EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 April 2013
EMA/CHMP/383457/2013
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Xtandi

enzalutamide

Procedure No **EMEA/H/C/002639**

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Product information

Name of the medicinal product:	Xtandi
Applicant:	Astellas Pharma Europe B.V. Sylviusweg 62 2333 BE Leiden The Netherlands
Active substance:	enzalutamide
International Nonproprietary Name/Common Name:	enzalutamide
Pharmaco-therapeutic group (ATC Code):	Not yet assigned
Therapeutic indication:	Treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy.
Pharmaceutical form:	Capsule, soft
Strength:	40 mg
Route of administration:	Oral use
Packaging:	blister (PVC/PCTFE/Alu)
Package size:	112 capsules

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List of abbreviations

ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	Androgen Receptor
AST	alanine aminotransferase
AUC	Area Under the Curve
AUC_{inf}	Area Under the Curve Extrapolated Based on the Elimination Rate Constant
BCS	Biopharmaceutics Classification System
BHA	Butylated hydroxyanisole
BHT	Butylated hydroxytoluene
Bic	bicalutamide
BUN	blood urea nitrogen
CCMG	Caprylocaproyl Macroglycerides
CEP	Certificate of Suitability to the Monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CL/F	Apparent Oral Clearance
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Plasma Concentration
CPP	Critical Process Parameter
CRPC	Castration Resistant Prostate Cancer
CSF	cerebrospinal fluid
CYP	Cytochrome P450
%CV	Percent Coefficient of Variation
DHT	dihydrotestosterone
dL	Deciliter
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
EC	European Commission
ECG	Electrocardiogram

ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EQ-5D	European Quality of Life Five-Domain Scale
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FDA	Food and Drug Administration
FDHT	16β-^{18}F-fluoro-5α-dihydrotestosterone
FOB	functional observational battery
FT-IR	Fourier Transform Infrared Spectroscopy
g	Grams
GABA	Gamma Aminobutyric Acid
GC	Gas Chromatography
GCP	Good Clinical Practice
GnRH	Gonadotropin Releasing Hormone
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug Application
IR	Infrared Spectroscopy
ITT	Intent-to-Treat
KF	Karl Fischer Titration
kg	Kilogram
L	Litre
LC-MS/MS	Liquid Chromatography with Tandem Mass Spectrometry
LLQ	lower limit of quantitation
MAA	Marketing Authorisation Application
mg	Milligram
mL	Millilitre
MRP2	Multidrug Resistance Associated Protein 2
ms	Millisecond
M1	Major Human Metabolite MDPC0001 (Inactive)
M2	Major Human Metabolite MDPC0002 (Active)

m^2	Meters Squared
MTD	Maximum Tolerated Dose
NA	Not Applicable
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NF	National Formulary
ng	Nanograms
NM	Estimate Not Met
NMDA	N-methyl-D-aspartate
NMP	*N*-Methylpyrollidinone
NMR	Nuclear Magnetic Resonance Spectroscopy
NR	Not Reported
OATP	Organic Anion-transporting Polypeptide
OCT	Organic Cation Transporter
PARP	poly(adenosine diphosphate-ribose) polymerase
PCTFE	Polychlorotrifluoroethylene
PCWG2	Prostate Cancer Clinical Trials Working Group 2
PD	Pharmacodynamics
PET	Positron Emission Tomography
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopeia
PK	Pharmacokinetics
PS	Performance Status
PSA	Prostate-Specific Antigen
PVC	Polyvinyl Chloride
PXR	Pregnane X Receptor
Q	Quartiles
QOL	Quality of Life
QRS	Electrographic Interval Between the Q, R, and S Waves
QSAR	quantitative structure-activity relationship
QT	Electrographic Interval Between the Q and T waves
QT_c	Corrected QT Interval
QWBA	quantitative whole-body autoradiography

RECIST	Response Evaluation Criteria in Solid Tumours
RH	Relative Humidity
SAE	Serious Adverse Event
SD	Standard Deviation
SEM	standard error of the mean
SmPC	Summary of Product Characteristics
SSC	solid scintillation counting
$t_{1/2}$	Terminal Half-Life
TSE	Transmissible Spongiform Encephalopathy
US	United States
USP	United States Pharmacopoeia
UV	Ultra-violet Spectroscopy
V/F	Apparent Volume of Distribution
XRPD	X-ray Powder Diffraction
YFP	yellow fluorescent protein

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Astellas Pharma Europe B.V. submitted on 26 June 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Xtandi, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 September 2011.

The applicant applied for the following indication:

Xtandi is indicated for the treatment of adult men with metastatic castration-resistant prostate cancer who have received docetaxel therapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance enzalutamide contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 24 June 2010 and a follow-up Scientific Advice on 20 January 2011. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following country: United States of America.

Manufacturer responsible for batch release

Astellas Pharma Europe BV
Sylviusweg 62
2333 BE Leiden
The Netherlands

The product was not licensed in any country at the time of submission of the application.

Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Arantxa Sancho-Lopez **Co-Rapporteur: Bengt Ljungberg**

- The application was received by the EMA on 26 June 2012.
- The procedure started on 15 August 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 2 November 2012 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 2 November 2012 (Annex 2).
- During the meeting on 13 December 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 14 December 2012 (Annex 3).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 January 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 18 February 2013 (Annex 4).
- During the CHMP meeting on 21 March 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 6).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 25 March 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 April 2013 (Annex 7).
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 19 April 2013 (Annex 9).
- During the meeting on 25 April 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Xtandi.

2. Scientific discussion

2.1. Introduction

Problem statement

Disease

Worldwide, prostate cancer ranks second in cancer incidence and sixth in cancer mortality in men (Jemal, 2011). In prostate cancer, hormonal therapies include surgical or medical castration therapy. Tumours that progress despite castrate levels of testosterone in the blood are considered castration-resistant. Despite the early sensitivity of these tumours to hormonal strategies, castration-resistant progression generally represents a transition to the lethal state of the illness, and most patients ultimately succumb to this disease. The median survival of patients with castration-resistant disease is approximately 1–2 years (Lassi, 2010, Petrylak, 2004).

Treatment

Results of clinical investigations and studies on the molecular profiles of these progressing prostate tumours show that the androgen receptor remains functional and that the tumours should respond to strategies directed at the androgen receptor signalling axis. Over-expression of the androgen receptor has been documented in upwards of 50% of castration-resistant prostate cancer specimens and is believed to contribute to tumour progression (Pienta, 2006, Chen, 2004). Currently approved anti-androgens, including bicalutamide and flutamide, have the potential to agonize or stimulate androgen receptor signalling in the setting of androgen receptor over-expression, thereby exacerbating or accelerating castration-resistant tumour growth (Kelly, 1993, Small, 1995). The resulting decline in serum levels of prostate-specific antigen (PSA) seen in some patients upon discontinuation of these agents is consistent with the agonist effects ("anti-androgen withdrawal syndrome";).

In clinical practice, treatment of advanced prostate cancer is limited by the development of resistance to currently available anti-androgen therapies. Most patients receive 2 or more hormonal manipulations and are then offered chemotherapy as their disease continues to progress (Chen, 2004). Three agents have demonstrated a survival advantage and are approved for the treatment of castration-resistant prostate cancer: docetaxel with prednisone as front-line chemotherapy; cabazitaxel with prednisone following docetaxel; and abiraterone acetate with prednisone or prednisolone (a hormonal therapy that blocks androgen synthesis).

The randomized study in metastatic castration-resistant prostate cancer comparing docetaxel administered every 3 weeks to docetaxel weekly and to mitoxantrone demonstrated a 2.4 months survival benefit for docetaxel every 3 weeks (Tannock, 2004). Once patients progress on docetaxel, cabazitaxel is approved as second-line chemotherapy with a 2.4 month survival advantage over mitoxantrone plus prednisone (de Bono, 2010). This intravenous chemotherapy is complicated by febrile neutropenia, neutropenic deaths, and serious gastrointestinal side effects including diarrhoea. Recently, abiraterone acetate, an oral inhibitor of androgen biosynthesis, has been approved for patients with metastatic castration-resistant prostate cancer who have previously received docetaxel after demonstrating a 3.9-month survival advantage over placebo (de Bono, 2011). Treatment with abiraterone acetate requires the co-administration of prednisone and is complicated by the side effects of mineralocorticoid excess (hypertension, hypokalaemia, and fluid overload), hepatotoxicity, and adrenal insufficiency. Abiraterone is also indicated with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

About the product

Enzalutamide (MDV3100) is an oral androgen receptor signalling inhibitor designed to block multiple steps in the androgen receptor signalling pathway and to be devoid of agonist activity in castration-resistant prostate cancer. In initial pharmacology experiments, MDV3100 competitively inhibited androgen-induced receptor activation (binding of androgens to androgen receptor in the cytosol), inhibited nuclear translocation of activated androgen receptors, and inhibited the association of the

activated androgen receptor with chromatin, even in the setting of androgen receptor overexpression and in prostate cancer cells resistant to anti-androgens. The consequences of androgen receptor signalling inhibition by MDV3100 include reduced expression of androgen receptor dependent genes, decreased growth of prostate cancer cells, induction of cancer cell death, and tumour regression.

The applicant claimed the approval for the following indication:

Xtandi is indicated for the treatment of adult men with metastatic castration-resistant prostate cancer who have received docetaxel therapy.
The final indication following CHMP review of this application is:

Xtandi is indicated for the treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy.

Type of Application and aspects on development

This application has been submitted in accordance with the Article 8(3) of Directive 2001/83/EC, concerning a new active substance in the centralised procedure containing administrative, quality, non-clinical and clinical data.

A request for accelerated assessment has been rejected by the CHMP on 21 June 2012 as the CHMP considered the applicant's claims related to the unmet medical need were not substantiated by submitted data.

Scientific Advice on the design of the CRPC2 study was not requested from the CHMP. However, Scientific Advice on other aspects of the nonclinical, pharmacology, and clinical program was requested from the CHMP on 24 June 2010 (EMA/CHMP/SAWP/372658/2010) with follow-up advice received on 20 January 2011 (EMA/CHMP/SAWP/18792/2011). The CHMP concurred that the elements of a comprehensive electrocardiogram (ECG) evaluation, including QT/QTc assessments performed by a central laboratory, embedded into the CRPC2 study would be acceptable to support the clinical development program in patients with castration-resistant prostate cancer.

Although the initial CHMP Scientific Advice stated that the metabolism of MDV3100 could be conducted with cold material, a standard 14C metabolism study (9785-CL-0001) was conducted in healthy subjects to provide definitive information on the metabolic fate of MDV3100. The final approach for examining metabolism was agreed upon by the CHMP at the follow-up Scientific Advice. The results of the 14C-metabolism study were consistent with the advice from the CHMP, including nearly 90% recovery of total radioactivity over the 77-day collection period (mean 84.6%, range: 75.4%–92.0%, n = 6). The CHMP also noted that data derived from the 14C-study, as well as in vitro data supporting expected bioavailability (i.e., Caco-2 permeability), could be used instead of an absolute bioavailability study assuming that high bioavailability was predicted.

The CHMP agreed that the completed parallel design food-effects study (MDV3100-05) could be used to support labelling.

2.2. Quality aspects

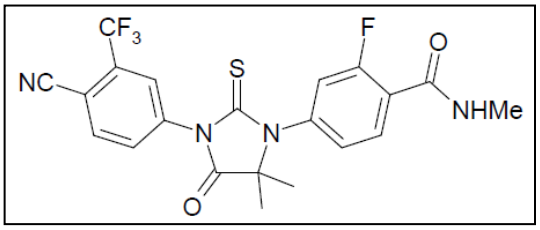
2.2.1. Introduction

The finished product is presented as soft capsules containing 40 mg of Enzalutamide as active substance. The composition is described in section 6.1. of the SmPC.

The product is available in PVC/PCTFE/Alu blisters.

2.2.2. Active substance

Enzalutamide is a white to off-white, non-hygroscopic crystalline solid, freely soluble in NMP and acetonitrile, sparingly soluble in absolute ethanol, and practically insoluble in water between pH 1 and 11. The chemical name is 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide, also known as 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide, 3-(4-cyano-3-trifluoromethylphenyl)-1-[3-fluoro-4-(methylcarbamoyl)phenyl]-5,5-dimethyl-2-thioxoimidazolin-4-one, and benzamide, 4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-1-imidazolidinyl]-2-fluoro-*N*-methyl and has the following structure:



The structure of enzalutamide was unambiguously confirmed by ^{1}H and ^{13}C NMR, UV spectroscopy, FT-IR spectroscopy, mass spectrometry and elemental analysis.

Enzalutamide is achiral, therefore no stereoisomerism is observed. A single polymorphic form has been observed which is consistently produced by the manufacturing process. The pure drug substance thus produced melts at 201 ^{o}C. Four other solvates have been observed but are not produced from the manufacturing process.

Manufacture

Enzalutamide is synthesized in four main steps from three commercially available, well defined starting materials. Detailed information about the manufacturing process, control of starting materials, reagents and solvents, control of critical steps and intermediates along with process development and validation has been provided. Step 1 is performed by a single manufacturer. Step 2 is carried out by a different single manufacturer. Steps 3 and 4 are performed by a further single manufacturer.

The manufacturing process is adequately described. Appropriate specifications have been adopted for the starting materials, taking into account their route of synthesis, as well as for intermediates, solvents and reagents. All relevant impurities, including degradation products and residual solvents have been appropriately characterised and are controlled at safe limits. Several critical process parameters (CPPs) were identified which are well-controlled in the process by the choice of adequate set-points and operation within achievable operating ranges. Therefore, the manufacturer has good control over the manufacturing process and the described in-process controls are considered adequate to ensure the required quality of intermediates and active substance.

The active substance is packaged in double polyethylene bags with twist ties and then stored in steel drums.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC), assay (HPLC) impurities (HPLC), genotoxic impurities (GC), residual solvents (GC), heavy metals (USP method II), and residue on ignition (Ph. Eur.). Rationale for the absence of water content specification was considered justified. The specifications and test proposed are compliant with the relevant ICH guidelines and general requirements of Ph. Eur., except for the heavy metals test for which USP

method is used since this was considered more sensitive. The specifications are adequate to control the quality of the active substance. The impurity profile of the active substance has been thoroughly evaluated. The applicant has provided information about the origin of impurities and levels observed in the drug substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data on three commercial scale batches of the active substance are provided. The results comply with the proposed specifications and confirm consistency and uniformity of the active substance manufacture.

Stability

One commercial scale batch of the active substance packed in the intended commercial package from the proposed manufacturer was put on stability testing as per ICH conditions, under long term conditions (25 °C / 60% RH) for up to 24 months, and under accelerated conditions (40 °C / 75% RH) for up to 6 months. Two further commercial scale batches of the active substance from a different manufacturer packed in double polyethylene bags but in a HDPE drum were also put on stability testing as per ICH conditions: under long term conditions (25 °C / 60% RH) for up to 18 months, and under accelerated conditions (40 °C / 75% RH) for up to 6 months. Stability was also tested under stressed conditions. In the solid state, the active substance was stored in an open dish, heated, and exposed to light. Stability was also tested under stressed conditions in solution: acid hydrolysis, base hydrolysis, oxidation and light. The following parameters were tested: appearance, assay (HPLC), impurities (HPLC), water content (KF) and form (XRPD). The active substance was stable to ICH long term storage conditions, heat, humidity, and light, and in solution, to acid. Degradation was observed in solution on exposure to peroxide, base, and light. The results demonstrate that the analytical methods are stability indicating. In conclusion, no special storage conditions are required and the results justify the proposed re-test conditions in the proposed container.

2.2.3. Finished medicinal product

Pharmaceutical development

The objectives of formulation development were to develop an immediate-release oral dose of enzalutamide. The active substance is a crystalline solid, routinely manufactured as a single polymorphic form. It is practically insoluble in aqueous media between pH 1-11 but highly permeable (BCS class II) and thus, dissolution of the active substance is rate-limiting for bioavailability. Early animal studies demonstrated that bioavailability was greater when enzalutamide was dosed as a solution rather than as a suspension or solid formulation. Therefore, the primary goal of the pharmaceutical development program was to formulate the active substance in the liquid state, encased within a capsule. As a result, and despite the low aqueous solubility, particle size and morphology were not considered as critical quality attributes of the active substance.

Caprylocaproyl macroglycerides (CCMG) was identified as the solvent in which the active substance has the greatest solubility, allowing a reasonably sized capsule to be manufactured containing the intended 40 mg strength of enzalutamide. Studies to address the precipitation risk at this concentration were carried out and indicated the long-term solution stability of this formulation. Anti-oxidants are included to prevent oxidative degradation of the active substance on storage. Their use has been justified as the oxidative degradants are not controllable by other means. A hard shell capsule was used for phase I clinical studies, but the applicant switched to a more robust soft shell capsule for later clinical studies and the commercial product.

All of the chosen excipients are well-known and widely used in the production of soft capsules and liquid formulations. The excipients include: CCMG (solvent); water; butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA, both antioxidants); gelatin (shell material); sorbitol sorbitan solution and glycerol (plasticizer); titanium dioxide (colorant and opacifier); black printing ink. CCMG, BHA, BHT, gelatin and titanium dioxide are controlled in accordance with Ph. Eur. monographs. The plasticizer agents met the following standards respectively, sorbitol sorbitan solution (NF) and glycerol (Ph. Eur.). The black printing ink is a mixture of compendial components including iron oxide black (EC directive) and polyvinyl acetate phthalate (NF) which also meet in-house specifications. The active substance was demonstrated to be compatible with the excipients.

The formulation used during phase II and III clinical studies is slightly different from that planned for commercial use. There is a small reduction in anti-oxidant level and compensatory increase in CCMG, but these are not considered likely to affect the bioavailability. A single impurity, not present in the active substance, was identified as forming by oxidation during secondary manufacture and on storage. Its formation is controlled by the antioxidants throughout shelf-life and thus oxidative stability of the commercial formulation has been demonstrated.

The primary packaging proposed is PVC/PCTFE/Alu blisters, with four capsules per blister. The material complies with Ph. Eur. requirements and is adequate to support the stability and use of the product.

Adventitious agents

Bovine derived gelatin is used in the capsule shell. A valid TSE CEP from the suppliers of the gelatin used in the manufacture is provided.

Manufacture of the product

The manufacturing process consists of 4 main steps: (i) enzalutamide, BHA, BHT, and CCMG are mixed to form the fill solution; (ii) a blend of gelatin, water, plasticizers and colorant are mixed to form the gel mass; (iii) the gel mass is used to form the capsule and the fill solution is added (iv) the capsule is sealed, washed and dried. A detailed description and flow diagram of the manufacturing process has been provided. Adequate process controls are in place for each of these steps to ensure the quality of the finished product. The process is considered standard for the production of soft liquid-filled gel capsules. Therefore, formal validation of the process in the production facilities has not yet been completed but will be carried out prior to release of Xtandi soft gel capsules to the market. A process validation scheme has been provided and the applicant has committed to validating the process before commercialisation.

A risk assessment was carried out to identify potential critical steps in the manufacturing process and these were investigated experimentally. A single critical step was identified which affects assay, content uniformity, and appearance. Operating ranges for the key process parameters were defined to ensure quality of the Xtandi capsules.

Product specification

The finished product release specification includes appropriate tests for appearance (visual description), identification (HPLC and UV), assay (HPLC), degradants (HPLC), uniformity of dosage unit (HPLC), anti-oxidants (HPLC), dissolution (Ph. Eur.), and microbiological limits (Ph. Eur.). No tests for water content or active substance impurities are included and this has been justified by the applicant.

Batch analysis results from three pilot scale (30% of commercial scale) batches confirm consistency and uniformity of manufacture and indicate that the process is capable and under control.

Stability of the product

Stability data from three pilot scale batches in the proposed commercial packaging stored under long-term conditions (25 ºC / 60% RH) for up to 12 months and under accelerated conditions (40 ºC / 75% RH) for up to 6 months according to ICH guidelines were provided. The capsules were stored in the proposed commercial packaging. Samples were tested for appearance, assay, degradants, anti-oxidant content, dissolution, rupture test, and microbial limits. The analytical procedures used were stability indicating.

The applicant commits to further testing at up to 36 months under long-term conditions (25 ºC / 60% RH) for each of the aforementioned batches. After approval, one commercial batch per year will be placed on stability.

In addition, stability under stressed conditions was investigated.One pilot batch was exposed to both UV and visible light as defined in the ICH Guideline Q1B on Photostability Testing of New Drug Substances and Products. The drug product was tested for appearance, assay, degradants, and rupture in water. No significant changes in Xtandi soft gel capsule quality attributes were observed and thus, the product is not sensitive to light.

One development batch was exposed to four freeze-thaw cycles (-25 – 20 ^{o}C) over 4 weeks. No significant changes in Xtandi soft gel capsule quality attributes were observed, and in particular, no precipitation of active substance was noted, and thus, the product is stable to low temperature conditions.

One pilot batch was stored under long-term conditions (25 ºC / 60% RH) and under intermediate conditions (30 ºC / 65% RH) for up to 8 weeks in an open dish. The drug product was tested for appearance, assay, degradants, rupture in water, and water content. An increase in water content was observed but this did not result in significant changes to Xtandi soft gel capsule quality attributes.

Based on available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

Repeat-dose toxicity studies used the once-daily oral administration regimen, and were conducted in mice, rats and dogs. The rat and dog were selected as the main species for the toxicology program.

The pivotal toxicology studies supporting the safety of MDV3100 were conducted in compliance with Good Laboratory Practice (GLP) regulations and International Conference on Harmonization (ICH) guidelines, with the exception of single dose toxicity studies and preliminary repeated-dose toxicity studies.

All non-clinical data (pharmacology, pharmacokinetics, toxicology) are original data and have been obtained from non-clinical studies performed by the applicant. In this assessment report, several CHMP/ICH guidelines have been considered, including CPMP/ICH/286/95 M3(R2) "Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals" and CHMP/ICH/646107/2008 S9 "Nonclinical evaluation for anticancer pharmaceuticals".

2.3.2. Pharmacology

Primary pharmacodynamic studies

The binding of MDV3100 to the AR was evaluated using in vitro and cell-based binding assays. MDV3100 competed for ligand binding to the AR wild-type (LNCaP/AR) and the mutated type (LNCaP) with inhibition concentration 50% (IC_{50}) values of 0.021 µM (0.0098 µg/mL) and 0.062 µM (0.029 µg/mL), respectively.

