neutrophil counts also appeared to be small (maximum mean decline of approximately 800/μL and 700/μL in leukocyte counts and neutrophil counts, respectively). Neutropenia was not implicated in any SAEs in study CRPC2, and the overall incidence of AEs of leucopenia and neutropenia in the enzalutamide group was low (≤ 1.3%). In addition this effect on leukocyte and neutrophil counts is monitorable by routine clinical laboratory tests.

Of main clinical concern was the potential risk of seizures with enzalutamide. The risk of seizures appeared to be dose-dependent. In the dose-escalation study, Study S-3100-1-01, seizures occurred only at doses ≥ 360 mg. In Study CRPC2, where patients were on a dose of 160 mg/day, the incidence of seizures with enzalutamide was low, although it was higher compared to placebo (0.8% vs. 0% with placebo). Study CRPC2 excluded patients with medical conditions that could predispose them to seizures and medications known to decrease the seizure threshold. It is noted that the potential risk of seizure has been clearly indicated in the proposed PI under the heading of "Precautions", including the need for caution in patients with history of seizures or predisposing factors to seizures, or receiving concomitant medicines that could lower the seizure threshold.

# 10. First round recommendation regarding authorisation

It is recommended that the application for the registration of enzalutamide for the treatment of patients with metastatic CRPC who have previously received docetaxel be approved. This is subject to a satisfactory response to the clinical questions raised in Section 11.

# 11. Clinical questions

## 11.1. Pharmacokinetics

None.

## 11.2. Pharmacodynamics

None.

## 11.3. Efficacy

None.

## 11.4. Safety

Please provide analysis of the results for systolic and diastolic blood pressure measurements study S3100-1-01 according to the dose groups.

As described in the section on *Vital signs Other studies (Integrated studies S3100-1-01, CRPC-MDA-1, and 9785-CL-0111)*, above, analyses of systolic and diastolic blood pressure in the integrated safety results of the 3 open-label studies did not show any obvious dose relationship. However, as noted by the sponsor, the interpretation of dose relationships in the integrated

analysis was limited by the method of assigning patients to dose group. An attempt to look at possible dose-related trend in the dose-escalation study S3100-1-01 could not be done as systolic and diastolic blood pressures in different dose groups in Study S3100-1-01 was not presented in the clinical study report of the study.

# 12. Second round evaluation of clinical data submitted in response to questions

Overall, the sponsor has adequately addressed all the questions posed in the first round of evaluation. In this section on the evaluation of the sponsor's responses to the questions posed in the first round of evaluation, each question will be re-stated for ease of reference, followed by the evaluation.

## 12.1. Sponsor's response to the safety question

The Sponsor assessed the systolic and diastolic blood pressure measurements from Study S3100-1-01, a phase 1, open-label, uncontrolled, dose-escalation safety and pharmacokinetic study with dose-expansion at the tolerated doses for patients with progressive castration-resistant prostate cancer (CRPC), both pre- and post-chemotherapy.

In this study, the dose of any individual patient could have changed after week 13 (as described in the study report). Therefore, analyses of systolic and diastolic blood pressure measurements, as requested by the Agency, have been conducted from baseline through week 13 of enzalutamide treatment. As pre-specified in the protocol, only a small number of patients were included in each dose group during this study. A summary of the mean change in blood pressure measurements is presented by dose groups below [Table 11].

**Table 11: Mean change in systolic and diastolic blood pressure measurements from Baseline to Week 13**

| Dose (mg) | N | Mean Change (Baseline to Week 13) | |
|---|---|---|---|
| | | Systolic (mmHg) | Diastolic (mmHg) |
| 30 | 3 | 0.67 | -2.33 |
| 60 | 26 | 6.35 | 0.35 |
| 150 | 25 | 9.60 | -0.08 |
| 240 | 24 | 0.83 | 2.58 |
| 360 | 24 | -0.42 | 1.71 |
| 480 | 15 | 9.00 | 2.33 |
| 600 | 1 | -31.00 | -11.00 |

Based on this data, there was no apparent dose-response for systolic or diastolic blood pressure measurements. Overall, the benefit/risk ratio of enzalutamide is favourable in the intended patient population, metastatic CRPC patients who have previously received docetaxel.

> **Evaluator's Comments**: The sponsor provided additional analyses of systolic and diastolic blood pressure measurements in study S3100-1-01 according to the dose groups. As the dose of the study drug any individual patient could have changed after week 13 in this study, the sponsor looked at changes in systolic and diastolic blood pressures from baseline through week 13 of enzalutamide treatment. This is considered by the evaluator to be appropriate. The results showed that there was no obvious dose relationship for systolic or diastolic blood pressure measurements, although the small sample size in each dose group made interpretation difficult. The sponsor's response to this question has not resulted in any changes to the conclusions of the first round of evaluation.

# 13. Second round benefit-risk assessment

## 13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of enzalutamide in the proposed usage are unchanged from those identified in Section 9.1.

## 13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of enzalutamide in the proposed usage are unchanged from those identified in Section 9.2.

## 13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of enzalutamide, given the proposed usage, is favourable.

# 14. Second round recommendation regarding authorisation

It is recommended that the application for the registration of enzalutamide for the treatment of patients with metastatic CRPC who have previously received docetaxel be approved.

# 15. References

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