In competition binding studies performed with the synthetic AR agonist ^{3}H-R-1881 (methyltrienolone), MDV3100 inhibited the agonist in a concentration-dependent manner. The inhibition constant was largely unaffected by the concentration of ^{3}H-R-1881 used in the assay, indicating competitive inhibition.

In an in vitro study using a fluorescence resonance energy transfer assay, binding of MDV3100 to AR prevented the conformational change necessary for AR co-activator protein association, whereas binding of dihydrotestosterone (DHT) or bicalutamide induced this conformational change required for optimum AR signalling.

Inhibition of Androgen Receptor Nuclear Translocation

Inhibition of AR signalling was evaluated using cell-based activity assays specific for nuclear translocation and association with nuclear co-activator protein. Androgen receptor nuclear translocation was evaluated by a qualitative method using an AR-fluorescent fusion protein system as well as a quantitative method using a beta-galactosidase (β-gal) enzyme fragment complementation system. The assays were performed in the presence of a synthetic AR agonist (R-1881) to measure the inhibitory effects of MDV3100. In the AR-fluorescent fusion protein system, MDV3100 inhibited DHT-induced nuclear translocation. In the quantitative β-gal enzyme complementation assay, MDV3100 inhibited AR agonist-induced nuclear translocation in a concentration-dependent manner with an IC_{50} of approximately 1.9 µM.

Inhibition of Androgen Receptor Chromatin Association

The effects of MDV3100 on AR association with chromatin were assessed in a cell-based activity assay using a chromatin immunoprecipitation method. MDV3100 treatment inhibited the association of AR

with the chromatin of AR-regulated genes (prostate-specific antigen [PSA] and transmembrane protease, serine 2 [TMPRSS2]). AR chromatin interactions were also assessed with a cell-based assay that uses a VP16-AR fusion protein with an AR-dependent luciferase transcription reporter system. While androgens are not required to induce nuclear localization of the VP16-AR fusion protein, they are required to activate the AR-dependent gene expression reporter system. In this assay system, MDV3100 inhibited R-1881-induced activation of the luciferase reporter, consistent with inhibition of nuclear AR signalling, independent of the nuclear translocation step.

Inhibition of Androgen Receptor-Dependent Transcription and Cancer Cell Proliferation, and Induction of Cell Death and Tumour Regression

The consequence of AR signalling inhibition by MDV3100 in prostate cancer cells was demonstrated in cell-based assays of AR-dependent transcription, cell growth, and cell death. MDV3100 consistently inhibited AR-mediated gene expression, reduced cell growth, and increased cell death by apoptosis in castration-resistant cell lines (LNCaP/AR, VCaP, and W741C-LNCaP).

In a mouse xenograft model implanted with LNCaP/AR cells MDV3100 inhibited tumour cell growth and induced tumour regression.

Lack of Androgen Receptor Agonist Activity

MDV3100 was tested in a series of tissue culture assays as described above that included several distinct steps in AR signalling (nuclear translocation, AR co-activator protein association, and AR association with chromatin), as well as the consequence of AR signalling. In all of these assays, MDV3100 lacked agonist activity while the agonist activity of the anti-androgens such as bicalutamide was apparent. MDV3100 inhibited tumour cell growth and induced tumour regression in a dose-dependent fashion in an in vivo mouse LNCaP/AR xenograft model. In this model, bicalutamide acts as an agonist promoting tumour cell growth and increasing tumour volume.

Primary Pharmacodynamics of MDV3100 Metabolites

Six metabolites (M1, M2, M3, M4, M5, and M6) have been characterised in nonclinical studies. Of these metabolites, only M1 and M2, also known as MDPC0001 and MDPC0002, respectively, have been detected in plasma in humans as major metabolites. M1 and M2 were evaluated for activity related to the key primary pharmacodynamics of MDV3100: AR binding in vitro and inhibition of AR nuclear translocation. These assays determined that M2, the prominent MDV3100 metabolite in humans, is an active metabolite. M2 has high affinity for the AR (IC_{50} = 0.176 µM) with a potency similar to that of the parent and inhibited AR nuclear translocation in response to an agonist (IC_{50} = 3.2 µM) with a potency similar to parent. M1 is an inactive metabolite in these primary pharmacodynamic assays. The other metabolites had either no detectable or much lower AR binding affinity.

Secondary pharmacodynamic studies

The secondary pharmacodynamics of MDV3100 and major metabolites M1 and M2 were assessed in several binding and enzyme activity assays, including neurotransmitter receptor binding, ion channels, enzymes and intracellular kinases. MDV3100 and metabolite M2 showed significant interaction was with the human progesterone receptor (IC50 = 16.1 µM for MDV3100, 6.2 µM for M2) and the rat GABA-gated chloride channel (IC50 = 2.6 µM for MDV3100, 7.1 µM for M2). A cell-based activity assay for the GABA-gated chloride channel (α1β3 GABA-A receptor subtype) demonstrated that both parent and metabolite M2 were functional inhibitors of this channel. On the other hand, major metabolite M1 only bound weakly to the GABA-gated chloride channel, and no interactions of M1 were detected in binding and activity screening assays.

Safety pharmacology programme

Single-dose safety pharmacology studies were performed in mice, rats, and dogs to assess any acute effects on central nervous system, respiratory, and cardiovascular parameters as described in table 1.

Table 1: Safety Pharmacology Studies of MDV3100

Study No./GLP	Study Title	Noteworthy findings
PRO3100NC91/No	Effect of MDV3100 on Cloned hERG Potassium Channels Expressed in Mammalian Cells	IC_{50} of 17.6 µM
PRO3100NC104/Yes	Effects of MDV3100 on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells	MDV3100 inhibited the hERG current with an IC_{50} of 15.7 µM
PRO3100NC92/No	Effects of M2 on Cloned hERG Potassium Channels Expressed in Mammalian Cells	IC_{50} of 14.8 µM
PRO3100NC107/Yes	Effects of M2 on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells	M2 inhibit the hERG channel with an IC_{50} of 18.6 µM
PRO3100NC96/Yes	Neurobehavioral Evaluation of Orally Administered MDV3100 in Rats	There were no test article-related effects on any functional observational battery endpoint (i.e., general activity or arousal, neuromuscular function, sensorimotor function, autonomic function, or general physiological measurements) at any time interval for scheduled evaluations. Dose ≤ 200 mg/kg.
9785-PT-0005/No	Convulsion Effects of MDV3100 in Mice	*Repeated dose(7d)* 60 mg/kg:Bradypnea (3/10).200 mg/kg: tremor (2/10), bradypnea and hypolocomotion (9/10). Clonic convulsions (CC) and tonic convulsions (TC) were observed in 9/10 animals within 3 days of dosing. *Single dose* 400 mg/kg: tremor (5/10), bradypnea (4/10) and hypolocomotion (7/10). CC and TC were observed in 7/10 animals within 24 hours after dosing.
PRO3100NC95/Yes	Respiratory Evaluation of Orally Administered MDV3100 in Male Rats	MDV3100 had no effect on any clinical observations or respiratory function assessments at doses up to and including 200 mg/kg.
PRO3100NC94/Yes	Cardiovascular Safety Pharmacology Evaluation of MDV3100 Administered by Oral Gavage to Naïve Telemetry-Instrumented Conscious Male Beagle Dogs with a Toxicokinetic Arm	The ECG data (PR, QRS, QT and QTc) were qualitatively and quantitatively within normal limits. Dose ≤ 30 mg/kg.

As MDV3100 inhibits the GABA-gated chloride channel, additional studies were performed to assess convulsion potential in mice (Table 2).

Table 2: Nonclinical Studies Related to the Convulsion Potential of MDV3100

	Studies	Observation	Study Number
In vitro	Chloride channel binding	MDV3100 binds to the GABA-gated chloride channel: IC_{50} = 2.6 µM (1.2 µg/mL) Ki = 2.1 µM (1.0 µg/mL)	PRO3100NC50
		M1 does not bind to the GABA-gated chloride channel	PRO3100NC63
		M2 binds to the GABA-gated chloride channel: IC_{50} = 7.1 µM (3.2 µg/mL) Ki = 5.9 µM (2.7 µg/mL)	PRO3100NC154
	Inhibition of GABA-gated chloride channel activity in whole cells	MDV3100 inhibits the GABA-gated chloride channel IC_{50} = 3.0 µM (1.4 µg/mL)	PRO3100NC72
		M2 inhibits the GABA-gated chloride channel IC_{50} = 2.3 µM (1.04 µg/mL)	PRO3100NC72

In vivo	Brain penetration studies in rodents	MDV3100 and M2 crossed the blood-brain barrier in rats and mice. Based on the brain-to-plasma ratios in rats, MDV3100 and M2 concentrations in brain are approximately the same as those in the plasma.	PRO3100NC84 9785-ME-5016
	2-week oral gavage bridging toxicity study in rats	MDV3100 treatment was associated with a convulsion in a single rat at a dose of 100 mg/kg.	PRO3100NC31
	Single-dose study in mice	MDV3100 treatment was associated with convulsions in mice at a dose ≥ 400 mg/kg	9785-TX-0002
	Repeat-dose oral toxicity study in mice	MDV3100 treatment was associated with a convulsion in a single female mouse (1/5 per group) at a dose of 300 mg/kg on Day 2	9785-TX-0007
	Convulsion model in mice	MDV3100 treatment was associated with a dose-dependent incidence of convulsions in mice at doses ≥ 200 mg/kg	9785-PT-0005
	4-week dog toxicity study	MDV3100 treatment in 28-day dog toxicity study was associated with a single convulsion on Day 28 in a dog receiving 60 mg/kg/day.	PRO3100NC18

Pharmacodynamic drug interactions

No nonclinical pharmacodynamic drug interaction studies have been performed.

2.3.3. Pharmacokinetics

Absorption

In the permeability study, MDV3100 showed low solubility and high permeability across Caco-2 monolayers. MDV3100 is eliminated slowly from plasma with a long t ½ across species; plasma clearance is low. With daily oral administration, the mean accumulation index is approximately 1 to 3 in rats, 1 to 4 in dogs and 8.3 in humans, reflecting the long t ½ relative to the dosing interval. A gender difference in PK is apparent in rats, with a 2-fold higher exposure in females, but not in mice, dogs or monkeys.

In the absorption studies it was shown that MDV3100 as a caprylocaproyl macrogolglycerides (CCMG) solution is well absorbed after oral administration in mice, rats, dogs and monkeys. At low doses, oral bioavailability in rats and dogs is greater than 70% and decreases with increasing size. On the other hand, in the PK studies in dogs performed to support formulation development it was shown that oral bioavailability is higher when dosed as a CCMG solution than when dosed as a suspension in CCMG or other particulate formulation. In addition, MDV3100 as a CCMG solution has high oral bioavailability, which is not increased by combining CCMG with other solvents or surfactants. The CCMG formulation was chosen as the final formulation for the preclinical and clinical studies.

Distribution

Tissue distribution data in rats show rapid and extensive distribution to all tissues. The tissues with the higher concentrations are fat, stomach and liver. MDV3100 and the metabolites M1 and M2 were detected in the brain of rats, indicating that they can cross the blood-brain barrier in rats. Based on

brain-to-plasma concentration ratios, MDV3100 and M2 appear to readily partition into brain, while M1 appears to have low penetration into brain.

MDV3100, M1 and M2 showed a high binding to plasma protein in vitro (>90% for all species) over a wide range of concentrations. After a single oral dose of 14C-MDV3100 in rats and dogs, the mean CB/CP ratios generally range from 0.456 to 0.659, indicating that drug-derived radioactivity is preferentially retained in the plasma component of blood.

Metabolism

In the metabolism studies performed with 14C-MDV3100, it was shown that MDV3100 is extensively metabolised in rats, dogs and humans via the same Phase I pathways, mainly demethylation, oxidation and hydrolysis reactions. Phase II products were observed in animals only in bile, these metabolites were not detected in humans, although bile was not collected in patients. Based on recovery of radioactivity through the sample extraction process, it appears that there is no formation of reactive metabolites in rats, dogs or humans.

Excretion

Orally administered MDV3100 is mainly eliminated as metabolites in the urine and feces in rats and dogs. In rat, urine and feces have a similar importance, whereas in dogs and humans urinary is the major route of excretion.

2.3.4. Toxicology

Single dose toxicity

Table 3 Single dose toxicity studies:

Study ID	Species/ Sex/Number/ Group	Dose [mg/kg]/oral gavage	Approx. lethal dose / observed max non-lethal dose	Major findings
9785-TX-0002	Crlj:CD1(ICR) mice/male and female/3 per gender per dose per time point	50,100,200, 400, 800, 1600	400/200	≥400: Decreased activity, clonic convulsions and/or tremors, irregular respiration, prone/lateral position and/or lacrimation. MTD=200 mg/kg
9785-TX-0003	Cynomolgus monkeys/male and female/3 per gender	single dose of 30 mg/kg on Day 1, a single dose of 100 mg/kg on Day 14, and two 30 mg/kg doses 4 hours apart (i.e., total dose of 60 mg/kg) on Day 35 under fed conditions.	No mortality	Muddy stools and vomiting at all dose levels. MTD was not achieved.

In a single dose toxicity study in mice, mortality and clonic convulsions occurred at doses ≥ 400 mg/kg. The only histopathological finding in this study was dark reddish focus on the mucosa of the glandular stomach in some animals. In an escalating single dose study in cynomolgus monkeys muddy stools and vomiting were observed.

Repeat dose toxicity

The dosing schedules in the repeat-dose toxicity studies were the same as the clinical regimen of once-daily oral administration, and they were conducted in mice, rats and dogs. The rat and dog were selected as the main species for the toxicology program. MDV3100 was dosed as a CCMG solution, but for several high-dose treatment groups, solubility limitations led to the use of CCMG suspensions.

Table 4: Repeat-dose toxicity studies

Study ID/GLP	**Species/Sex/ Number/Group**	**Dose [mg/kg]/oral gavage**	**Duration**	**NOEL/ NOAEL (mg/kg/day)**
9785-TX-0007/No	Mouse/Crlj:CD1(ICR)	30,100, 300	1 week	Not reported
Major findings: One male in the 100 mg/kg dose group and 4 males and 4 females in the 300 mg/kg group died or were sacrificed on day 2. 100: ↓bw(M), food cons. (F),↑ platelet count and ↓ haemoglobin, hematocrit and corpuscular vol. ↓ cholesterol (M+F), ↑ ALP (M). 300: ↑ AST,ALT, glucose and BUN (1F). 100+300: Changes in liver, adrenal, thymus, spleen, stomach, ileum and seminal vesicle. MTD 30-100mg/kg				
9785-TX-0011/No	Rat /Crl:CD(SD)/ 6M, 6F per dose group	10, 30, 100, 200	1 week	Not reported
(A one-week toxicokinetics study conducted to provide data on M1 and M2 exposure in rats) **Major findings:** No abnormalities were observed in clinical signs or body weight in any group.				
PRO3100NC15/No	Rat/SpragueDawley/6M/6F (main group); 9M/9F (toxicokinetic group)	10, 30, 100	2 weeks	Not reported
Major findings: Clear oral discharge, audible or irregular respiration, alopecia, and brown or yellow haircoat. Slightly ↓ hemoglobin and hematocrit at 100 mg/kg; slightly ↑ cholesterol at all dose levels; slight ↓ in albumin in females in the 100 mg/kg group. ↓ prostate, seminal vesicle, and epididymis weights at all dose levels (correlating with small prostate or seminal vesicle at 100 mg/kg); ↓ testes weight (males) and ↑ liver, heart, adrenal, and lung weights (females) at 100 mg/kg.				
PRO3100NC17/GLP	Rat/Crl:CD(SD)	10, 30, 100	28 days	100 mg/kg/day
Major findings: Slight ↓ in red blood cell, hemoglobin, and hematocrit values in rats given 100 mg/kg/day, ↑ in serum protein, and cholesterol at doses ≥ 30 mg/kg/day, and ↑ in albumin in males given ≥ 30 mg/kg/day. ↓ absolute and relative weights of epididymides, seminal vesicles, and prostate in all MDV3100-treated male rats. Slight to minimal diffuse hepatocellular hypertrophy was noted in males (100 mg/kg/day) and females (30 and 100 mg/kg/day). Incidence of chronic nephropathy was minimal in the males treated at 100 mg/kg/day compared with the CCMG-treated control males.				
PRO3100NC39/GLP	Rat/Sprague-Dawley	10,30,100,200	26 weeks	100 mg/kg

Major findings: Body weight gain ↓M and ↑F. At all doses, slight ↓ in red blood cell, hemoglobin, and hematocrit values (F). ↑cholesterol M+F. Decreases in prostate gland size at ≥ 30 mg/kg/day and in seminal vesicle size at ≥ 10 mg/kg/day, mild uterine enlargement at 100 mg/kg/day, and minimal ↑ in pituitary gland in females at ≥ 10 mg/kg/day. At all doses, ↑ in liver, pituitary, and adrenal gland weights, ↓ in prostate, epididymides, and seminal vesicles' weights. Histopathological findings included hypertrophy in the liver, atrophy in hormone-sensitive tissues (prostate, seminal vesicles, mammary glands, and uterus with cervix), hypertrophy/hyperplasia in endocrine tissues (pituitary, thyroid and adrenal glands) and nephropathy in kidneys. ↑ incidence of minimal to mild chronic progressive nephropathy was not associated with changes in renal function.				
PRO3100NC14/No (Phase 1)	Dog/Beagle/1M/1F	10, 80, 202 (CCMG solution)	2 weeks	Not reported
Major findings: Phase 1: Two dogs (1 female at 202 mg/kg/day; 1 male at 80 mg/kg/day) were euthanized in a moribund condition on days 8 and 15, respectively. Clinical signs included difficulty dosing, hypoactivity, lateral recumbency, vomitus, excessive salivation, fecal changes (liquid, mucoid, colored). Macroscopic findings in male included mottled uncollapsed lungs and a firm lobe, dark red pancreas, discolored serosa of glandular stomach (few red foci). Aspiration of dose formulation was considered possible. Clinical pathology changes in moribund animals (e.g., elevated total leukocyte, neutrophil and monocyte counts, mild hyperglycemia) were consistent with nervous excitement. Mild panhypoproteinemia was additionally observed in the female. Surviving dogs in all groups exhibited emesis, fecal changes, and excessive salivation; incidence and/or severity was higher with MDV3100 treatment. Slight, progressive decreases in reticulocytes were noted at 202 mg/kg/day. Control female had ALT and GGT elevations on day 3, and the male at 202 mg/kg/day had occult blood in urine at time of red feces. It was unclear if this observation was treatment-related or contamination by feces. All animals except the control male lost weight.				
PRO3100NC14/No (Phase 2)	Dog/Beagle/1M/1F	56.25 (group 5: Oral gavage/CCMG sol. Group 6: Oral gelatine capsule/CCMG)	1 week	Not reported
Major findings: All dogs survived to termination (day 8). Vomitus was seen less frequently in dogs receiving capsules relative to gavage. All dogs lost body weight and had a reduction in food consumption. No notable clinical pathology findings.				
PRO3100NC18/GLP	Dog/Beagle/6M/6F	10, 30, 100/60 (100 reduced to 60 on day 8)	28 days	10 mg/kg
Major findings: 7 dogs (1 vehicle control male, 3 high-dose males, and 3 high-dose females) were euthanized in extremis. Convulsion in 1 dog at 100/60 mg/kg/day. ↑ in serum glucose, cholesterol, and alkaline phosphatase were primarily observed in the high-dose group. ↓ in absolute and relative prostate weights. Histopathological changes were observed in the prostate, testes, and epididymides at all dose levels. At the end of the 4-week recovery period, all microscopic findings persisted in males in the low-dose group (10 mg/kg/day) except for hypospermia and exfoliated cells in the epididymides. ↓ in mean body weight were noted in males (−11.3%) and females (−15.6%) in the high-dose group (100/60 mg/kg/day) and with a ↓ in food consumption.				
PRO3100NC38/GLP	Male Dog/Beagle/5	4, 20, 45	13 weeks	Not reported
Major findings: ↓ in absolute and relative prostatic weights and epididymal weights were seen at all dosage levels. Atrophy of the prostate and epididymides and testicular hypospermatogenesis at all dose levels. Epididymal atrophy and oligospermia/germ cell debris were partially reversible with 45 mg/kg/day and fully reversible with 4 and 20 mg/kg/day. All other findings were reversed.				

Genotoxicity

Table 5: Genotoxic effects of MDV3100

Type of test / study ID / GLP	**Test system**	**Concentrations / Concentration range / Metabolising system**	**Results Positive / negative / equivocal**
Salmonella-Escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay/ PRO3100NC35/GLP	*Salmonella typhimurium* (TA98, TA100, TA1535, and TA1537), *Escherichia coli* (WP*2uvr*A)	156, 313, 625, 1250, 2500, 5000 +/- S9	Negative
L5178Y $TK^{+/-}$ Mouse Lymphoma Forward Mutation Assay with a Confirmatory Assay/ PRO3100NC34/GLP	Mouse lymphoma (L5178Y) cells	5 – 200 µg/ml +/- S9	Negative
A Micronucleus Test in Mice Orally Treated with MDV3100 / 9785-TX-0005/GLP	Chromosomal aberrations, Mice/Crlj:CD1(ICR)	0, 7.5, 15, and 30 mg/kg/day	Negative

Carcinogenicity

No carcinogeniocity studies have been submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

Table 6: Preliminary (non-GLP) Study for Effects of Orally-administered MDV3100 on Embryo-Fetal Development in Mice.

Study type / Study ID	**Species; Number Female / group**	**Route & dose**	**Dosing period**	**Major findings**
Embryo-fœtal development / 9785-TX-0006	Mice/Crlj:CD1(ICR)/8	Orally by Gavage 10, 30 60 mg/kg	G6-15	10, 30, 60: Decreased anogenital distance 30, 60: Cleft palate. 60: Low fetal body weight. Skeletal abnormalities and variations. Delayed ossification.

Effects of MDV3100 on the reproductive system were evaluated during the general toxicology studies, with findings and organ weight changes in the prostate gland, seminal vesicles, testes and epididymides. In a study conducted to assess the effects of the treatment on reproductive tissues in male dogs, transient effects on male reproductive organs were observed. In a non-GLP embryo-foetal development study in mice, MDV3100 induced premature deliveries in dams and embryo-foetal deaths. Decreased foetal body weights and high incidence of external and skeletal abnormalities, such as decreased anogenital distance and cleft palate were also observed.

Toxicokinetic data

In the metabolism studies performed with 14C-MDV3100, it was shown that MDV3100 is extensively metabolised in rats, dogs and humans via the same Phase I pathways, mainly demethylation, oxidation and hydrolysis reactions. In a 1-week toxicokinetic study in rats and an ongoing 39-week toxicity study in dogs, the highest mean M1 exposures in rats and dogs were 31-62% and 96-125%, respectively, of the mean M1 exposures in humans when patients were treated 160 mg/day of MDV3100 to steady state. On the other hand, the highest mean M2 exposures in rats and dogs were less than 10% of the mean M2 exposures in humans.

Orally administered MDV3100 is mainly eliminated as metabolites in the urine and faeces in rats and dogs. In rat, urine and faeces have a similar importance, whereas in dogs and humans urinary is the major route of excretion.

Local Tolerance

No local tolerance studies were submitted (see discussion on non-clinical aspects).

Other toxicity studies

Impurities

The Applicant presented a bridging study to assess the toxic potential of impurities that were observed at higher levels in the intended clinical lot of MDV3100 than in the lot used in the previous 4-week rat toxicity study (PRO3100NC31). The toxicological adverse effects observed in this study were similar to those detected in the previous 4-week study in rats (PRO3100NC17). There were no additional toxicological findings attributable to the impurity profile based on comparisons to the results of other rat toxicity studies.

Process-related impurities of MDV3100 were evaluated for structural alerts using the DEREK software. Alerts for genotoxicity included P1 and P2 precursors of MDV3136 (a 5-amino-2-cyanobenzotrofluoride precursor to MDV3100). Further evaluation consisting of a mini-Ames test, where only 2 strains of *Salmonella typhimurium* were used. In this study, both compounds were cytotoxic and one caused a small increase in revertants in the strain T100 at the highest concentration tested. The Applicant concluded that these potentially genotoxic precursor should be controlled by manufacturing processes to a threshold of toxicological concern of 5.0 µg/day or 30 ppm. Although the testing (mini-Ames test) did not comply with the established guidelines and recommendations, considering the indication of Xtandi and that these impurities are appropriately controlled in the manufacturing process, no further studies are required.

CCMG toxicity

CCMG (caprylocaproyl polyoxylglycerides [NF] or caprylocaproyl macrogolglycerides [Ph. Eur.]) is a non-ionic amphiphilic excipient for pharmaceutical preparations. It is used as a solubilizing agent for poorly soluble drugs in oral liquid and capsule formulations. CCMG showed low toxicity in rats with an oral LD50 value of 22 g/kg (Table 7).

Table 7: Summary of CCMG toxicity

Species	Route	Duration	Dose	Noteworthy Findings
Mouse	Aspiration	Up to 28 days	0.02%, 1%	1% Labrasol ↑ total protein and MPO; mild pulmonary congestion at both concentrations.
Rat	Oral (gavage)	Acute	20, 22.4, 25.1, 28.21, 31.6 g/kg	LD_{50}: 22 g/kg; non toxic
		ADME	10, 150 mg/kg/day	No findings reported
		Embryo-fetal development	0, 1000, 2000, 3000 mg/kg/day	NOEL: 3000 mg/kg/day; no indication of teratogenicity
		14 days	0, 100, 300, 1000, 3000 mg/kg/day	NOAEL: 3000 mg/kg/day
		6 months	0, 300, 1000, 3000 mg/kg/day	NOEL: 300 mg/kg/day; NOAEL: 3000 mg/kg/day
	Intravenous	28 days	10 mg/kg/day	Well tolerated
	Cutaneous	Patch Test	0.02 mL/rat	Very well tolerated
	Ocular	Acute	topical	Slight irritant
Dog	Oral (capsule)	14 days	0, 100, 300, 1000, 3000 mg/kg/day	In high-dose group, moderate suppurative inflammation of the lungs. No adverse effects on survival and clinical signs
		13 weeks	0, 300, 1000, 3000 mg/kg/day	NOEL: 1000 mg/kg/day; NOAEL: 3000 mg/kg/day
Rabbit	Cutaneous	Patch Test	0.5 mL	Well tolerated
	Ocular	Acute	0.1 mL	Slight irritant

↑ Increase; ADME, absorption, distribution, metabolism, excretion; g/kg, grams per kilogram; LD_{50}, lethal dose for 50% of animals; mg/kg/day, milligrams per kilogram per day; mL, milliliters; MPO, myeloperoxidase; NOEL, no observable effect level; NOAEL, no observable adverse effect level.

Phototoxicity

The phototoxic potential of MDV3100 (Study no. 9785-TX-0001) was assessed in cultured mouse fibroblast cells (Balb/c 3T3) using light with ≥280 nm wavelength. MDV3100 did not induce phototoxicity in cultured mammalian cells.

2.3.5. Ecotoxicity / environmental risk assessment

The applicant submitted an environmental risk assessment on the active ingredient enzalutamide. The ERA included a Phase I assessment.

Table 8: Summary of main study results

Substance (INN / Invented Name): Enzalutamide/Xtandi			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log10Pow value of 3	Potential PBT N

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	Not determined	-
	BCF	Not determined	-
Persistence	DT50 or ready biodegradability	Not determined	-
Toxicity	NOEC or CMR	Not determined	-
PBT-statement :	As the log10Pow value is <4.5, there is no requirement to screen MDV3100 for PBT.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0084	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**		
Not applicable			
Phase IIa Effect studies			
Study type	**Test protocol**		
Not applicable			

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed:

To conduct the fish early life cycle test (OECD 210) and the fish sexual development test (OECD 234).

2.3.6. Discussion on non-clinical aspects

The primary pharmacodynamics studies have demonstrated the proof of concept and mode of action of MDV3100 and the active major metabolite M2. MDV3100 did not show androgen receptor agonist activity.

The safety pharmacology studies concerning the central nervous system showed that MDV3100 is associated with dose-dependent convulsions in mice. These convulsions occurred at plasma concentrations that are higher than those expected in humans at the proposed clinical dose of 160 mg/day.

Both MDV3100 and metabolite M2 are antagonists of the GABA-gated chloride channel. This interaction may be the mechanism for the convulsions, as some compounds that inhibit the chloride channel induce seizures. However, the α1β3 GABAA receptor subtype is not abundant in human brain; hence the quantitative extrapolation from these *in vitro* data is limited. Convulsions were also observed in several general toxicology studies at high doses in rats and dogs.

The respiratory and cardiovascular safety pharmacology studies performed in rats and dogs, respectively, showed no other adverse effects. In the in vitro hERG assay MDV3100 and the metabolite

M2 were able to inhibit the hERG current, although in the in vivo studies in rats and dogs no effects on the ECG were detected. In patients, some ECG alterations were observed.

In the pharmacokinetic studies it was shown that MDV3100 is eliminated slowly from plasma with a long t ½ across species. With daily oral administration, the mean accumulation index is approximately 1 to 3 in rats, 1 to 4 in dogs and 8.3 in humans, reflecting the long t ½ relative to the dosing interval. A gender difference in PK is apparent in rats, with a 2-fold higher exposure in females, but not in mice, dogs or monkeys.

Considering the clinical data on pharmacodynamic interactions with other medicinal products or substances, no non-clinical drug interactions studies are required.

In the absorption studies it was shown that MDV3100 as a CCMG solution is well absorbed after oral administration in mice, rats, dogs and monkeys. In the PK studies in dogs it was shown that oral bioavailability is higher when dosed as a CCMG solution than when dosed as a suspension in CCMG or other particulate formulation. Tissue distribution data in rats show rapid and extensive distribution to all tissues. The tissues with the higher concentrations are fat, stomach and liver. MDV3100 and the metabolites M1 and M2 were detected in the brain of rats, indicating that they can cross the blood-brain barrier in rats. MDV3100, M1 and M2 showed a high binding to plasma protein in vitro (>90% for all species) over a wide range of concentrations. In the metabolism studies performed with 14C-MDV3100, it was shown that MDV3100 is extensively metabolized in rats, dogs and humans via the same Phase I pathways, mainly demethylation, oxidation and hydrolysis reactions. Orally administered MDV3100 is mainly eliminated as metabolites in the urine and faeces in rats and dogs. In rat, urine and faeces have a similar importance, whereas in dogs and humans urinary is the major route of excretion.

The general toxicology studies were conducted in mice, rats and dogs. Mortality was observed in most studies in rats and dogs. In some cases this was attributed to gavage error or accidental aspiration of the CCMG formulation. Nonetheless, some of the deaths occurred during the toxicity studies could not be explained by the CCMG aspiration and several of the premature deaths seem to be related to the treatment with MDV3100.

The macroscopic and microscopic findings observed in prostate gland, seminal vesicles, testes and epididymides in rats and dogs are consistent with the primary pharmacological properties of MDV3100 and have been previously observed with non-steroidal anti-androgen compounds such as bicalutamide. Qualitatively similar effects in male reproductive organs have been described for the androgen biosynthesis inhibitor abiraterone[1]. These findings were fully or partially reversed at the end of the recovery period.

There were no apparent gender differences in systemic exposures in dogs after repeat administration. In rats, systemic exposure to MDV3100 was consistently higher in females than in males at all dosage levels. With daily oral administration, the mean accumulation index was approximately 1 to 3 in rats and 1 to 4 in dogs. The magnitude of accumulation did not appear to increase with the dose. Systemic exposure to MDV3100 in repeat dose toxicity studies was similar (dogs) or up to 3-fold (rats) that observed in patients. The two major human metabolites M1 and M2 were measured in some toxicity studies in rat and dog. Dedicated toxicity studies for M2 have not been performed, and according to the guideline EMEA/CHMP/ICH/646107/2008 S9 a separate toxicological evaluation of metabolites is generally not warranted for patients with advanced cancer.

Although rat and dog exposures to M2 in the toxicity studies were lower than patient exposures to M2, the Applicant does not consider this a significant issue relevant to the use of MDV3100 in advanced

[1] Zytiga: EPAR public assessment report (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002321/WC500112860.pdf)

cancer. Based on the similarity of the molecular structures of MDV3100 and M2, and also the comparability of the potency against all primary and secondary pharmacodynamic endpoints, the toxicity profile is likely to be similar for the 2 molecules. Therefore, low exposure to M2 in the toxicity studies is unlikely to have a major impact on the overall benefit-risk assessment for patients with advanced cancer.

The in vitro and in vivo genotoxicity studies were negative. As suggested by the Scientific Advice by the EMA (EMA/CHMP/SAWP/372658/2010) on 24th June 2010, the Applicant has performed an in silico QSAR analysis for the human metabolites. No structural alert was found in this study; considering this study and the guideline EMEA/CHMP/ICH/646107/2008 S9, no further genotoxicity testing is necessary.

No carcinogenicity studies were performed, according to the guideline EMEA/CHMP/ICH/646107/2008 S9, carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer.

Considering the indication and the target patient population, no reproductive and development toxicity studies would be required. The effects of MDV3100 on the reproductive system were evaluated during the general toxicology studies, with findings and organ weight changes in the prostate gland, seminal vesicles, testes and epididymides. In a study conducted to assess the effects of the treatment on reproductive tissues in male dogs, transient effects on male reproductive organs were observed. Changes in the reproductive organs in both species were consistent with the pharmacological activity of enzalutamide and reversed or partially resolved after an 8-week recovery period. In the non-GLP embryo-foetal development study in mice submitted, MDV3100 induced premature deliveries in dams, embryo-foetal deaths and abnormalities.

The need for nonclinical dependence studies was assessed based on the in vitro binding data, in vivo data on the penetration and accumulation in the CNS, findings in the in vivo safety pharmacology studies, and the available clinical data. The nonclinical data suggest that MDV3100 is unlikely to have abuse liability.

The Applicant presented a bridging study to assess the toxic potential of impurities A, C, G, that were observed at higher levels in the intended clinical lot of MDV3100 than in the lot used in the previous 4-week rat toxicity study (PRO3100NC31). The impurities A, C and G have been qualified within this study.

Considering the result of the general toxicology studies performed via oral administration, no further local tolerance studies are necessary.

The doses of CCMG in the rat and dog toxicity studies were approximately 6.2- and 4.9-fold higher, respectively, than the human dose of CCMG. Therefore, considering that the margins of safety with the nonclinical studies are sufficient and the toxicity data for CCMG provided by the Applicant, no further studies are required.

According to applicable guideline on the ERA of medicinal products (EMEA/CHMP/SWP/4447/00), certain substances, such as highly lipophilic compounds and potential endocrine disruptors, may need to be addressed irrespective of the quantity released into the environment. The active ingredient enzalutamide is a hormone and a potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. A complete Phase II environmental fate and effect analysis is therefore recommended.

As a result of the above considerations, further data is needed to conclude definitively on the potential risk of enzalutamide to the environment. It is recommended that the Applicant conducts the fish early life cycle test (OECD 210) and the fish sexual development test (OECD 234). The expected starting

time of these studies is December 2013, and the Applicant is recommended to submit the final report by June 2015. In the meantime a more restrictive wording has been included in section 6.6 of the SmPC regarding disposal of enzalutamide.

2.3.7. Conclusion on the non-clinical aspects

The pharmacologic, pharmacokinetic, and toxicological characteristics of MDV3100 are well characterised. Enzalutamide is a potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study	Phase Design Objectives	Enrolled N	MDV3100 Daily Doses Evaluated	Status[a]	
Controlled Double-Blind Study in Patients with Castration-resistant Prostate Cancer					
CRPC2	Phase 3 Randomized, double-blind, placebo-controlled Efficacy, safety, comprehensive ECG evaluation (including QT/QTc)	1199 MDV3100 n = 800 Placebo n = 399	160 mg	25 SEP 2011	Ongoing Enrolment complete 250 patients ongoing (MDV3100 n = 231 placebo n = 19)
				31 JAN 2012	Ongoing
Uncontrolled Open-Label Studies in Patients with Castration-resistant Prostate Cancer					
S-3100-1-01	Phase 1 Open-label dose escalation Safety (determine MTD), PK, preliminary efficacy	140	30, 60, 150/160[b], 240, 360, 480, and 600 mg	25 SEP 2011	Ongoing Enrolment complete 6 patients ongoing
				31 JAN 2012	Ongoing
CRPC-MDA-1	Phase 2 Open-label single arm Pharmacodynamics, safety, efficacy	60	160 mg	26 AUG 2011	Ongoing Enrolment complete 2 patients ongoing
				31 JAN 2012	Ongoing

Study	Phase Design Objectives	Enrolled N	MDV3100 Daily Doses Evaluated	Status[a]	
9785-CL-0111	Phase 1-2 Open-label dose escalation Japanese patients Safety, efficacy, PK	43	80, 160, and 240 mg	07 OCT 2011	Ongoing Enrolling 27 patients enrolled 15 patients ongoing
				31 JAN 2012	Ongoing Enrolling 43 patients total enrolled
9785-CL-0007	Phase 1 Open-label Drug-drug interaction (pioglitazone, S-warfarin, omeprazole, midazolam)	14	160 mg	21 FEB 2012	Completed
9785-CL-0121	Phase 2 Open-label extension for 9785-CL-0007	9	160 mg	31 JAN 2012	Ongoing Enrolling 9 patients enrolled
Uncontrolled Open-Label Studies in Hormone-Naïve Prostate Cancer Patients					
9785-CL-0321	Phase 2 Open-label Safety/efficacy	67	160 mg	31 JAN 2012	Ongoing Enrolment complete 67 patients total enrolled
Clinical Pharmacology Study in Subjects with Hepatic Impairment and Healthy Volunteers					
9785-CL-0009	Phase 1 Single-dose, open-label PK in mild/ moderate hepatic impairment	33	160 mg	05 JAN 2012	Completed
Single-Dose Clinical Pharmacology Studies in Healthy Volunteers					
9785-CL-0001	Phase 1 Single-dose, open-label Mass balance PK, metabolism, excretion	6	160 mg	15 JUL 2011	Completed
MDV3100-05	Phase 1 Single-dose, open-label, 2-period crossover Bioequivalence, food effect	60	160 mg	22 NOV 2011	Completed
9785-CL-0006	Phase 1 Single-dose, open-label Drug-drug interaction (gemfibrozil, itraconazole)	41	160 mg	16 DEC 2011	Completed

- a. For CRPC2, S-3100-1-01, CRPC-MDA-1, 9785-CL-0111, status as of cut-off date for inclusion of safety data in integrated analyses and status as of cut-off date for updated death/SAE information. For 9785-CL-0121 and 9785-CL-0321, status as of cut-off date for inclusion of updated death/SAE information. For completed studies, date is date of last patient/last visit.
- b. The daily dose was changed from 150 to 160 mg in this study because of a change from five 30 mg capsules to four 40 mg capsules.
- ECG, electrocardiogram, MTD, maximum tolerated dose; PK, pharmacokinetic.

The applicant claimed the approval for the following indication:

Xtandi is indicated for the treatment of adult men with metastatic castration-resistant prostate cancer who have received docetaxel therapy.

The final indication following CHMP review of this application is:

Xtandi is indicated for the treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy.

2.4.2. Pharmacokinetics

The single dose clinical pharmacology program was performed in healthy male volunteers, whereas the multiple dose studies were done in prostate cancer patients. One of the two main plasma metabolites, M2, has an activity similar to that of the parent compound and has a higher plasma AUC and lower protein binding than MDV3100 itself, and is thus expected to contribute substantially to drug effect.

Absorption

Maximum plasma concentrations (C_{max}) of enzalutamide in patients are observed 1 to 2 hours after administration. No oral bioavailability study has been performed.

Based on a mass balance study in humans, oral absorption of enzalutamide is estimated to be at least 84.2%. Enzalutamide is not a substrate of the efflux transporters P-gp or BCRP. At steady state, the mean C_{max} values for enzalutamide and its active metabolite are 16.6 µg/mL (23% coefficient of variation (CV)) and 12.7 µg/mL (30 %CV), respectively.

The in vitro permeability of MDV3100 is high, and in the mass balance study, 71% of the dose was recovered in urine and 13% of the dose as metabolites in faeces, indicating a high extent of absorption. Together with low aqueous solubility, MDV3100 can be considered a BCS class II substance.

The solubility of MDV3100 is increased with CCMG (an emulsifier/surfactant). With the proposed dosing, almost 4 g CCMG will be administered on one occasion. In addition to increasing the solubility of poorly dissolved substances, CCMG may also be a Pgp inhibitor according to literature.

A high-fat meal resulted in no effect on total exposure of MDV3100, but decreased C_{max} around 30% and delayed absorption (t_{max} 2 hours instead of 1 hour in the fasting state).

Distribution

The mean apparent volume of distribution (V/F) of enzalutamide in patients after a single oral dose is 110 L (29% CV). In vitro data show high protein binding of both MDV3100 (97-98%) and major plasma metabolites (M1 98%, M2 95-97%). Albumin seems to be the most important binding protein. Data suggests no concentration-dependence in binding. The impact of mild-to-moderate renal impairment on the extent of protein binding was considered low. The impact of severe renal impairment on the extent of protein binding has not been explored. The protein binding of M2 was

95% in the in vitro protein binding study and 97% in the hepatic impairment study. The in vitro protein binding indicates a substantially higher unbound fraction of M2 (3-5%) than of MDV3100 (2-3%). Ex vivo data indicate a slightly higher unbound fraction for M2 (2.6-3.6%; protein binding 96-97%) than for MDV3100 (1.5-2.4%, protein binding 98%), but not as large difference as indicated in the in vitro data.

Elimination

In the mass-balance study after a single dose of MDV3100, in parallel to parent drug (29% of total radioactivity AUC) two major plasma metabolites were identified, M1 (10% of total AUC) and M2 (49% of total AUC), both of which had a slower elimination than parent compound. As MDV3100 and the two metabolites M1 and M2 together constituted almost 90% of total radioactivity AUC, and no unidentified metabolites were found, it seems unlikely that there would be other quantitatively or pharmacologically/toxicologically important plasma metabolites.

After a single dose in the mass balance study, M2 has a 70% higher AUC than parent, and probably contributes substantially to the clinical activity of MDV3100. In addition, M2 has a higher (up to double) free fraction. Despite the somewhat higher free fraction of M2, the unbound levels of parent compound and M2 can be considered to be of similar magnitude in the average patient at steady state. In light of the similar potency in vitro pharmacology screens and the proposed high permeability of both entities, the applicant suggest that parent compound and M2 play similar roles in contributing to the overall safety and efficacy profiles of Xtandi in patients.

In vitro studies in human liver microsomes and recombinant CYP isoforms indicate that CYP3A4/5 and CYP2C8 were capable of catalysing the degradation of MDV3100. The main metabolite identified in microsomal incubations was M6. The importance of CYP2C8, and to a lower extent CYP3A4, was verified in vivo in interaction studies with the CYP2C8 inhibitor gemfibrozil (the AUC of the total active moiety, MDV3100 plus M2, was increased by 117%, up to 5-fold increase in MDV3100 AUC) and the CYP3A4 inhibitor itraconazole (40% increase in MDV3100 AUC).

In many studies with CYP2C8 substrates, no clinically significant effects of enzyme polymorphism have been detected. Some studies have shown a somewhat higher enzyme activity of the CYP2C8*3 allele. This is in line with the trend towards lower enzalutamide exposure observed for patients with CYP2C8 wt/*3 seen in the 61 patients with known CYP2C8 genotype in the enzalutamide trials. Data on homozygotes are lacking, but this genotype is uncommon.

MDV3100 is mainly hepatically eliminated, and renal excretion of unchanged drug is low (<0.2% of dose). MDV3100 is a low extraction drug with an oral clearance of around 0.55 L/h. Mean terminal half-life in patients after a single dose is 5.8 days. With daily administration, MDV3100 accumulates approximately 8-fold.

The metabolites of MDV3100 are excreted mainly in urine, and the most abundant metabolites in urine are M1 followed by M7. No relevant biliary excretion seems to occur.

The mean apparent clearance (CL/F) of enzalutamide in patients ranges from 0.520 and 0.564 L/h.

Following oral administration of ^{14}C-enzalutamide, 84.6% of the radioactivity is recovered by 77 days post dose: 71.0% is recovered in urine (primarily as the inactive metabolite, with trace amounts of enzalutamide and the active metabolite), and 13.6% is recovered in faeces (0.39% of dose as unchanged enzalutamide).

Dose proportionality and time dependencies

No major deviations from dose proportionality were detected over the dose range 40 to 160 mg, neither after a single dose nor at steady state. No time dependent pharmacokinetics was detected at therapeutic dose levels, whereas a slight tendency to increased AUC with time was discerned at higher dose levels. An 8-fold accumulation and around one month to steady state is expected from the long half-life (around 6 days) of MDV3100.

In vitro as well as clinical interaction studies show that CYP3A4 is induced by MDV3100 and CYP3A4 is suggested to contribute to the metabolism of MDV3100. Thus an autoinduction would be expected. Due to the long half-life of MDV3100 and its metabolites, it could well be that auto induction is evident also after a single dose and thus time-dependent pharmacokinetics would be difficult to detect in the data available.

Special populations

No formal studies have been completed to assess the effect of intrinsic factors, such as age, race, weight, height, or renal function, on MDV3100 exposure and response. The influence of patient covariates (weight, age, serum creatinine) on MDV3100 exposure were assessed with linear regression and population PK analyses showing that dosing adjustments are not indicated and that these covariates do not have clinically meaningful on the exposures to MDV3100.

Renal impairment

No formal renal impairment study for enzalutamide has been completed. Patients with serum creatinine > 177 µmol/L (2 mg/dL) were excluded from clinical trials. No clinically relevant effects of renal function on MDV3100 clearance was observed in the phase III data.

Liver impairment

The pharmacokinetics of enzalutamide 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. Following a single oral 160 mg dose of enzalutamide, the AUC and C_{max} for enzalutamide in subjects with mild impairment increased by 5% and 24%, respectively, and the AUC and C_{max} of enzalutamide in subjects with moderate impairment increased by 29% and decreased by 11%, respectively, compared to healthy control subjects. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC and C_{max} in subjects with mild impairment increased by 14% and 19%, respectively, and the AUC and C_{max} in subjects with moderate impairment increased by 14% and decreased by 17%, respectively, compared to healthy control subjects. The patients in the moderate hepatic impairment group however had only modest impairment in parameters indicative of metabolic function (albumin, prothrombin time), and thus a larger effect in other patients with moderate hepatic impairment cannot be excluded.

Patients with baseline severe hepatic impairment (Child-Pugh C) were excluded from clinical trials.No data is available in patients with severe renal or hepatic impairment.

Race

Most patients in the clinical trials (> 92%) were Caucasian, thus no conclusions on the impact of race on enzalutamide pharmacokinetics can be drawn.

Age

No clinically relevant effect of age on enzalutamide pharmacokinetics was seen in the population pharmacokinetic analysis.

Pharmacokinetic interaction studies

- ***In vitro***

All in vitro experiments were limited in their concentration range by the low aqueous solubility of MDV3100. To assess the clinical relevance of the in vitro data, data from the multiple dose study (9785-CL-0007) and in vitro protein binding study (9785-ME-0018) is shown below:

	Cmax at ss (ug/ml)	Protein binding (%)	Unbound Cmax (ug/ml)	Unbound Cmax (uM)
MDV3100	17	97-98%	0.5	1.1
M1	9	98%	0.2	0.4
M2	13	95%	0.7	1.4

CYP induction

Study **PRO3100NC23** evaluated the in vitro induction potential of MDV3100. In human hepatocytes from 3 donors, the mRNA level of CYP3A4 and CYP2B6 (PXR/CAR markers) and CYP1A2 (marker for Ah-receptor induction) was performed before and after 72 h incubation with MDV3100. The concentrations 2.5 (maximum solubility), 0.5 and 0.1 μM were used.

Hepatocytes from all three donors had an inducing effect of MDV3100 on CYP3A4 mRNA, whereas there was a concentration-dependent induction trend in 2 of the 3 donors for CYP2B6. The results for CYP1A2 were less obvious, with no consistent concentration-dependent increase in mRNA. The effects observed were substantially lower than the effects of the positive controls.

CYP inhibition

Study **PRO3100NC24** evaluated the in vitro CYP inhibitory potential of MDV3100. CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5 were studied in pooled liver microsomes with specific marker substrates. MDV3100 concentrations from 0.04 to 39 μg/ml were used, and both reversible and time-dependent (30 minutes pre-incubation) was tested.

MDV3100 caused direct inhibition of CYP2B6,CYP2C8, CYP2C9 and CYP2C19 with IC50 values of 42 μM, 10 μM, 50 μM and 23 μM, for the other enzymes inhibitory IC50 was >84 μM. The lowest IC50 were seen for CYP2C8 and CYP2C19, and the Ki for these inhibitions were determined to be 5.5 and 8.6 μM, respectively.

A slight increase in inhibition potential with pre-incubation (time-dependent inhibition) was observed for CYP1A2, but not for the other enzymes tested. Further experiments performed showed that the increase in inhibition did not require NADPH but was not resistant to dilution, and the applicant suggests that the time-dependent phenomenon may be due to the formation of a metabolite which is a more potent CYP1A2 inhibitor.

Study **9785-ME-0009** was a similar study on the metabolite M1, suggesting IC50> the highest concentration tested 300 μM for all enzymes except CYP2C8 (IC50 20 μM), and no evidence of time-dependency. Study **9785-ME-0010** investigated M2, and found an IC50 below the highest tested concentration 100 μM for the same four enzymes as for MDV3100 (CYP2B6,CYP2C8, CYP2C9 and CYP2C19), with the lowest IC50 for CYP2C8 (28 μM).

MDV3100 as substrate for transporters

In study **9785-ME-0026**, it was investigated whether MDV3100, M1 and M2 are substrates of Pgp, comparing transport in monolayers of porcine kidney epithelial LLC-PK1 cells transfected with human MDR1 compared with transport in cells transfected with vector alone. The efflux ratio was below 2 (predefined cutoff for a Pgp substrate) in all experiments for both MDV3100 (<1.3), M1 (<1.7) and M2 (1.5), and Pgp inhibitors ketoconazole and verapamil had no or minor effect on efflux ratio.

In study **9785-ME-0028** the uptake of MDV3100 (10 μM) into BCRP expressing Sf9 membrane vesicles and control vesicles was studied in the presence and absence of ATP. ATP caused a 5-fold increase in the uptake of the positive control metotrexate but did not affect MDV3100 uptake, and it was concluded that MDV3100 is not a BCRP substrate.

In study **9785-ME-0030** it was investigated whether MDV3100 is a substrate of the hepatic uptake transporters OATP1B1, OATP1B3 and OCT1, by measuring MDV3100 uptake (1 and 10 μM) in HEK293 cells transfected with vectors including cDNA for the transporters compared with vector alone. The uptake in transporter tranfected cells was similar as in control cells, suggesting that MDV3100 is not a substrate for OATP1B1, OATP1B3 and OCT1.

MDV3100 as an inhibitor of transporters

The three studies above were also used to study inhibition of transport by MDV3100 of known transporter substrates. Pgp mediated efflux of digoxin (1 μM) (study **9785-ME-0026**) was measured in the absence or presence of MDV3100 (0.3-80 μM), M1 (0.3-80 μM) and M2 (0.1-25 μM). MDV3100 and M2 inhibited digoxin efflux with an IC50 of 1.7 and 1.1 μM, respectively. No inhibition was seen for M1 (IC50>80 μM).

For MRP2 and BCRP inhibition the transport of H-estradiol-17β-D-glucuronide and methotrexate were studied in the absence or presence of MDV3100 (0.15-50 μM), M1 (0.3-100 μM) and M2 (0.15-50 μM)(**9785-ME-0028)**. Neither of the substances affected MRP2-mediated uptake. BCRP uptake was stimulated, and after correcting for stimulation an inhibitory IC50 was estimated in the range 32-54 μM.

In study **9785-ME-0029**, the inhibitory effects of MDV3100 (0.3 to 50 μM), M1 (0.3 to 80 μM), and M2 (0.1 to 25 μM) on OATP1B1, OATP1B3, OCT1, OCT2, OAT1, or OAT3 mediated uptake were studied in transporter-expressing HEK293 cells (OATP1B1 and 3, OCT1 and 2) and mouse kidney-derived S2 cells (OAT1 and 3). Probe substrates 3H-estradiol 17β-D-glucuronide(3H-E217βG) for OATP1B1 and OATP1B3, 14C-tetraethylammonium bromide (14C-TEA) forOCT1, 14C-metformin for OCT2, 3H-p-aminohippuric acid (3H-PAH) for OAT1, and 3H-estrone sulfate (3H-ES) for OAT3).

Inhibition of substrate transport with an IC50 within the tested concentration range was seen for several of the transporters.

- ***In vivo***

Effects of other substances on MDV3100

To elucidate the role of CYP2C8 and CYP3A4 in MDV3100 metabolism, **study 9785-CL-0006** was performed. It was a 3-arm parallel group study in 41 male healthy volunteers. One group was randomised to a single oral 160 mg dose of MDV3100 and the other two groups were pre-treated with either 600 mg gemfibrozil (CYP2C8 inhibitor) twice daily or 200 mg itraconazole (CYP3A4 inhibitor) once daily for 3 days before and 18 days after receiving a 160 mg MDV3100 single dose. PK-samples for analysing MDV3100, M1 and M2 were collected for 49 days after MDV3100 dose. Primary pharmacokinetic variable was Cmax, AUCinf and AUC0-18 days for parent compound.

Co-administration of gemfibrozil coincided with higher plasma concentrations and slower elimination of MDV3100, whereas a more modest effect was seen of itraconazole.

After 18 days, when gemfibrozil administration was discontinued, the elimination rate of MDV3100 increased, and the plasma level of M2 started to rise. Due to the concern that gemfibrozil administration was too short to mirror the worst-case effect of a CYP2C8 inhibitor, the interaction was quantified using compartmental modelling and simulation to predict the change with no discontinuation of gemfibrozil. The result suggested a T/R ratio of 4.26 (90% CI 3.59-5.01). The T/R when comparing AUC for the first 18 days with noncompartmental methods was 2.53 (90% CI 2.19-2.91), and no AUCinf was calculated with non-compartmental methods. The effect of withdrawing itraconazole on the plasma concentration time curve of MDV3100 was smaller, and thus AUCinf was estimated using standard non-compartmental methods. A small rise in M1 levels was seen when itraconazole was discontinued.

Gemfibrozil caused an increase in M1 (AUC 2.7-fold higher) whereas the levels of M2 decreased by 25%. Thus the effect of CYP2C8 inhibition on active moiety (parent+M2) is lower (2.2-fold) compared to the effect of MDV3100 itself (4.3-fold). Itraconazol, on the other hand, did not seem to affect M1 whereas the AUC of M2 was slightly increased (20%).

Effects of MDV3100 on other substances

To elucidate the effect of MDV3100 at steady state on the PK of substrates for CYP2C8, CYP2C9, CYP2C19 and CYP3A4, study **9785-CL-0007** was performed.

It was an open-label, single-sequence cross-over study in 14 CRPC patients, aiming to investigate the effect of multiple once daily oral dosing (160 mg) of MDV3100 on the PK of a single dose of pioglitazone (CYP2C8 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), and midazolam (CYP3A4 substrate).

Pioglitazone (CYP2C8 substrate) AUC increased by 20% at steady-state administration with MDV3100, whereas its metabolite OH-piglitazone had an AUC decrease by 37%. The AUC of the other three drugs decreased – S-warfarin (CYP2C9 substrate) by 56%, omeprazole (CYP2C19 substrate) by 70% and midazolam (CYP3A4 substrate) by 86%. The applicant concludes that MDV3100 has no clinically relevant effect on CYP2C8, but is a moderate inducer of CYP2C9 and CYP2C19 and a strong inducer of CYP3A4.

Pharmacokinetics using human biomaterials

2.4.3. Pharmacodynamics

Mechanism of action

Prostate cancer is known to be androgen sensitive and responds to inhibition of androgen receptor signalling. Despite low or even undetectable levels of serum androgen, AR signalling continues to promote disease progression. Stimulation of tumour cell growth via the androgen receptor requires nuclear localization and DNA binding. MDV3100 is a potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. MDV3100 competitively inhibits binding of androgens to androgen receptors, 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. MDV3100 treatment decreases the growth of prostate cancer cells and can induce cancer cell death and tumour regression. In preclinical studies MDV3100 lacks androgen receptor agonist activity.

Primary and Secondary pharmacology

Primary pharmacology

CRPC-MDA-1 was a non-randomized, single arm, phase II study with the objective of studying the effect of MDV3100 treatment on androgen receptor signaling and expression of survival/resistance pathways in the bone marrow metastases of patients with castration-resistant metastatic prostate. Eligible were patients with histologically- or cytologically-confirmed adenocarcinoma of the prostate without neuroendocrine differentiation and who had presence of metastatic disease to the bone. The study enrolled 60 patients (16 docetaxel chemotherapy-naïve patients and 44 patients who had had prior docetaxel chemotherapy). All patients received MDV3100 at a daily dose of 160 mg. Paired bone marrow samples (biopsy/aspirates) were collected prior to and after 8 weeks of MDV3100 therapy. The analysis for androgen receptor expression required paired bone marrow samples to have interpretable immunohistochemistry results and was conducted on 16 (26.7%) of patients. Analysis of androgen receptor expression and subcellular localization by immunohistochemistry in paired bone marrow tumor samples at baseline and Week 9 (n = 16) demonstrated reduction in nuclear androgen receptor in all evaluable PSA responders (n = 5) and two of the 11 PSA non-responders. A statistical correlation was not assessed due to low numbers of evaluable patients. Sampling of blood and bone marrow biopsies showed that 160 mg daily of MDV3100 was associated with increases in both plasma and bone marrow testosterone levels. A larger increase in mean plasma testosterone and dihydrotestosterone was observed in the PSA responder group though not statistically significant. There was an increase in bone marrow testosterone (non significant) but not bone marrow dihydrotestosterone observed compared to baseline.

Secondary pharmacology

An independent review of ECGs in CRPC2 was performed as a randomised, placebo controlled, triple-blind substudy, intended to be done on all randomised patients. The objectives 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 ICH E14, this threshold was chosen to provide reasonable assurance that the mean effect of the study drug on the QT/QTc interval is 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.

Compared to placebo, treatment with 160 mg MDV3100 daily resulted in no clinically relevant changes in heart rate, atrioventricular conduction as determined by the PR interval, or cardiac depolarization as determined by the QRS duration. The effect of MDV3100 on cardiac repolarization as determined by the QTcF interval using PK/PD data suggests that there may be a 3 ms effect with an upper confidence interval (CI) of ≤ 4 ms (CRPC2).

2.4.4. Discussion on clinical pharmacology

Study CRPC-MDA-1 showed that in evaluable patients with a PSA response, the shift from nuclear to cytoplasmic localization of the androgen receptor is consistent with non-clinical data showing that MDV3100 blocks nuclear translocation of the androgen receptor. The increase in serum and bone marrow testosterone levels is consistent with a potential adaptation of prostate cancer to overcome MDV3100 androgen receptor axis blockade.

In relation to plasma concentration and effect, a daily dose of 160 mg appears sufficient for efficacy studies considering effects on PSA concentrations and the side-effect of fatigue.

The volume of distribution of enzalutamide is greater than the volume of total body water, indicative of extensive extravascular distribution. It seems that MDV3100 was preferentially retained in the plasma

component of blood (blood-to-plasma ratio was 0.55). MDV3100 and M2 cross the blood-brain barrier in mice and rats, achieving tissues concentrations equivalent to plasma.

In general, the metabolism of MDV3100 is sufficiently characterised, whereas it is recommended to the Applicant to further investigate the formation and elimination of the active metabolite M2 considering its importance for efficacy and safety. The Applicant has proposed a plan to identify the enzyme(s) catalysing the metabolism of M2. Upon identification of the enzymes, further interaction studies with inhibitors or inducers may be needed.

The small effects of CYP2C8 polymorphism seen in the literature, together with the data provided on CYP2C8 phenotypes in the 61 patients in the clinical trials and the rather small between-patient variability in the phase III trial suggest that CYP2C8 genetic polymorphism is not of clinical importance. In addition, when the major enzymes responsible for M2 metabolism are identified, genetic polymorphism needs to be taken into consideration if a polymorphic enzyme is found to be of importance.

Potential for other medicinal products to affect enzalutamide exposures

CYP2C8 inhibitors and inducers

CYP2C8 plays an important role in the elimination of enzalutamide and in the formation of its active metabolite. Following oral administration of the strong CYP2C8 inhibitor gemfibrozil (600 mg twice daily) to healthy male subjects, the AUC of enzalutamide increased by 326% while C_{max} of enzalutamide decreased by 18%. The effect of drug-drug interactions on MDV3100 pharmacokinetics was re-evaluated based on unbound (mean ex vivo fu of 1.7% and 2.8% of parent and M2) active moiety. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC increased by 77% while C_{max} decreased by 19%. 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 .

CYP3A4 inhibitors and inducers

CYP3A4 plays a minor role in the metabolism of enzalutamide. Following oral administration of the strong CYP3A4 inhibitor itraconazole (200 mg once daily) to healthy male subjects, the AUC of enzalutamide increased by 41% while C_{max} was unchanged. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC increased by 27% while C_{max} was again unchanged. No dose adjustment is necessary when Xtandi is co-administered with inhibitors or inducers of CYP3A4.

Potential for enzalutamide to affect exposures to other medicinal products

Enzyme induction

Enzalutamide is a potent enzyme inducer and increases the synthesis of many enzymes and transporters; therefore, interaction with many common medicinal products that are substrates of enzymes or transporters is expected. The reduction in plasma concentrations can be substantial, and lead to lost or reduced clinical effect. There is also a risk of increased formation of active metabolites. Enzymes that may be induced include CYP3A in the liver and gut, CYP2C9, CYP2C19, CYP1A2 and uridine 5'-diphospho-glucuronosyltransferase (UGTs - glucuronide conjugating enzymes). The transport protein P-gp may also be induced, and probably other transporters as well, e.g. multidrug resistance-associated protein 2 (MRP2), breast cancer resistant protein (BCRP) and the organic anion transporting polypeptide 1B1 (OATP1B1).

In vivo studies have shown that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Co-administration of enzalutamide (160 mg once daily) with single oral doses

of sensitive CYP substrates in prostate cancer patients resulted in an 86% decrease in the AUC of midazolam (CYP3A4 substrate), a 56% decrease in the AUC of S-warfarin (CYP2C9 substrate), and a 70% decrease in the AUC of omeprazole (CYP2C19 substrate). UGT1A1 may have been induced as well.

Interactions with certain medicinal products that are eliminated through metabolism or active transport are expected. If their therapeutic effect is of large importance to the patient, and dose adjustments are not easily performed based on monitoring of efficacy or plasma concentrations, these medicinal products are to be avoided or used with caution. The risk for liver injury after paracetamol administration is suspected to be higher in patients concomitantly treated with enzyme inducers.

The full induction potential of enzalutamide may not occur until approximately 1 month after the start of treatment, when steady-state plasma concentrations of enzalutamide are reached, although some induction effects may be apparent earlier. Patients taking medicinal products that are substrates of CYP3A4, CYP2C9, CYP2C19, CYP1A2 or UGT1A1 should be evaluated for possible loss of pharmacological effects (or increase in effects in cases where active metabolites are formed) during the first month of enzalutamide treatment, and dose adjustment should be considered as appropriate. In consideration of the long half-life of enzalutamide (5.8 days), effects on enzymes may persist for one month or longer after stopping enzalutamide. A gradual dose reduction of the concomitant medicinal product may be necessary when stopping enzalutamide treatment.

CYP2C8 substrates

Enzalutamide (160 mg once daily) did not cause a clinically relevant change in the AUC or C_{max} of pioglitazone (CYP2C8 substrate). The AUC of pioglitazone increased by 20% while C_{max} decreased by 18%. No dose adjustment is indicated when a CYP2C8 substrate is co-administered with Xtandi.

P-gp substrates

In vitro data indicate that enzalutamide may be an inhibitor of the efflux transporter P-gp. The effect of enzalutamide on P-gp substrates has not been evaluated *in vivo*; however, under conditions of clinical use, enzalutamide may be an inducer of P-gp via activation of the nuclear pregnane receptor (PXR). Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g. colchicine, dabigatran etexilate, digoxin) should be used with caution when administered concomitantly with Xtandi and may require dose adjustment to maintain optimal plasma concentrations.

BCRP, MRP2, OAT3 and OCT1 substrates

Based on in vitro data, inhibition of BCRP and MRP2 (in the intestine), as well as organic anion transporter 3 (OAT3) and organic cation transporter 1 (OCT1) (systemically) cannot be excluded. Theoretically, induction of these transporters is also possible, and the net effect is presently unknown.

In order to clarify whether enzalutamide would act as and inducer (or inhibitor) of CYP1A2 in vivo, the applicant plans to perform a clinical study to investigate the effect of enzalutamide on a specific CYP1A2-substrate.

It seems probable that enzalutamide can induce CYP2B6 in vivo, but since clinically relevant specific CYP2B6 substrates are rare, in vivo studies of CYP2B6 are not requested at this point. Since induction through PXR/CAR seems probable, there may be a risk of induction also of e g Pgp and UGT1A1. The applicant agrees that there is a risk for induction also of transporters (e g Pgp, MRP2, MRP3 and OATP1A2).

The solubility of MDV3100 is increased with CCMG (an emulsifier/surfactant). It is unfortunate that the interaction study was performed with CCMG in the placebo treatment, meaning that the potential additional interaction effects of CCMG are not studied. The applicant has performed an ambitious

comparison with literature data, concluding that an inhibition of intestinal Pgp cannot be excluded. Caution for Pgp substrate is present in the SmPC.

The small effect of food on absorption rate can be considered clinically irrelevant for maintenance dosing of a drug with long half-life. No food restrictions are considered necessary, and in the pivotal clinical studies the drug has been taken regardless of food intake.

The recovery in the mass balance study (85%) was somewhat low, but acceptable in view of the long half-life and the long sampling period in the study, and more than 80% of the recovered radioactivity was identified.

Special population

In the clinical study performed in subjects with mild and moderate hepatic impairment study, patients with moderate hepatic impairment are not considered to be fully representative and caution should therefore be advised in patients with moderate hepatic impairment. The Applicant has committed to conduct a new clinical study in patients with moderate hepatic impairment (as reflected in the RMP) and this issue will be further discussed in light of the results of this study to be submitted by December 2015.

There are no data in patients with severe renal or hepatic impairment. Caution is therefore advised in patients with severe renal impairment and no major increase in active moiety is expected. In order to provide further information on the safety in this patient population, the Applicant committed to conduct a study in patients with severe hepatic impairment and to submit the results by November 2014. In the meantime, taking into consideration that MDV3100 and its active metabolite are eliminated primary by hepatic metabolism, the low grade of moderate impairment in the PK study (9785-CL-0009), and the absence of data in patients with severe hepatic impairment, MDV3100 should not be recommended in patients with severe hepatic impairment.

ECG and specifically QT data obtained in the setting of the CRPC2 study did not raise any clinically relevant safety concerns.

2.4.5. Conclusions on clinical pharmacology

In general, the pharmacokinetics of MDV3100 is well described. The metabolism and elimination of the active metabolite M2 needs to be elucidated further and the Applicant committed to conduct necessary studies post-approval. MDV3100 is a strong to moderate enzyme inducer, which needs further considerations when it comes to extrapolation to enzymes, and transporters that are not studied in vivo and recommendations in the SmPC.

2.5. Clinical efficacy

2.5.1. Dose response study

Study **S-3100-1-01** was a Phase 1, open-label, uncontrolled, dose-escalation study with dose-expansion at the tolerated doses for patient with progressive castration-resistant prostate cancer, both pre- and post-chemotherapy. The key roles of this study in the development plan were to determine the maximum tolerated dose and initial safety profile of MDV3100, to provide data on the PK of MDV3100, to identify evidence of an anti-tumor effect, and if observed, to determine the optimal dose to move forward into Phase 3 clinical evaluation.

140 patients were enrolled (65 chemotherapy-naïve patients; 75 patients who had received prior chemotherapy). Doses of 30, 60, 150, 240, 360, 480, and 600 mg/day were studied in 7 cohorts of patients. Patients must have demonstrated progression defined as 1 or more of the following 3 criteria: progression as defined by the RECIST; progression as defined by a minimum of 3 rising PSA levels with

an interval of ≥ 1 week between each determination; and/or progression as defined by 2 or more new lesions on bone scan. Patients previously treated with chemotherapy must have not had more than 2 prior chemotherapy regimens 1 of which was docetaxel-based. Patients not previously treated with chemotherapy must have been ineligible for, intolerant of, or had declined chemotherapy. Efficacy analyses included a description of the changes in PSA, progression on imaging, circulating tumor cell counts, bone turnover markers (serum bone-specific alkaline phosphatase and urinary N-telopeptide) and the frequency and timing of disease progression following 12 weeks of treatment with MDV3100.

In this study MDV3100 PSA decreases occurred at all doses and in men with and without previous chemotherapy. The extent and proportion of patients showing PSA decreases appeared to be dose-dependent from 30 mg to 150 mg daily, but reached a plateau between 150 mg and 240 mg daily, above which were seen no additional effects. The proportion of patients showing a 50% reduction from baseline in PSA increased in a dose-dependent manner up to 150 mg/day (33.3% of patients at 30 mg/day, 59.3% at 60 mg/day and 66.7% at 150 mg/day) with no obvious additional benefit recorded for increased doses above 150 mg daily day (58.6% at 240 mg/day, 67.9% at 360 mg/day, 28.6% at 480 mg/day, and 66.7% at 600 mg/day).

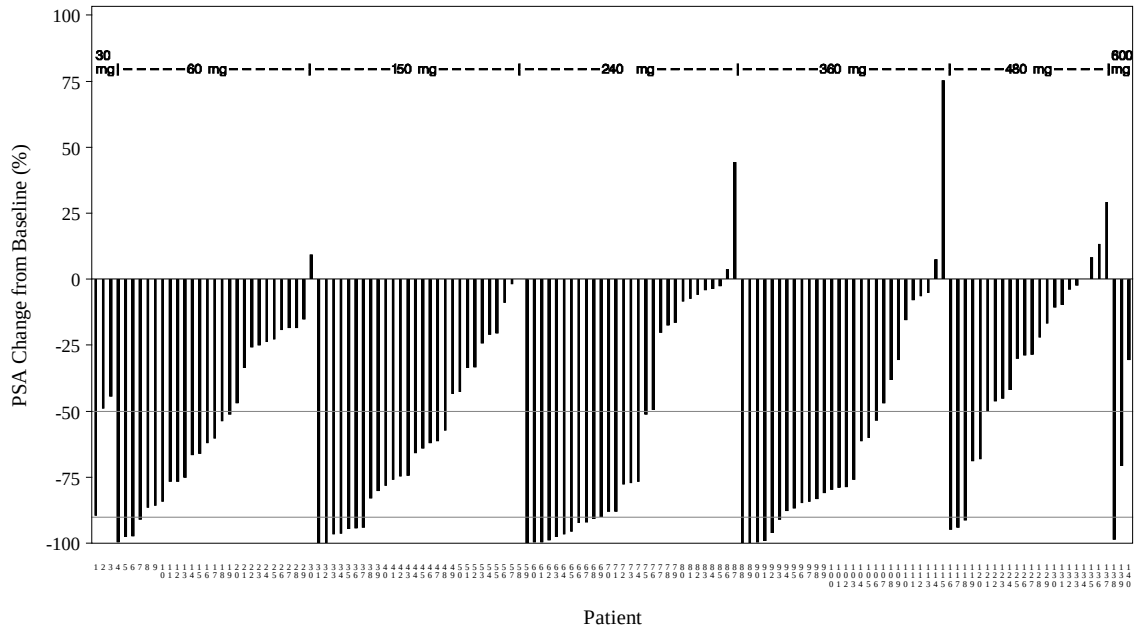


Figure 1: S-3100-1-01 Waterfall Plot of Best Change in PSA from Baseline by Dose: Safety Population

NOTE: Baseline is defined as the last value recorded prior to first dose of study drug.

The maximum tolerated dose was determined to be 240 mg/day, based upon the occurrence of dose-limiting toxicities as well as adverse events of fatigue leading to dose reductions at higher doses. During this study 5 dose-limiting toxicities were observed in 4 patients: seizure (1 patient each at daily doses of 360 mg, 480 mg, and 600 mg [the last being reported with a concurrent event of confusion]) and rash (1 patient at a daily dose of 600 mg). There was also a dose-dependent increase in adverse events of fatigue leading to dose reduction, with no incidence at 150 mg daily, 2.9% incidence at 240 mg daily, 7.5% incidence at 360 mg daily, and 20.0% incidence at 480 mg daily.

Based on data from study S-3100-1-01, the dose for further investigation was the dose level below the MTD i.e. 150 mg. However, as a result of changes in the capsule formulation (40 mg capsules), the dose of 160 mg given once daily was recommended for further clinical development.

2.5.2. Main study(ies)

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

Methods

Study Participants

Main Inclusion Criteria:

1. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features;

2. Ongoing androgen deprivation therapy with a gonadotropin-releasing hormone (GnRH) analogue or orchiectomy (i.e., surgical or medical castration);

3. For patients who had not had an orchiectomy, there must have been a plan to maintain effective (GnRH)-analogue therapy for the duration of the study;

4. Serum testosterone level < 1.7 nmol/L (50 ng/dL) at the Screening visit;

5. Patients receiving bisphosphonate therapy must have been on stable doses for at least 4 weeks;

6. Progressive disease by PSA or imaging after docetaxel-based chemotherapy in the setting of medical or surgical castration. Disease progression for study entry was defined as one or more of the following three criteria:

- PSA progression defined by a minimum of three rising PSA levels with an interval of ≥ 1 week between each determination. The PSA value at the Screening visit was to have been ≥ 2 µg/L (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;

7. No more than two prior chemotherapy regimens with at least 1 regimen containing docetaxel;

8. ECOG performance status of 0–2;

Main Exclusion criteria:

1. Metastases in the brain or active epidural disease (NOTE: patients with treated epidural disease were allowed);

2. Total bilirubin (Tbili), alanine aminotransferase (ALT), or aspartate aminotransferase (AST) > 2 times the upper limit of normal at the Screening visit;

3. Creatinine > 177 µmol/L (2 mg/dL) at the Screening visit;

4. Albumin < 30 g/L (3.0 g/dL) at the Screening visit;

5. Treatment with androgen receptor antagonists (bicalutamide, flutamide, nilutamide), 5α-reductase inhibitors (finasteride, dutasteride), estrogens, or chemotherapy within 4 weeks of enrolment (Day 1 visit), or plans to initiate treatment with any of these treatments during the study;

6. Treatment with therapeutic immunizations for prostate cancer (e.g., sipuleucel-T) or plans to initiate treatment with any of these treatments during the study;

7. History of seizure, including any febrile seizure, loss of consciousness, or transient ischemic attack within 12 months of enrolment (Day 1 visit), or any condition that may pre-dispose to seizure (e.g., prior stroke, brain arteriovenous malformation, head trauma with loss of consciousness requiring hospitalization);

8. Clinically significant cardiovascular disease

9. Had used or planned to use from 30 days prior to enrolment (Day 1 visit) through the end of the study the following medications known to lower the seizure threshold or prolong the QT interval

Treatments

Patients were randomized 2:1 to receive MDV3100, 160 mg/day, administered as 4 × 40 mg capsules, or matching placebo

MDV3100 was administered orally once daily without regard to food. Study drug doses were to be taken as close to the same time each day as possible. Patients who experienced a Grade 3 or greater

toxicity that could not be ameliorated by the use of adequate medical intervention were to have their treatment interrupted until the toxicity improved to a Grade 2 or lower severity. Patients could subsequently be restarted on study drug at the same dose or at a reduced dose.

Treatment continued until unacceptable toxicity, documented and confirmed disease progression (i.e., confirmed radiographic progression or the occurrence of a skeletal-related event), subsequently, the patient was scheduled to initiate a new systemic antineoplastic therapy, death, or withdrawal.

Objectives

Primary Objective

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

Secondary Objectives

- Secondary objectives included determination of the benefit of MDV3100 as compared to placebo as assessed by time to PSA progression, radiographic progression-free survival, time to first skeletal-related event, quality of life, pain palliation, circulating tumor cell count conversion rate; to determine the safety of treatment with MDV3100 as compared to placebo, ECG changes, covariates that may affect variability in PK parameters.

Further exploratory objectives included determination of benefit of MDV3100 as compared to placebo as assessed by best overall radiographic response, by the European Quality of Life 5-Domain Scale (EQ-5D), by ECOG performance status, by pain progression rate and by time to pain progression.

Outcomes/endpoints

The study endpoints are described in table 9.

Disease progression in this study was defined as per the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) recommendations, with some protocol-specific modifications, and required at least 1 of the following: the appearance of ≥ 2 new lesions on bone scan; soft-tissue progression as per the Response Evaluation Criteria in Solid Tumor criteria (version 1.1; RECIST v1.1); a skeletal-related event (defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain).

The protocol-specific modifications to the PCWG2 criteria were: for nodal disease, only lymph nodes ≥ 1.5 cm in (short axis) diameter at screening were used to assess for a change in size; and directed pelvic imaging to document presence or absence of disease at screening was not required. Progression at the first scheduled reassessment at Week 13 required a confirmatory scan 6 or more weeks later. Confirmatory scans had to show progressively worsening disease (e.g., at least 2 new lesions on bone scan, or progressive disease by RECIST v1.1 on soft tissue imaging by CT or MRI). Patients were instructed to continue on treatment until this confirmatory scan was performed to document radiographic disease progression AND the patient was scheduled to initiate another systemic antineoplastic therapy. Increases in PSA, especially during the first 12 weeks of therapy, were not considered disease progression.

Table 9: Endpoints in the AFFIRM study

Endpoint	Definition of Endpoint
Primary endpoint	

Overall Survival	Time from randomization to death from any cause. Survival status was determined 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, survival status and cause of death is assessed every 12 ± 1 weeks.
Key secondary endpoints	
Time to PSA Progression	Time from randomization to the date of PSA progression. According to the consensus guidelines of the PCWG2, PSA progression: • ≥ 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 or more weeks later. Serum PSA levels were measured by a central laboratory at baseline and every visit from Week 13 while on study drug.
Radiographic Progression-Free Survival	Time to the earliest objective evidence of radiographic progression or death. Defined by RECIST v1.1 for soft tissue disease and by the PCWG2 criteria for bone disease. The assessment was made by the Investigator using the results of CT or MRI and bone scans. • Bone Disease: Appearance of 2 or more new bone lesions on bone scan • Soft Tissue Disease: As defined by RECIST v1.1 on CT/MRI Unless warranted sooner, disease progression was first assessed (by the Investigator) 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.
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. Patients were assessed for skeletal-related events at all Study visits, Long-Term Follow-Up visits, Safety Follow-Up visits, and Survival Follow-Up telephone calls. The assessment of radiographic disease progression was asking the patient, patient's family, or patient's regular physician about the occurrence of skeletal-related events.
Other secondary endpoints	
Quality of Life (Functional Assessment of Cancer Therapy – Prostate)	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"). Each item can be answered on a scale of 0–4. The sum of scores on all 5 domains constitutes the FACT-P. Patients were defined as having a positive 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. FACT-P was assessed at baseline and then at every regular study visit beginning at Week 13. (Patients were given the FACT-P questionnaire to fill out on their own, with the instructions that their responses should apply to the 7-day period preceding their next clinic visit).

	NOTE: protocol defines response as a 16-point improvement in global FACT-P score, however, during the conduct of this trial, data became available showing that a 6–10 point improvement in the global FACT-P score represented a clinically meaningful change (Cella, 2009) and SAP was modified accordingly.
Pain Palliation	To be eligible for this analysis, patients must have had: • Metastatic bone disease at baseline; • Provided answers to BPI-SF Q#3 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); • Had an average pain score during the baseline run-in period ≥ 4. Pain palliation was defined as a ≥ 30% reduction in average pain score at Week 13 compared to baseline with a ≤ 30% increase in analgesic use. Patients filled the questionnaire on their own (their responses should apply to the 7-day period preceding their screening or Week 13 visit).

Sample size

The sample size for this study was determined as follows: an observed 650 deaths provided approximately 90% power to detect a 3.7 month difference in median survival (estimated median survival for placebo = 12 months; estimated median survival for MDV3100 = 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, the study required approximately 1080 patients (720 MDV3100-treated patients, 360 placebo-treated patients) to achieve the targeted 650 deaths. A survival analysis was to be performed when 650 events of death were observed. 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).

Randomisation

Patients were randomised to MDV3100 or placebo treatment groups in a 2:1 ratio, respectively, using a centrally administered, randomized, permuted block method and stratified by the following factors:

- Baseline ECOG performance status score (0–1 vs. 2);
- Baseline mean Brief Pain Inventory – Short Form Question #3 score averaged over the 7 days prior to randomization (< 4 vs. ≥ 4).

Blinding (masking)

The MDV3100 and placebo capsules were identical in regards to appearance, number of capsules/day, and formulation (gelatin capsules containing CCMG). All patients, Investigators, site personnel, and the Sponsor's staff involved in the conduct of the study were blinded to treatment assignment. Study treatment assignment could be unblinded when a participant experienced progressive disease and when the knowledge of treatment assignment could make a difference in subsequent treatment (e.g., if the patient wanted to participate in a clinical study which excluded prior MDV3100 therapy).

Statistical methods

Interim analysis

a single formal interim overall survival analysis was conducted on event data through the date of the 520th death event (80% of the 650 target number of deaths) by the independent statistical unit.

Primary efficacy analysis

A log-rank test stratified by baseline ECOG performance status and mean Brief Pain Inventory – Short Form score (Question #3) was used to compare the MDV3100-treated and placebo groups. This comparison was a 2-sided test at the 0.05 level of significance. Kaplan-Meier median survival times and their 95% CIs as well as survival curves were used for statistical description.

Additionally, 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 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.

Key Secondary Efficacy Analyses

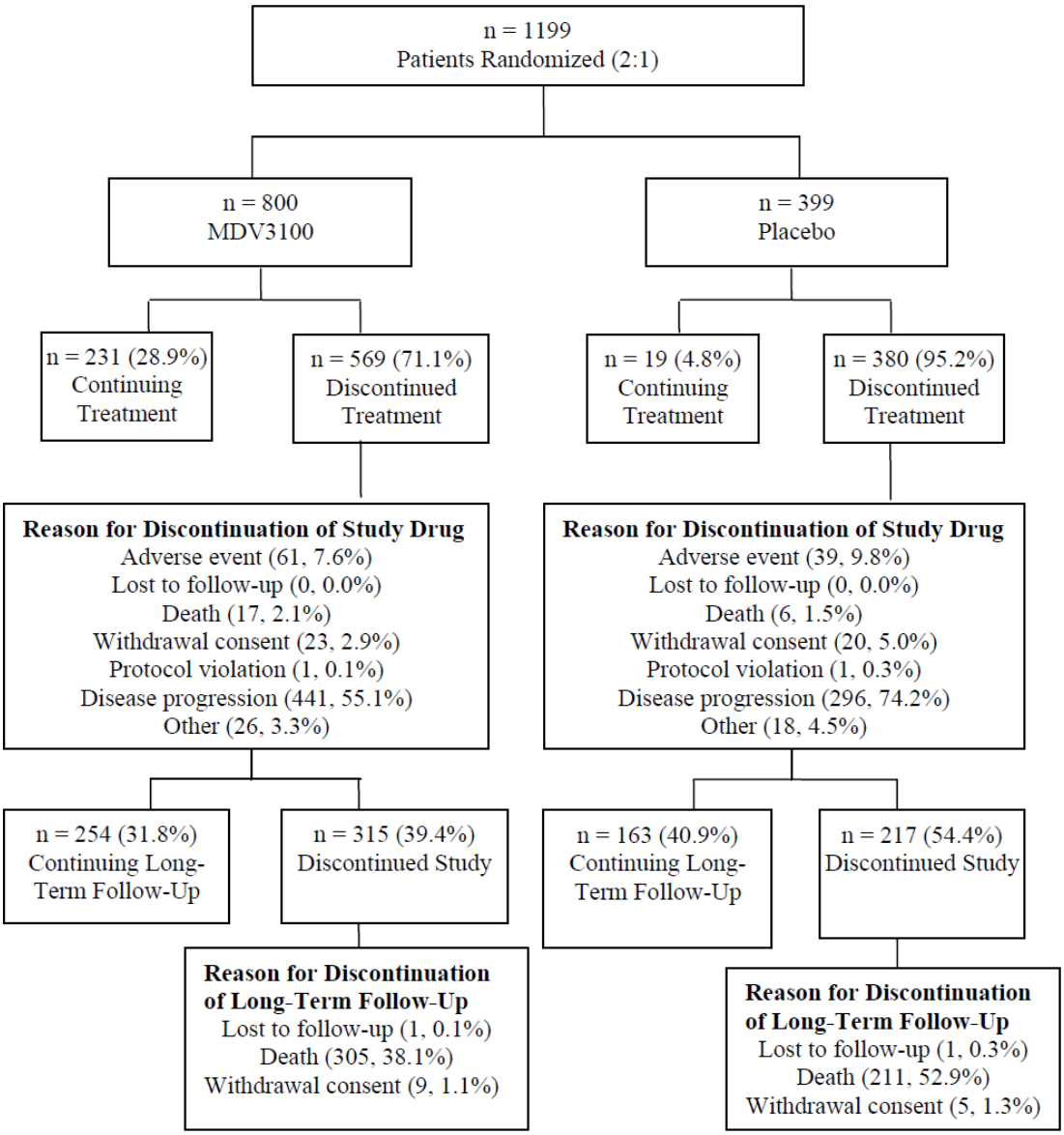
The key secondary analyses were:

- Comparison of time to PSA progression between treatment arms;
- Comparison of duration of radiographic progression-free survival between treatment arms;
- Comparison of time to first skeletal-related event between treatment arms.

The key secondary analyses were to be performed only if MDV3100 therapy resulted in a statistically significant prolongation of overall survival 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 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.

Results

Participant flow



Recruitment

Between 22 September 2009 and 15 November 2010, 1199 patients were randomized into this study: 800 into the MDV3100 arm, and 399 into the placebo arm. This comprises the ITT population.

Study CRPC2 was carried out in 156 centres in 15 countries grouped into three regions: North America, Europe, and Rest of the world (Table 10). The number of patients randomised at study centres ranged from 1 to 90.

Table 10: Geographic Distribution of Randomised Study Patients

Geographic Region	**MDV3100 (n = 800)**	**Placebo (n = 399)**	**Total (n = 1199)**
North America	263 (32.9%)	132 (33.1%)	395 (32.9%)
United States	181 (22.6%)	107 (26.9%)	288 (24.0%)
Canada	82 (10.3%)	25 (6.3%)	107 (8.9%)
Europe	461 (57.6%)	223 (55.9%)	684 (57.0%)
Austria	15 (1.9%)	10 (2.5%)	25 (2.1%)
Belgium	27 (3.4%)	18 (4.5%)	45 (3.8%)
France	193 (24.1%)	80 (20.1%)	273 (22.8%)
Germany	62 (7.8%)	24 (6.0%)	86 (7.2%)
Italy	20 (2.5%)	10 (2.5%)	30 (2.5%)
Netherlands	32 (4.0%)	14 (3.5%)	46 (3.8%)
Poland	7 (0.9%)	4 (1.0%)	11 (0.9%)
Spain	23 (2.9%)	13 (3.3%)	36 (3.0%)
United Kingdom	82 (10.3%)	50 (12.5%)	132 (11.0%)
Rest of World	76 (9.5%)	44 (11.0%)	120 (10.0%)
Australia	60 (7.5%)	33 (8.3%)	93 (7.8%)
Argentina	7 (0.9%)	3 (0.8%)	10 (0.8%)
Chile	6 (0.8%)	5 (1.3%)	11 (0.9%)
South Africa	3 (0.4%)	3 (0.8%)	6 (0.5%)

Conduct of the study

Protocol amendments

The original study protocol (v 1.0) was issued on 21 of May, 2009. Three amendments were made to the protocol. A final protocol was produced on April 19, 2011.

The main amendments pertained to:

- dose reduction from 240 mg/day to 160 mg/day based on data from the Phase I S-3100-1-01 study showing comparable efficacy with improved safety profile at the lower dose (Amendment 1). This amendment was effective prior to the enrollment of any patient (30 July 2009).
- the addition of an interim analysis at approximately 520 deaths and the reduction of the number of death events required for the final analysis from 786 to 650 (Amendment 3).

Protocol deviations

Protocol deviations were reported for 117 (14.6%) patients in the MDV3100 arm and 50 (12.5%) patients in the placebo arm. The most common types of protocol deviations reported were not meeting

an eligibility or exclusion criteria and were: clinically significant cardiovascular disease (reported in 1.8% MDV3100-treated patients and 1.3% placebo-treated patients); received a medication known to lower the seizure threshold or prolong the QT interval (1.3% and 1.0%); more than 2 prior chemotherapy regimens (0.9% and 0.8%); and history of another malignancy (0.6% and 0.5%). Receiving an excluded concomitant medication was reported in 7.0% of MDV3100-treated patients and 5.5% of placebo-treated patients.

Baseline data

Patient demographic and baseline clinical characteristics are presented in table 11:

Table 11: CRPC2 Demographics Summary and Baseline Characteristics – Randomized Subjects

	MDV3100 (n = 800)	**Placebo (n = 399)**	**Total (n = 1199)**
Age (years)			
Mean (SD)	68.8 (7.96)	68.6 (8.39)	68.7 (8.11)
Median	69.0	69.0	69.0
Min, Max	41.0, 92.0	49.0, 89.0	41.0, 92.0
Age group (years)			
< 65	232 (29.0%)	130 (32.6%)	362 (30.2%)
65 to 74	369 (46.1%)	165 (41.4%)	534 (44.5%)
≥ 75	199 (24.9%)	104 (26.1%)	303 (25.3%)
Ethnicity			
Hispanic or Latino	32 (4.0%)	23 (5.8%)	55 (4.6%)
Not Hispanic or Latino	768 (96.0%)	376 (94.2%)	1144 (95.4%)
Race			
American Indian or Alaska Native	1 (0.1%)	1 (0.3%)	2 (0.2%)
Asian	5 (0.6%)	8 (2.0%)	13 (1.1%)
Black or African American	27 (3.4%)	20 (5.0%)	47 (3.9%)
Native Hawaiian or other Pacific Islander	1 (0.1%)	0 (0.0%)	1 (< 0.1%)
White	745 (93.1%)	366 (91.7%)	1111 (92.7%)
Other	21 (2.6%)	4 (1.0%)	25 (2.1%)
Weight (kg)	(n = 793)	(n = 394)	(n = 1187)
Mean (SD)	84.2 (14.51)	85.0 (16.56)	84.5 (15.22)
Median	83.0	83.0	83.0
Min, Max	46.0, 162.7	52.0, 151.7	46.0, 162.7
Baseline ECOG Performance Status			
0	298 (37.3%)	156 (39.1%)	454 (37.9%)
1	432 (54.0%)	211 (52.9%)	643 (53.6%)
2	70 (8.8%)	32 (8.0%)	102 (8.5%)
Average Pain Score as Assessed by Brief Pain Inventory – Short Form Question #3 During the Week Prior to Randomization			
< 4	574 (71.8%)	284 (71.2%)	858 (71.6%)
≥ 4	226 (28.3%)	115 (28.8%)	341 (28.4%)
Baseline Fatigue Severity as Assessed by the NCI-CTCAE (version 4.0)			
0	267 (38.1%)	124 (35.6%)	391 (37.3%)
1	369 (52.6%)	191 (54.9%)	560 (53.4%)
2	62 (8.8%)	31 (8.9%)	93 (8.9%)
3	3 (0.4%)	2 (0.6%)	5 (0.5%)
Missing	99	51	150
Baseline PSA (ng/mL)			
Mean (SD)	415.6 (930.76)	389.4 (1105.72)	406.9 (992.02)
Median	107.7	128.3	111.2
Min, Max	0.2, 11794.1	0.0, 19000.0	0.0, 19000.0

	MDV3100 (n = 800)	Placebo (n = 399)	Total (n = 1199)
Baseline Hemoglobin (g/dL)	(n = 799)	(n = 399)	(n = 1198)
Mean (SD)	119.1 (15.27)	119.5 (16.16)	119.2 (15.57)
Median	120.0	120.0	120.0
Min, max	63.0, 156.0	68.0, 171.0	63.0, 171.0
Baseline Alkaline Phosphatase (U/L)			
Mean (SD)	233.1 (380.87)	236.6 (420.65)	234.3 (394.38)
Median	115.0	109.0	114.0
Min, Max	30.0, 5598.0	28.0, 5676.0	28.0, 5676.0
Baseline Lactate Dehydrogenase (U/L)	(n = 800)	(n = 397)	(n = 1197)
Mean (SD)	271.7 (277.23)	269.0 (169.73)	270.8 (246.75)
Median	209.0	213.0	211.0
Min, Max	78.0, 5978.0	91.0, 1821.0	78.0, 5978.0
Baseline Serum Albumin (g/dL)	(n = 800)	(n = 397)	(n = 1197)
Mean (SD)	37.5 (4.03)	37.5 (4.20)	37.5 (4.09)
Median	38.0	38.0	38.0
Min, Max	26.0, 50.0	24.0, 48.0	24.0, 50.0
New York Heart Association Class at Screening			
No congestive heart failure	699 (87.7%)	351 (88.4%)	1050 (87.9%)
Class I	76 (9.5%)	40 (10.1%)	116 (9.7%)
Class II	21 (2.6%)	5 (1.3%)	26 (2.2%)
Class III	1 (0.1%)	1 (0.3%)	2 (0.2%)
Class IV	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	3	2	5

ECOG, Eastern Cooperative Oncology Group; g/dL, grams per deciliter; kg, kilograms; NCI-CTCAE, National Cancer Institute's Common Terminology Criteria for Adverse Events; ng/mL, nanograms per milliliter; PSA, prostate-specific antigen; SD, standard deviation; U/L, units per liter.

CRPC2 Disease Related Characteristics are presented in table 12.

Table 12: CRPC2 Disease Related Characteristics; ITT Population

	MDV3100 (n = 800)	Placebo (n = 399)	Total (n = 1199)
Time (months) from Initial Diagnosis of Prostate Cancer to Randomization			
Mean (SD)	86.1 (54.83)	81.9 (50.89)	84.7 (53.56)
Median	70.9	71.6	**70.9**
Min, max	5.3, 284.6	10.6, 268.0	5.3, 284.6
Gleason Score at Diagnosis			
2–4	10 (1.4%)	8 (2.2%)	18 (1.6%)
5–7	349 (48.1%)	167 (45.5%)	516 (47.2%)
8–10	366 (50.4%)	193 (52.4%)	559 (51.1%)
Missing	74	31	105
Pathological Tumor Stage (pT) at Diagnosis			
pT2	125 (15.8%)	61 (15.5%)	186 (15.7%)
pT3	193 (24.4%)	101 (25.7%)	294 (24.9%)
pT4	21 (2.7%)	10 (2.5%)	31 (2.6%)
Unknown	451 (57.1%)	221 (56.2%)	672 (56.8%)
Missing	10	6	16
Pathological Regional Lymph Node Status at Diagnosis			
pNx	141 (17.8%)	57 (14.5%)	198 (16.7%)
pN0	167 (21.1%)	73 (18.5%)	240 (20.2%)
pN1	69 (8.7%)	45 (11.4%)	114 (9.6%)
Unknown	415 (52.4%)	219 (55.6%)	634 (53.5%)
Missing	8	5	13

	MDV3100 (n = 800)	Placebo (n = 399)	Total (n = 1199)
Distant Metastasis at Initial Diagnosis			
Mx	97 (12.1%)	58 (14.6%)	155 (12.9%)
M0	308 (38.5%)	143 (35.9%)	451 (37.6%)
M1	204 (25.5%)	101 (25.4%)	305 (25.5%)
Unknown	191 (23.9%)	96 (24.1%)	287 (24.0%)
Missing	0	1	1
Disease Localization at Screening			
Bone only	225 (28.1%)	123 (30.8%)	348 (29.0%)
Soft tissue only	62 (7.8%)	34 (8.5%)	96 (8.0%)
Both bone and soft tissue	505 (63.1%)	241 (60.4%)	746 (62.2%)
None	8 (1.0%)	1 (0.3%)	9 (0.8%)
Type of Disease Progression at Study Entry			
PSA progression only	326 (41.0%)	164 (41.2%)	490 (41.0%)
Radiographic progression	470 (59.0%)	234 (58.8%)	704 (59.0%)
Bone only	205 (25.6%)	117 (29.3%)	322 (26.9%)
Soft tissue only	127 (15.9%)	59 (14.8%)	186 (15.5%)
Both bone and soft tissue	138 (17.3%)	58 (14.5%)	196 (16.3%)
No evidence of bone or soft tissue disease	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	4	1	5
Measurable Soft Tissue Disease at Screening			
Yes	446 (55.8%)	208 (52.1%)	654 (54.5%)
No	354 (44.3%)	191 (47.9%)	545 (45.5%)
Distribution of Disease at Screening			
Bone	730 (92.2%)	364 (91.5%)	1094 (91.9%)
Lymph node	442 (55.8%)	219 (55.0%)	661 (55.5%)
Visceral liver	92 (11.6%)	34 (8.5%)	126 (10.6%)
Visceral lung	122 (15.4%)	59 14.8%)	181 (15.2%)
Other soft tissue	147 (18.6%)	70 17.6%)	217 (18.2%)
Missing	8	1	9
Number of Bone Metastases at Screening			
0	70 (8.8%)	35 (8.8%)	105 (8.8%)
1	28 (3.5%)	21 (5.3%)	49 (4.1%)
2–4	112 (14.0%)	45 (11.3%)	157 (13.1%)
5–9	121 (15.1%)	68 (17.0%)	189 (15.8%)
10–20	167 (20.9%)	79 (19.8%)	246 (20.5%)
> 20	302 (37.8%)	151 (37.8%)	453 (37.8%)

NOTE: Patients can be summarised for more than one category but can only be counted once for each category.
NOTE: Disease localisation is based on Target Lesion page, Non-Target Lesion page, and Bone Scan page.
PSA, prostate-specific antigen; SD, standard deviation.

CRPC2 Prior therapies for prostate cancer are presented in table 13.

Table 13: CRPC2 Prior Therapy for Prostate Cancer; ITT Population

	MDV3100 (n = 800)	Placebo (n = 399)	Total (n = 1199)
Number of Prior Chemotherapy Regimens			
1	579 (72.4%)	296 (74.2%)	875 (73.0%)
2	196 (24.5%)	95 (23.8%)	291 (24.3%)
≥ 3	25 (3.1%)	8 (2.0%)	33 (2.8%)
Previous Chemotherapy Treatment[a]			
Docetaxel	800 (100.0%)	399 (100.0%)	1199 (100.0%)
Cabazitaxel	3 (0.4%)	0 (0.0%)	3 (0.3%)
Anthracycline	77 (9.6%)	40 (10.0%)	117 (9.8%)
Prior Docetaxel Treatment			
Mean number of cycles (SD)	9.0 (4.73)	9.0 (4.47)	9.0 (4.64)

	MDV3100 (n = 800)	Placebo (n = 399)	Total (n = 1199)
Median number of cycles	8.5	8.0	8.0
Mean Total Dosage (mg/m^2) (SD)	664.5 (348.15)	667.0 (332.51)	665.3 (343.04)
Median Total Dosage (mg/m^2)	600.0	600.0	600.0
< 225 total dosage (mg/m^2)	21 (3.0%)	9 (2.7%)	30 (2.9%)
≥ 225 to < 450 total dosage (mg/m^2)	127 (18.1%)	48 (14.4%)	175 (16.9%)
≥ 450 to < 675 total dosage (mg/m^2)	216 (30.8%)	125 (37.5%)	341 (32.9%)
≥ 675 to < 900 total dosage (mg/m^2)	204 (29.1%)	87 (26.1%)	291 (28.1%)
≥ 900 total dosage (mg/m^2)	134 (19.1%)	64 (19.2%)	198 (19.1%)
Missing	98	66	164
Time (months) from First Docetaxel Exposure to Randomization			
Mean (SD)	17.4 (12.86)	17.2 (12.93)	17.3 (12.88)
Median	13.6	13.1	13.4
Min, Max	2.5, 95.9	1.8, 97.8	1.8, 97.8
Time (months) from Last Docetaxel Exposure to Randomization			
Mean (SD)	8.8 (8.50)	8.4 (9.06)	8.7 (8.69)
Median	6.1	5.8	6.0
Min, max	1.0, 80.0	0.9, 94.3	0.9, 94.3
Reason for Discontinuation of Last Docetaxel Regimen			
PSA progression	273 (34.1%)	137 (34.3%)	410 (34.2%)
Radiographic progression	109 (13.6%)	55 (13.8%)	164 (13.7%)
Clinical disease progression	41 (5.1%)	15 (3.8%)	56 (4.7%)
Adverse event	155 (19.4%)	80 (20.1%)	235 (19.6%)
Treatment break/intermittent treatment	5 (0.6%)	3 (0.8%)	8 (0.7%)
Unknown	65 (8.1%)	28 (7.0%)	93 (7.8%)
Other	250 (31.3%)	119 (29.8%)	369 (30.8%)
Number of Unique Prior Hormonal Therapies			
1	65 (8.2%)	35 (8.8%)	100 (8.4%)
2	336 (42.3%)	151 (37.9%)	487 (40.9%)
3	246 (31.0%)	120 (30.2%)	366 (30.7%)
≥ 4	147 (18.5%)	92 (23.1%)	239 (20.1%)
Missing	6	1	7
Prior Use of Agents that Block Androgen Synthesis or Androgen Receptor			
Bicalutamide	669 (83.6%)	347 (87.0%)	1016 (84.7%)
Flutamide	109 (13.6%)	59 (14.8%)	168 (14.0%)
Nilutamide	73 (9.1%)	41 (10.3%)	114 (9.5%)
Ketoconazole	21 (2.6%)	16 (4.0%)	37 (3.1%)
Abiraterone acetate	2 (0.3%)	4 (1.0%)	6 (0.5%)
Use of Bisphosphonates at Baseline			
Yes	415 (51.9%)	198 (49.6%)	613 (51.1%)
No	386 (48.1%)	201 (50.4%)	586 (48.9%)
History of Radiotherapy			
Yes	571 (71.4%)	287 (71.9%)	858 (71.6%)
No	229 (28.6%)	112 (28.1%)	341 (28.4%)
Type of Prior Radiotherapy			
Primary	300 (37.5%)	167 (41.9%)	467 (38.9%)
Salvage	68 (8.5%)	26 (6.5%)	94 (7.8%)
Metastatic disease/palliative	324 (40.5%)	151 (37.8%)	475 (39.6%)
History of Surgical Prostate Cancer Procedure			
Yes	531 (66.4%)	243 (60.9%)	774 (64.6%)
No	269 (33.6%)	156 (39.1%)	425 (35.4%)

	MDV3100 (n = 800)	Placebo (n = 399)	Total (n = 1199)
Type of Prior Surgical Cancer Procedure			
Prostatectomy	277 (34.6%)	122 (30.6%)	399 (33.3%)
Orchiectomy	44 (5.5%)	23 (5.8%)	67 (5.6%)
Transurethral resection of the prostate	115 (14.4%)	49 (12.3%)	164 (13.7%)
Other	278 (34.8%)	114 (28.6%)	392 (32.7%)

a Selected previous chemotherapy, for a complete list see Table 14.1.7.1.
mg/m2, milligrams per square meter; PSA, prostate-specific antigen; SD, standard deviation.

Numbers analysed

Analysis Populations for patients enrolled in the treatment and control arms are presented in Table14.

Table 14: Analysis population

	Enzalutamide (n = 800)	Placebo (n = 399)
Randomized (ITT Population)[a]	800	399
Not treated with study drug	0 (0.0%)	0 (0.0%)
Evaluable for FACT-P	651 (81.4%)	257 (64.4%)
Evaluable for PSA Response	731 (91.4%)	330 (82.7%)
Evaluable for Pain Palliation	49 (6.1%)	15 (3.8%)
Evaluable for Best Overall Radiographic Response	396 (49.5%)	167 (41.9%)
Evaluable for EQ-5D	146 (18.3%)	68 (17.0%)
Evaluable for Pain Progression Rate	625 (78.1%)	259 (64.9%)
Safety Population	800 (100 %)	399 (100 %)
PK Population[b]	796 (99.5%)	NA

[a]ITT Population was defined as all patients who were randomized into the study. Safety Population was defined as all randomized patients who received at least 1 dose of study drug. The ITT and Safety Populations both included all randomised patients.

[b]PK Population was defined as all randomized patients who received at least 1 dose of MDV3100 and had at least 1 MDV3100, M1, or M2 plasma concentration result. EQ-5D, European Quality of Life Five-Domain scale; FACT-P, Functional Assessment of Cancer Therapy– Prostate; ITT, Intent-to-Treat; NA, not applicable; PK, pharmacokinetics; PSA, prostate-specific antigen.

Patient disposition:

Overall, 231 (28.9%) patients on the MDV3100 arm and 19 (4.8%) patients on the placebo arm remained on study drug as of the data cut-off date.

Outcomes and estimation

Table 15: Results of main efficacy endpoints

Endpoint	MDV3100 (n=800)	Placebo (n=399)	Hazard Ratio	P-Value
Primary Efficacy Endpoint				

Overall Survival (median) Event rate	18.4 months 308 (38.5 %)	13.6 months 212 (53.1 %)	0.631	<0.0001
Key Secondary Efficacy Endpoints				
Time to PSA Progression (median) Event rate	8.3 months 400 (50.0 %)	3.0 months 190 (47.6 %)	0.248	< 0.0001
Radiographic Progression-Free Survival (median) Event rate	8.3 months 524 (65.5 %)	2.9 months 337 (84.5 %)	0.404	< 0.0001
Time to First Skeletal-Related Event (median) Event rate	16.7 months 287 (35.9 %)	13.3 months 161 (40.4 %)	0.688	0.0001
Other Secondary Efficacy Endpoints[a]				
FACT-P Response Rate	43.2%	18.3%	NA	< 0.0001
PSA Response Rate 50% Decrease 90% Decrease	 54.0% 24.8%	 1.5% 0.9%	 NA	 < 0.0001 < 0.0001

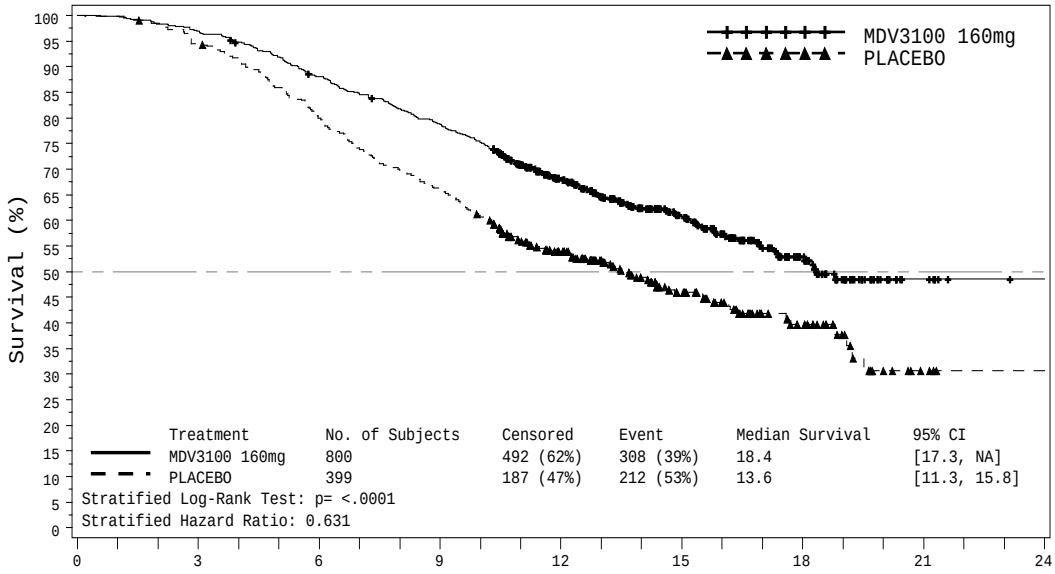
[a]No corrections for multiplicity were made for other secondary or exploratory efficacy endpoints.
ECOG, Eastern Cooperative Oncology Group; EQ-5D, European Quality of Life Five Domain Scale; FACT-P, Functional Assessment of Cancer Therapy-Prostate; PS, performance status; NA, not applicable; PSA, prostate-specific antigen.

Note the consistency between different outcome measures in terms of difference at the medians.

1. Primary Endpoint: **OVERALL SURVIVAL**

The formal interim analysis for the primary endpoint Overall Survival was performed, as issued in Amendment 3, at 520 events corresponding to 43% of events in the long run (considered borderline maturity). The date of the 520th death (25 September 2011) was used as the analysis data cut-off date. Stratified analysis of overall survival showed a statistically significant increase in the duration of survival among patients treated with MDV3100 as compared to placebo with a median overall benefit of 4.8 months in favour of the MDV3100-treated patients and corresponding to an approximately 37 % decrease in the risk of death Table 15). Kaplan-Meier curves for duration of survival are shown in Figure 02. To be noted is the uncertainty with respect to the MDV3100 arm around the median estimate.

Based on these results the Independent Data Monitoring Committee (IDMC) recommended the study to be halted and the patients in the placebo arm to be proffered to receive MDV3100. The study blind was maintained until database lock on 16 December 2011.



MDV3100 160mg:								
Event/Cum. Events	0/0	25/25	71/96	73/169	79/248	35/283	20/303	5/308	0/308
Patients at Risk	800	775	701	627	400	211	72	7	0
PLACEBO:									
Event/Cum. Events	0/0	22/22	58/80	54/134	47/181	19/200	8/208	4/212	0/212
Patients at Risk	399	376	317	263	167	81	33	3	0

Figure 2: CRPC2 Overall Survival: ITT- Population

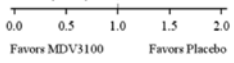
A supplementary descriptive summary of all deaths available at the closure of the database was made. At database closure, there were 344 (43.0%) deaths in the MDV3100 arm and 232 (58.1%) deaths in the placebo arm (48% of total events). The hazard ratio for death (95% CI) for MDV3100-treated patients from a stratified Cox regression model was 0.620 (95% CI: 0.525, 0.733).

To ascertain whether subsequent therapies following progression on study drug may have influenced the survival results, post-progression therapies were investigated. The analysis showed that administration of subsequent therapies for prostate cancer was consistently higher in patients receiving placebo as compared with patients receiving MDV3100.

The number of patients taking at least one subsequent therapy were 336 (42.0%) in the MDV3100 arm as compared to 245 (61.4%) in the placebo arm and it was mainly consistent regardless of the different regimens administered. This included the two recently approved second-line treatments for CRPC, abiraterone (20.9% of patients in the MDV3100 arm vs. 24.3% in the placebo arm) and cabazitaxel (9.8% vs. 13.8%).

As supportive analyses, Overall survival was examined in patient subgroups. The following subgroups were selected for this analysis because they were either accepted prognostic factors for prostate cancer, demographic features of interest, or represent different regional practice patterns:

Subgroup	Number of Patients MDV3100 160mg / Placebo	Overall Survival Median (mo) MDV3100 160mg / Placebo	Hazard Ratio for Death (95% CI) (Unstratified)
All Subjects	800 / 399	18.4 / 13.6	0.63 (0.53-0.75)
ECOG Performance Status at Baseline=0 or 1	730 / 367	---- / 14.2	0.62 (0.52-0.75)
ECOG Performance Status at Baseline=2	70 / 32	10.5 / 7.2	0.65 (0.39-1.07)
Average Pain Score Based on Question 3 from the Brief Pain Inventory (Short Form) at Baseline < 4	574 / 284	---- / 16.2	0.59 (0.47-0.74)
Average Pain Score Based on Question 3 from the Brief Pain Inventory (Short Form) at Baseline >= 4	226 / 115	12.4 / 9.1	0.71 (0.54-0.94)
Age < 65	232 / 130	---- / 12.4	0.63 (0.46-0.87)
Age >=65	568 / 269	18.4 / 13.9	0.63 (0.51-0.78)
Geographic Region - North America	263 / 132	17.4 / 12.3	0.63 (0.47-0.83)
Geographic Region - Europe	461 / 223	---- / 16.2	0.64 (0.50-0.82)
Geographic Region - Rest of the World	76 / 44	18.1 / 12.6	0.63 (0.37-1.07)
Total Gleason Score at Diagnosis <= 7	360 / 175	18.4 / 14.8	0.67 (0.51-0.88)
Total Gleason Score at Diagnosis >= 8	366 / 193	18.2 / 11.3	0.60 (0.47-0.76)
Number of Prior Chemotherapy Regimens=1	579 / 296	---- / 14.2	0.59 (0.48-0.73)
Number of Prior Chemotherapy Regimens >= 2	221 / 103	15.9 / 12.3	0.74 (0.54-1.03)
Type of Progression at Study Entry– PSA Progression Only	326 / 164	---- / 19.5	0.62 (0.46-0.83)
Type of Progression at Study Entry – Radiographic Progression with or without PSA Progression	470 / 234	17.3 / 13.0	0.64 (0.52-0.80)
Visceral Disease (Lung and/or Liver) at Screening - Yes	196 / 82	13.4 / 9.5	0.78 (0.56-1.09)
Visceral Disease (Lung and/or Liver) at Screening - No	604 / 317	---- / 14.2	0.56 (0.46-0.69)
Baseline PSA value <= Median	412 / 188	---- / 19.2	0.67 (0.50-0.89)
Baseline PSA value > Median	388 / 211	15.3 / 10.3	0.62 (0.50-0.78)
Baseline LDH value <= Median	411 / 192	---- / 19.2	0.63 (0.46-0.86)
Baseline LDH value > Median	389 / 205	12.4 / 8.5	0.61 (0.50-0.76)
Baseline Hemoglobin value <= Median	409 / 202	13.0 / 9.5	0.68 (0.55-0.85)
Baseline Hemoglobin value > Median	390 / 197	---- / 19.2	0.50 (0.37-0.68)



The results by baseline risk factors were all consistent with the results for the randomized population.

Results of the pre-planned interim analysis (25 September 2011) despite clearly positive, were considered of borderline maturity as they were based on events in 43% of the total study population. In spite of the unquantifiable impact that cross-over of patients may have the company was requested to submit as much information on OS as possible. Beyond the date database lock on 16 December 2011 the company submitted two additional updated analyses on OS:

- One at the time of a safety update for the FDA (Jan-2012) when 645 events had occurred, which represent events in 54% of the total study population (99% of the total targeted events), results remain in the same trend: HR: 0.672 (95%CI: 0.573-0.788) and a difference of 4.8 months in median time to death was observed. This result constitutes a reliable estimate of OS. In spite of the open-label nature of the trial at this point, OS is a robust endpoint that can hardly be biased by factors such as blinding; furthermore no patient had been crossed-over to placebo so far.

- An additional analysis has been submitted based on data cut-off of 29-June-2012, when 734 events had been reported (61.2% of the total study population) and only 22 patients were crossed to active treatment arm. Again, results remain in the same line: HR: 0.696 (95%CI: 0.599-0.809) and a difference of 4.9 months in median time to death was observed. Albeit bias cannot be ruled out and results are not fully reliable the impact of 22 patients crossed to active treatment can be considered minimal (surprisingly only 22 patients have been crossed over to active treatment arm 6 months after the database was locked).

Overall, results are reassuring and more mature than the initially reported results. As per the data provided the effect of MDV3100 in the target population is consistent and relevant from a clinical point of view.

2. Key Secondary Efficacy Endpoints

The key secondary endpoints were tested hierarchically in a pre-specified rank order, such that if statistical significance was not achieved for 1 of the endpoints, the following endpoints in sequence would not be analysed.

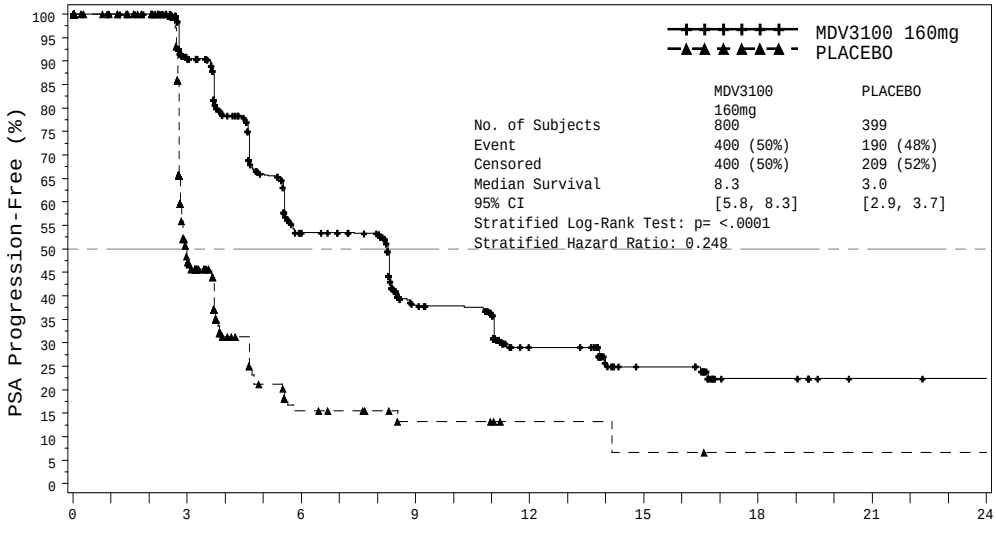
Time to PSA progression

Prostate-specific antigen progression was assessed for each patient using the PCWG2 criteria and could only be declared on or after the Week 13 assessment requiring a confirmation that was consecutive and conducted at least three weeks later. Patients who were not determined to have PSA progression were censored at the date of the last assessment showing no evidence of PSA progression.

A total of 400 patients in the MDV3100 arm and 190 patients in the placebo arm experienced PSA progression on study and 400 subjects and 209 subjects respectively were censored.

50.0 % of patients in the MDV3100 arm and 52.4% of patients in the placebo arm were censored with respect to Time To PSA Progression. Of them, 8.6% and 17.3% respectively were lost to follow-up (no PSA post-baseline). All other censored data were due to the lack of observed confirmation of PSA progression.

The analysis showed a statistically significant increase among MDV3100-treated patients compared to placebo with a median benefit of 5.3 months and corresponding to a hazard ratio of 0.248 (95% CI: 0.204, 0.303) (Figure 3).



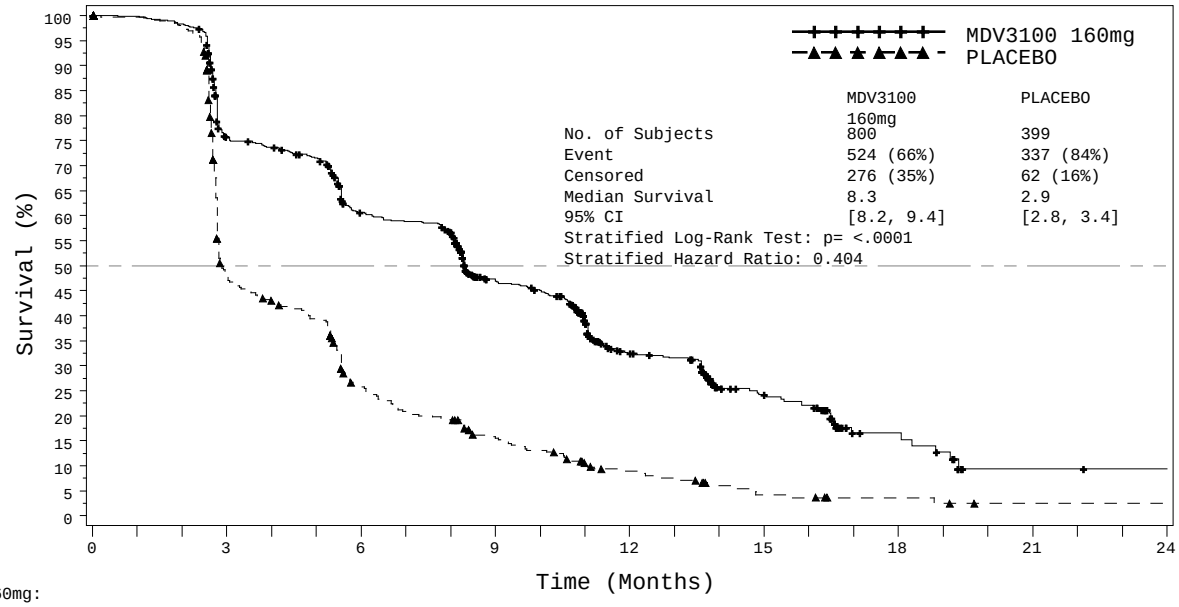
MDV3100 160mg:									
Event/Cum. Events	0/0	63/63	225/288	73/361	30/391	7/398	2/400	0/400	0/400
Patients at Risk	800	603	287	145	68	27	7	1	0
PLACEBO:									
Event/Cum. Events	0/0	144/144	44/188	1/189	0/189	1/190	0/190	0/190	0/190
Patients at Risk	399	107	12	5	2	1	0	0	0

Figure 3: CRPC2 Time to PSA: ITT Population

Radiographic progression free survival

In the MDV3100 arm a total of 65.5 % of the patients experienced an event as compared to 84.5 % in the placebo arm. Radiographic progression occurred in 49.9 % of the MDV3100 treated patients as compared to 61.7 % in the placebo arm while Death (defined as without documented radiographic progression) occurred in 15.6 % and 22.8 % respectively. The censor rate was 34.5% in the MDV3100 arm compared to 15.5% in the placebo arm.

A statistically significant increase in time to radiographic progression among MDV3100-treated patients compared with placebo-treated patients was observed with a median difference of 5.4 months in favour of the MDV3100 treated patients (Figure 04). The hazard ratio was 0.404 (95% CI: 0.350, 0.466).



MDV3100 160mg:									
Event/Cum. Events	0/0	189/189	115/304	93/397	79/476	29/505	14/519	5/524	0/524
Patients at Risk	800	583	447	287	140	58	13	1	0
PLACEBO:									
Event/Cum. Events	0/0	197/197	77/274	33/307	19/326	9/335	1/336	1/337	0/337
Patients at Risk	399	176	86	46	20	7	3	0	0

Figure 04 CRPC2 Radiographic Progression-Free Survival

A sensitivity analysis of rPFS in which documented clinical progressions are counted as events showed consistent results (median difference of time to event between study arms of 5.3 months and a HR = 0.363; 95% CI [0.316, 0.418], P<0.0001). Results are in line with the main analysis of rPFS which is reassuring.

Time to first skeletal-related event

A median difference of 3.4 months in favour of the MDV3100 treated patients was observed with a hazard ratio of 0.688 as compared with placebo. The rate of censored patients was 64.1% and 59.6% respectively. The vast majority received radiation to the bone, approximately 60 %, similar in both arms. About 10 % had a pathological bone fracture, likewise similar between the arms.

1. Other Secondary Efficacy Endpoints:

Quality of life (FACT-P)

In the MDV3100 arm there were 43.2 % of patients with improved quality of life compared to 18.3 % in the placebo arm. The difference was statistically significant.

Post base-line assessments which was provided by 85.9 % of the patients in the MDV3100 arm compared to 66.8 % in the placebo arm.

PSA response rate

Patients were evaluable for PSA response rate if they had a PSA level measured at baseline and at least 1 post-baseline assessment. Both PSA responses of > 50% and > 90% were determined. In the MDV3100 arm 731 patients were evaluable as compared to 330 patients in the placebo arm.

The difference in response rate was 52.5% for response > 50% and 23.9% for > 90% in favour of MDV3100 compared to placebo and both levels were statistically significant (p < 0.0001).

Pain palliation

The difference in rate of pain palliation was 38.2% in favour of MDV3100 and statistically significant. However, the number of patients who met the criteria for evaluability for this analysis was only 49 (6.1%) in the MDV3100 arm and 15 (3.8%) in the placebo arms.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 16: Summary of Efficacy for AFFIRM trial

Title: A Multinational Phase 3, Randomised, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Patients with Progressive Castration-Resistant Prostate Cancer Previously Treated with Docetaxel-Based Chemotherapy			
Study identifier	CRPC2 (AFFIRM)		
Design	Multinational, randomised, double-blind, placebo-controlled efficacy and safety study		
	Duration of main phase:		Until disease progression, initiation of other systemic antineoplastic therapy or unacceptable toxicity
Hypothesis	Superiority		
Treatments groups	Enzalutamide (MDV3100)		160 mg orally once daily (administered as 4 × 40 mg capsules) without regard to food. Study drug doses were to be taken as close to the same time each day as possible (N=800)
	Placebo		4 matching placebo tablets orally once daily without regard to food. Study drug doses were to be taken as close to the same time each day as possible (N=399)
Endpoints and definitions	Primary endpoint:	Overall survival (OS)	Time from randomisation to death from any cause.
	Key Secondary endpoint	Time to PSA Progression	Time from randomization to the date of PSA progression (PCWG2 criteria).
	Key Secondary endpoint	Radiographic Progression-Free Survival	Time to from randomization to progression as assessed by the Investigator (RECIST v1.1 and PCWG2 criteria for visceral and bone disease).
	Key Secondary endpoint	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.
Database lock	25 September 2011 (cut-off date for the IA) /database lock 16/12/2011		
Results and Analysis			

Analysis population and time point description	Intent to treat. 25/09/2011 (520 events of death observed)		
Descriptive statistics and estimate variability	Treatment group	MDV3100	Placebo
	Number of subject	800	399
	OS (median, in months)	18.4	13.6
	95% CI	(17.3, NM)	(6.8–NM)
	Time to PSA progression (median, in months)	8.3	3.0
	95% CI	(5.8, 8.3)	(2.9, 3.7)
	Radiographic PFS (median, in months) 95% CI	8.3 (8.2, 9.4)	2.9 (2.8, 3.4)
	Time to first skeletal-related event (median, in months) 95% CI	16.7 (14.6, 19.1)	13.3 (9.9, NM)
Effect estimate per comparison	Primary endpoint Overall Survival	Comparison groups	MDV3100 *vs* Placebo
		HR from stratified proportional hazards model (95%CI)	0.631 (0.529, 0.752)
		P-value	< 0.0001
	Key Secondary endpoint :Time to PSA progression	Comparison groups	MDV3100 *vs* Placebo
		HR from stratified proportional hazards model (95%CI)	0.248 (0.204, 0.303)
		P-value	< 0.0001
	Key Secondary endpoint: Radiographic PFS	Comparison groups	MDV3100 *vs* Placebo
		HR from stratified proportional hazards model (95%CI)	0.404 (0.350, 0.466)
		P-value	< 0.0001

	Key Secondary endpoint: Radiographic PFS	Comparison groups	MDV3100 *vs* Placebo
		HR from stratified proportional hazards model (95%CI)	0.688 (0.566, 0.835)
		P-value	0.0001
Notes	Stratification factors used to derive log-rank p-value and hazard ratio: baseline ECOG performance status and mean Brief Pain Inventory – Short Form score (Question #3).		

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

Supportive study(ies)

Study S-3100-1-01

See dose-response studies.

CRPC-MDA-1

See clinical pharmacodynamic studies.

2.5.3. Discussion on clinical efficacy

Design and conduct of the trial

One single pivotal trial, Study CRPC2, has been submitted in support of the efficacy of MDV3100 in patients with advanced Castration-Resistant Prostate Cancer (CRPC) in a population who had progressed after 1 or 2 prior chemotherapy regimens at least one docetaxel-based.

At the time the study was initiated there was not an established standard of care, thus a placebo control study is deemed acceptable, despite outcomes of this trial may be discussed within the context of the current clinical practice (i.e. abiraterone acetate and cabazitaxel have both shown benefit in terms of OS in the same target population).

Baseline characteristics properly define target population; however some exceptions have been highlighted. On the one hand, black race is underrepresented. On the other hand the number of patients entering with a baseline ECOG-PS=2 was low and one could wonder whether efficacy could be the same in this most damaged population, subgroup analyses somehow clarified this issue, though uncertainties regarding the low number of patients included remain. Both patients of non-White race and those with ECOG PS ≥ 2 have been included as missing information in the RMP.

Efficacy data and additional analyses

At the time of data cut-off of the pre-planned interim analysis (25 September 2011) results showed a significant improvement in terms of the primary endpoint Overall survival (OS): median time of

survival was improved in 4.8 months; median time was 18.4 in the MDV3100 arm and 13.6 months in placebo arm (HR: 0.633; 95%CI:0.531, 0.754; p< 0.0001).

Additionally analyses have been conducted in different subgroups showing consistent results.

The key secondary endpoints were comparison between treatment arms in relation to Time to PSA progression, duration of radiographic PFS and Time to first skeletal-related event. A statistically significant increase in Time to PSA progression was observed among MDV3100-treated patients compared with placebo with a benefit of 5.3 months and corresponding to a hazard ratio of 0.248 (95% CI: 0.204, 0.303). In addition, the key secondary endpoint radiographic progression-free survival that encompassed progression in soft tissue as well as in bone disease, showed a median benefit of 5.4 months in favour for the MDV3100 arm compared to placebo. The hazard ratio was 0.404 (95% CI: 0.350, 0.466).

The analysis of Time to first skeletal-related events revealed a statistically significant increase in favour of the MDV3100-treated patients compared with placebo with a benefit of 3.4 months with a hazard ratio of 0.688 (95% CI: 0.566, 0.835).

Furthermore, PSA response Rate measured by ≥ 50% and ≥ 90% PSA reduction from baseline was assessed. The difference in response rate was 52.5% and 23.9% respectively in favour of MDV3100 compared to placebo. Both levels were statistically significant (p < 0.0001).

2.5.4. Conclusions on the clinical efficacy

The clinical efficacy has been established based on compelling results in terms of primary and key secondary endpoints. The concordant results across the secondary objectives and ancillary analyses demonstrate the robustness of outcomes.

2.6. Clinical safety

The safety data to support the use of MDV3100 in the proposed indication is based mainly on the pivotal randomised Study CRPC2 [800 patients treated with MDV3100 and 399 patients treated with placebo] and also on the pooled data from several studies Uncontrolled open-label studies [<150 mg (n = 33), 150 or 160 mg (n = 109), and >160 mg (n = 85)]. An additional analysis was performed joining both populations in the Integrated safety Population [MDV3100 <150 mg (n = 33), MDV 150/160 mg (n = 909), MDV >160 mg (n = 85); placebo (n = 399)]. Further information or updates from individual clinical trials were provided as supportive information.

Patient exposure

Table 17: Extent of Exposure to Study Drug in Patients with Castration-Resistant Prostate Cancer

	MDV3100 < 150 mg	MDV3100 150–160 mg[a]	MDV3100 > 160 mg	Total MDV3100	Placebo
CRPC2					
n		800		800	399
Time on Study Drug (months)					
Mean (SD)		8.5 (5.08)		8.5 (5.08)	4.3 (3.44)
Median (Min, max)		8.3 (0.0, 23.2)		8.3 (0.0, 23.2)	3.0 (0.2, 20.7)
Time on Study Drug Category, n (%)					
≤ 2 Months		73 (9.1%)		73 (9.1%)	74 (18.5%)
> 2–< 6 Months		238 (29.8%)		238 (29.8%)	254 (63.7%)

	MDV3100 < 150 mg	MDV3100 150–160 mg[a]	MDV3100 > 160 mg	Total MDV3100	Placebo
≥ 6–<12 Months		291 (36.4%)		291 (36.4%)	53 (13.3%)
≥ 12 Months		198 (24.8%)		198 (24.8%)	18 (4.5%)
Open-Label Studies Population					
n	33	109	85	227	
Time on Study Drug (months)					
Mean (SD)	11.6 (11.51)	7.6 (9.36)	9.9 (12.43)	9.0 (10.97)	
Median (Min, Max)	5.9 (1.7, 50.1)	4.5 (0.0, 45.3)	4.3 (0.1, 43.9)	4.6 (0.0, 50.1)	
Time on Study Drug Category, n (%)					
≤ 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%)	
Integrated Safety Population					
n	33	909	85	1027	399
Time on Study Drug (months)					
Mean (SD)	11.6 (11.51)	8.4 (5.77)	9.9 (12.43)	8.6 (6.83)	4.3 (3.44)
Median (Min, Max)	5.9 (1.7, 50.1)	8.0 (0.0, 45.3)	4.3 (0.1, 43.9)	7.4 (0.0, 50.1)	3.0 (0.2, 20.7)
Time on Study Drug Category, n (%)					
≤ 2 Months	1 (3.0%)	95 (10.5%)	22 (25.9%)	118 (11.5%)	74 (18.5%)
> 2–< 6 Months	17 (51.5%)	288 (31.7%)	31 (36.5%)	336 (32.7%)	254 (63.7%)
≥ 6–<12 Months	4 (12.1%)	306 (33.7%)	12 (14.1%)	322 (31.4%)	53 (13.3%)
≥ 12 Months	11 (33.3%)	220 (24.2%)	20 (23.5%)	251 (24.4%)	18 (4.5%)

a 160 mg was used in all studies except S-3100-1-01; in this study a formulation occurred necessitating dose change from 150 mg to 160 mg during the study.

Adverse events

Table 18: Summary of Adverse Events

	Controlled CRPC2	
Number of Patients Reporting ≥ 1	**MDV3100 160 mg (n = 800)**	**Placebo* (n = 399)**
Adverse Event	785 (98.1%)	390 (97.7%)
Adverse Event Associated with Study Drug Discontinuation	128 (16.0%)	73 (18.3%)
Adverse Event as Primary Reason for Study Drug Discontinuation	61 (7.6%)	39 (9.8%)
Adverse Event Leading to Dose Reduction of Study Drug	17 (2.1%)	11 (2.8%)
Adverse Event Leading to Temporary Interruption of Study Drug Dosing	102 (12.8%)	61 (15.3%)
Adverse Event Leading to Death	23 (2.9%)	14 (3.5%)
Serious Adverse Event	268 (33.5%)	154 (38.6%)
Grade 3 or Higher Adverse Event	362 (45.3%)	212 (53.1%)
Source: Tables 3.10, 3.105		

Table 19: Adverse Events Reported in at Least 5% of Patients in Any Treatment Group

	Controlled CRPC2	
System Organ Class Preferred Term	**MDV3100 160mg (n = 800)**	**Placebo* (n = 399)**
Number of Patients Reporting ≥ 1 Adverse Event	785 (98.1%)	390 (97.7%)
Blood and Lymphatic System Disorders	134 (16.8%)	84 (21.1%)
Anaemia	115 (14.4%)	76 (19.0%)
Gastrointestinal Disorders	539 (67.4%)	279 (69.9%)
Nausea	265 (33.1%)	167 (41.9%)
Constipation	188 (23.5%)	110 (27.6%)
Diarrhoea	**171 (21.4%)**	**70 (17.5%)**
Vomiting	130 (16.3%)	88 (22.1%)
Abdominal pain	41 (5.1%)	23 (5.8%)
General Disorders and Administration Site Conditions	506 (63.3%)	231 (57.9%)
Fatigue	**269 (33.6%)**	**116 (29.1%)**
Edema peripheral	**122 (15.3%)**	**53 (13.3%)**
Asthenia	140 (17.5%)	67 (16.8%)
Pyrexia	54 (6.8%)	28 (7.0%)
Infections and Infestations	285 (35.6%)	117 (29.3%)
Urinary tract infection	63 (7.9%)	28 (7.0%)
Investigations	148 (18.5%)	77 (19.3%)
Weight decreased	94 (11.8%)	41 (10.3%)
Metabolism and Nutrition Disorders	280 (35.0%)	155 (38.8%)
Decreased appetite	225 (28.1%)	121 (30.3%)
Musculoskeletal and Connective Tissue Disorders	516 (64.5%)	259 (64.9%)
Back pain	197 (24.6%)	96 (24.1%)
Arthralgia	152 (19.0%)	69 (17.3%)
Pain in extremity	119 (14.9%)	65 (16.3%)
Musculoskeletal pain	**116 (14.5%)**	**46 (11.5%)**
Bone pain	101 (12.6%)	61 (15.3%)
Muscular weakness	**74 (9.3%)**	**27 (6.8%)**
Musculoskeletal chest pain	62 (7.8%)	34 (8.5%)
Myalgia	50 (6.3%)	26 (6.5%)
Nervous System Disorders	389 (48.6%)	149 (37.3%)
Headache	**93 (11.6%)**	**22 (5.5%)**
Dizziness	55 (6.9%)	22 (5.5%)
Paresthesia	**52 (6.5%)**	**18 (4.5%)**
Spinal cord compression	51 (6.4%)	18 (4.5%)
Psychiatric Disorders	199 (24.9%)	77 (19.3%)
Insomnia	**70 (8.8%)**	**24 (6.0%)**
Anxiety	**51 (6.4%)**	**16 (4.0%)**
Depression	44 (5.5%)	18 (4.5%)
Renal and Urinary Disorders	185 (23.1%)	97 (24.3%)
Haematuria	**52 (6.5%)**	**18 (4.5%)**
Respiratory, Thoracic, and Mediastinal Disorders	210 (26.3%)	102 (25.6%)
Dyspnoea	79 (9.9%)	39 (9.8%)
Cough	47 (5.9%)	25 (6.3%)
Vascular Disorders	249 (31.1%)	78 (19.5%)
Hot flush	**162 (20.3%)**	**41 (10.3%)**
Hypertension	**49 (6.1%)**	**11 (2.8%)**

mg, milligrams

Across MDV3100 and placebo groups, the most frequently reported AEs were fatigue (40.3% and 29.1% in the MDV3100 and placebo groups, respectively), nausea (32.7% and 41.9%, respectively), decrease appetite (28.6% and 30.3%, respectively), back pain (24.8% and 24.1%, respectively) and constipation (24.8% and 27.6%, respectively), consistent with the natural history of mCRPC.
Adverse events more common in the combined MDV3100 treatment group (n=1027) with at least a 2% absolute difference in incidence from placebo group were diarrhoea (20.5% vs. 17.5%), fatigue (40.3% vs. 29.1%), edema peripheral (16.1% vs.13.3%), arthralgia (20.4% vs. 17.3%), musculoskeletal pain (14.8% vs. 11.5%), muscular weakness (9.2 %vs. 6.8%), headache (12.1% vs. 5.5%), dizziness (8.6% vs. 5.5%), dysgeusia (6.2% vs. 3.5%), insomnia (9.3% vs. 6.0%), haematuria (6.6% vs. 4.5%), pollakiuria (5.7% vs. 2.5%), dyspnoea (12.2% vs. 9.8%), hot flush (19.3% vs. 10.3%), hypertension (6.1% vs. 2.8%).

Table 20: Adverse Events Reported in at Least 5% of Patients in Any Treatment Group in CRPC2, Adverse Events Starting within First 60 Days of Start of Treatment, and Events per 100 Patient-Years

	Adverse Events		**Adverse Events Starting ≤60 Days after Start of Treatment**		**Events/ 100 pt-yrs**	
Preferred Term	**MDV3100 160mg (n = 800)**	**Placebo (n = 399)**	**MDV3100 160mg (n = 800)**	**Placebo (n = 399)**	**MDV3100 160mg (n = 800)**	**Placebo (n = 399)**
Fatigue	**269 (33.6%)**	**116 (29.1%)**	**166 (20.8%)**	**82 (20.6%)**	**49.9**	**72.0**
Nausea	265 (33.1%)	167 (41.9%)	174 (21.8%)	123 (30.8%)	52.5	124.8
Decreased appetite	225 (28.1%)	121 (30.3%)	124 (15.5%)	79 (19.8%)	5.6	10.8
Back pain	197 (24.6%)	96 (24.1%)	81 (10.1%)	63 (15.8%)	39.0	63.0
Constipation	188 (23.5%)	110 (27.6%)	98 (12.3%)	83 (20.8%)	34.5	74.4
Diarrhoea	**171 (21.4%)**	**70 (17.5%)**	**90 (11.3%)**	**44 (11.0%)**	**36.3**	**47.4**
Hot flush	**162 (20.3%)**	**41 (10.3%)**	**132 (16.5%)**	**39 (9.8%)**	**27.4**	**24.6**
Arthralgia	152 (19.0%)	69 (17.3%)	65 (8.1%)	43 (10.8%)	31.4	52.2
Asthenia	140 (17.5%)	67 (16.8%)	92 (11.5%)	46 (11.5%)	26.3	45.0
Vomiting	130 (16.3%)	88 (22.1%)	72 (9.0%)	60 (15.0%)	29.4	67.8
Edema peripheral	**122 (15.3%)**	**53 (13.3%)**	**63 (7.9%)**	**32 (8.0%)**	**21.6**	**34.2**
Pain in extremity	119 (14.9%)	65 (16.3%)	55 (6.9%)	44 (11.0%)	24.0	45.6
Musculoskeletal pain	**116 (14.5%)**	**46 (11.5%)**	**47 (5.9%)**	**25 (6.3%)**	**20.2**	**24.6**
Anaemia	115 (14.4%)	76 (19.0%)	45 (5.6%)	40 (10.0%)	24.4	62.4
Bone pain	101 (12.6%)	61 (15.3%)	41 (5.1%)	41 (10.3%)	21.8	48.0
Weight decreased	94 (11.8%)	41 (10.3%)	40 (5.0%)	24 (6.0%)	16.0	25.8
Headache	**93 (11.6%)**	**22 (5.5%)**	**58 (7.3%)**	**15 (3.8%)**	**17.8**	**14.4**
Dyspnoea	79 (9.9%)	39 (9.8%)	33 (4.1%)	20 (5.0%)	13.9	24.0
Muscular weakness	**74 (9.3%)**	**27 (6.8%)**	**30 (3.8%)**	**12 (3.0%)**	**12.4**	**16.8**
Insomnia	**70 (8.8%)**	**24 (6.0%)**	**46 (5.8%)**	**14 (3.5%)**	**11.9**	**14.4**
Urinary tract infection	63 (7.9%)	28 (7.0%)	21 (2.6%)	14 (3.5%)	13.2	19.2
Musculoskeletal chest pain	62 (7.8%)	34 (8.5%)	21 (2.6%)	25 (6.3%)	12.6	22.2
Dizziness	55 (6.9%)	22 (5.5%)	33 (4.1%)	13 (3.3%)	9.9	13.2
Pyrexia	54 (6.8%)	28 (7.0%)	23 (2.9%)	14 (3.5%)	10.4	21.0
Paresthesia	**52 (6.5%)**	**18 (4.5%)**	**24 (3.0%)**	**14 (3.5%)**	**9.3**	**11.4**
Haematuria	**52 (6.5%)**	**18 (4.5%)**	**27 (3.4%)**	**11 (2.8%)**	**11.9**	**13.2**
Spinal cord compression	51 (6.4%)	18 (4.5%)	17 (2.1%)	9 (2.3%)	8.8	11.4

	Adverse Events		Adverse Events Starting ≤60 Days after Start of Treatment		Events/ 100 pt-yrs	
Preferred Term	**MDV3100 160mg (n = 800)**	**Placebo (n = 399)**	**MDV3100 160mg (n = 800)**	**Placebo (n = 399)**	**MDV3100 160mg (n = 800)**	**Placebo (n = 399)**
Anxiety	**51 (6.4%)**	**16 (4.0%)**	**26 (3.3%)**	**10 (2.5%)**	**8.8**	**9.6**
Myalgia	50 (6.3%)	26 (6.5%)	19 (2.4%)	15 (3.8%)	8.8	18.6
Hypertension	**49 (6.1%)**	**11 (2.8%)**	**31 (3.9%)**	**4 (1.0%)**	**8.4**	**7.2**
Cough	47 (5.9%)	25 (6.3%)	16 (2.0%)	13 (3.3%)	7.9	15.6
Depression	44 (5.5%)	18 (4.5%)	18 (2.3%)	11 (2.8%)	7.4	10.8
Abdominal pain	41 (5.1%)	23 (5.8%)	22 (2.8%)	16 (4.0%)	7.4	14.4

Note: Events/100 patient-years data are obtained from the CRPC2 clinical study report; adverse events were coded using an earlier version of MedDRA than used in the Summary of Clinical Safety analyses.

As the median duration of exposure was substantially longer in the experimental arm, 8.3 months vs. 3.0 months in the placebo arm, the absolute frequencies of AEs may not be relevant for comparison. Therefore, AEs occurring during the first 60 days and events per 100 patient years were analysed, considered more appropriate than the total AE incidence comparison. Among AEs reported in ≥5% of patients in any treatment group only hot flush, headache and hypertension occurred more commonly in the MDV3100 group in both of these analyses.

Comments on selected AEs

- Fatigue

Total incidence of fatigue was higher in the experimental arm of CRPC2 and a dose-related finding in the open-labelled studies, and also showed a positive correlation with exposure to active drug and metabolite. However, in the time-normalised analyses, fatigue in the MDV3100 arm of CRPC2 was reported at similar or lower frequency than in the placebo arm. Grade ≥3 events occurred at a lower incidence in the MDV3100 arm. At the intended dose, 160 mg daily, data does not support a clear relationship between MDV3100 and fatigue/asthenia

- Neutropenia

While neutrophil levels remained constant over time in the placebo arm of the pivotal study a modest decline of neutrophil counts with nadir at week 5 was noted in the MDV3100 arm. The maximum decrease of 700/µL is considered clinically relevant.

- Non-pathological fracture

Non-pathological fracture was reported more frequently in the MDV3100 arm in CRPC2, also in a time-normalised analysis (5.6 vs. 1.8 events per 100 patient years).

- Seizure

MDV3100 penetrates the blood brain barrier and has been associated with a potential for seizure in preclinical studies, possibly through binding to the GABA receptor. In the clinical setting, seizure was a DLT in the dose-finding study and PK data support the relation to dose. A total of 13 MDV3100 treated patients experiencing seizure is reported in the SCS at the cut-off at 31 January 2012 whereof 10 at a 150/160 mg daily dose and 7/800 (0.9%) in the CRPC2 study. The seizures spanned from partial to generalised and occurred without relation to treatment time, from day 26 to 601 with a median of day 66. Potentially contributing factors were present in 8 of the patients.

Grade 3 or higher AEs

Grade ≥3 AEs were overall seen less frequently in the MDV3100 arm of the CRPC2 study, 45.3% vs. 53.1% in the placebo arm, also within 60 days of treatment, 20.0% vs. 29.6%, respectively. Median time to first grade ≥3 event was longer in the MDV3100 arm, 12.6 vs. 4.2 months. Decreased appetite, back pain, pathological fracture, metastatic pain and spinal cord compression of grade ≥3 were reported more commonly in the MDV3100 group but out of these only grade ≥3 decreased appetite and back pain occurred at a higher frequency within 60 days of treatment, as did also grade ≥3 hypertension.

Taking grouped AEs and differences in duration of treatment into consideration, metastatic pain, back pain, decreased appetite, pathological fracture and spinal cord compression are unlikely to represent safety signals.

ADRs

The adverse events identified in study CRPC2 for which a causal relationship with enzalutamide is at least a reasonable possibility are described in table 21.

Table 21: Enzalutamide adverse drug reactions identified in study CRPC2

System Organ Class **Preferred Term**	**MDV3100 160mg (n = 800)**	**Placebo (n = 399)**
Blood and Lymphatic System Disorders		
Neutropenia	9 (1.1%)	0 (0.0%)
Leucopenia	7 (0.9%)	1 (0.3%)
Psychiatric disorders		
Anxiety	51 (6.4%)	16 (4.0%)
Visual hallucinations	10 (1.3%)	0 (0.0%)
Nervous system disorders		
Headache	93 (11.6%)	22 (5.5%)
Memory impairment	13 (1.6%)	4 (1.0%)
Cognitive disorder	8 (1.0%)	1 (0.3%)
Amnesia	7 (0.9%)	1 (0.3%)
Disturbance in attention	7 (0.9%)	1 (0.3%)
Seizure	6 (0.8%)	0 (0.0%)
Vascular disorders		
Hot flush	162 (20.3%)	41 (10.3%)
Hypertension	49 (6.1%)	11 (2.8%)
Skin and subcutaneous tissue disorders		
Pruritus	29 (3.6%)	5 (1.3%)
Dry skin	28 (3.5%)	5 (1.3%)
Musculoskeletal and connective tissue disorders		
Fractures*	28 (3.5%)	3 (0.8%)
Injury, poisoning and procedural complications		
Falls	32 (4.0%)	5 (1.3%)
* Includes all fractures with the exception of pathological fractures		

Serious adverse event / deaths / other significant events

Compared with placebo in the Integrated Safety Population, treatment with MDV3100 does not increase the incidence of Grade 3 or higher AEs (46.5% vs. 53.1%), SAEs (31.8% vs. 38.6%), AEs leading to death (2.9% versus 3.5%), AEs as the primary reason for discontinuation (8.0% vs. 9.8%), AEs associated with permanent discontinuation (15.8% vs.18.3%), AEs that caused temporary discontinuation (14.5% vs. 15.3%) or AEs leading to dose reduction (2.3% vs. 2.9%), respectively, indicating that these events were likely related to the subjects' prostate cancer.

Table 22: Serious Adverse Events Occurring in at Least 1% of Patients in Any Treatment Group

	Controlled CRPC2	
System Organ Class Preferred Term	**MDV3100 160 mg (n = 800)**	**Placebo (n = 399)**
Number of Patients Reporting ≥ 1 Serious Adverse Event	268 (33.5%)	154 (38.6%)
Blood and Lymphatic System Disorders	25 (3.1%)	15 (3.8%)
Anaemia	21 (2.6%)	12 (3.0%)
Gastrointestinal Disorders	31 (3.9%)	22 (5.5%)
Vomiting	2 (0.3%)	8 (2.0%)
General Disorders and Administration Site Conditions	32 (4.0%)	25 (6.3%)
General physical health deterioration	17 (2.1%)	8 (2.0%)
Pyrexia	2 (0.3%)	5 (1.3%)
Infections and Infestations	42 (5.3%)	23 (5.8%)
Pneumonia	13 (1.6%)	6 (1.5%)
Urinary tract infection	7 (0.9%)	5 (1.3%)
Musculoskeletal and Connective Tissue Disorders	52 (6.5%)	17 (4.3%)
Back pain	11 (1.4%)	7 (1.8%)
Pathological fracture	**12 (1.5%)**	**2 (0.5%)**
Bone pain	11 (1.4%)	4 (1.0%)
Neoplasms Benign, Malignant, and Unspecified (Incl Cysts and Polyps)	33 (4.1%)	21 (5.3%)
Metastatic pain	**12 (1.5%)**	**3 (0.8%)**
Cancer pain	8 (1.0%)	5 (1.3%)
Metastases to bone	1 (0.1%)	5 (1.3%)
Nervous System Disorders	89 (11.1%)	33 (8.3%)
Spinal cord compression	**48 (6.0%)**	**15 (3.8%)**
Nerve root compression	3 (0.4%)	4 (1.0%)
Renal and Urinary Disorders	35 (4.4%)	23 (5.8%)
Haematuria	12 (1.5%)	5 (1.3%)
Urinary retention	3 (0.4%)	8 (2.0%)
Respiratory, Thoracic, and Mediastinal Disorders	17 (2.1%)	10 (2.5%)
Pulmonary embolism	3 (0.4%)	4 (1.0%)

Treatment-emergent SAEs with at least a 0.5% absolute higher incidence in the combined group of MDV3100-treated patients (n=1027) than placebo patients in the Integrated Safety Population were pathological fracture (1.2% vs. 0.5%), metastatic pain (1.4% vs. 0.8%) and spinal cord compression (5.2% vs. 3.8%).

Overall, SAEs were reported more commonly in the placebo arm of the CRPC2 study, despite the significantly longer duration of therapy in the experimental arm.

Table 23: Deaths and Causes of Death in CRPC2

	Database Lock on 25 September 2011		Database Lock on 16 December 2011	
	MDV3100 (n = 800)	Placebo (n = 399)	MDV3100 160 mg (n = 800)	Placebo (n = 399)
Total Number of Deaths at or Prior to Data Cut-off Date[a]	308 (38.5%)	212 (53.1%)	344 (43.0%)	232 (58.1%)
Cause of Death				
Disease progression	274 (34.3%)	192 (48.1%)	303 (37.9%)	207 (51.9%)
Other	22 (2.8%)	13 (3.3%)	25 (3.1%)	16 (4.0%)
Unknown	12 (1.5%)	7 (1.8%)	16 (2.0%)	9 (2.3%)
Deaths Occurring Within 30 Days of the First Dose of Study Drug	2 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
Deaths Occurring Within 30 Days of the Last Dose of Study Drug	64 (8.0%)	25 (6.3%)	64 (8.0%)	25 (6.3%)

At the time of database lock, 16 December 2011, a substantially larger fraction of patients in the placebo arm had died from progressive disease, 51.9% vs. 37.9% in the MDV3100 arm. Fractions of patients dying of unknown or other reasons as well as within 30 days of first dose of study drug were roughly similar between the study arms while a slightly larger fraction of patients in the MDV3100 arm died within 30 days of last dose of study drug, 8.0% vs. 6.3%.

Fewer patients in the experimental arm experienced AEs leading to death, 2.9% vs. 3.5% in the placebo arm. The only notable AEs leading to death that in terms of incidence occurred more commonly in the MDV3100 group were in the SOC of infections and infestations (0.9% vs. 0.3%) with 2 events of sepsis, and 2 events of acute myeloid leukaemia, whereas none of these events were reported in the placebo group.

Laboratory findings

The most noteworthy hematologic finding was an association of MDV3100 treatment with decreased leukocyte and neutrophil counts.

Grade 4 low lymphocyte counts were noted in 2 patients in the hepatic impairment study.

Safety in special populations

Gender

The safety of MDV3100 has not been established in women.

Race

The impact of race on the safety of MDV3100 treatment could not be adequately assessed since the majority of patients in the CRPC2 trial were Caucasian (> 92%).

Elderly

AEs of fatigue and in the Infections and infestations SOC were more common in the ≥65 years group and diarrhoea, fatigue and peripheral oedema were more common in the ≥75 years group.

Table 24: Summary of Treatment Emergent Adverse Events by Age Group – Total (Safety Population)

Age (years)	< 65 n = 232	65-74 n = 369	75-84 n = 191	85 + n = 8	Overall n = 800
Total†	97.0%	98.1%	99.5%	100%	98.1%
Fatal	2.6%	2.4%	3.1%	25.0%	2.9%
Serious	32.3%	33.1%	34.6%	62.5%	33.5%
Withdrawal‡	6.5%	7.3%	8.9%	25.0%	7.6%
CNS (Confusion§/Extrapyramidal¶)	5.2%	6.2%	5.8%	12.5%	5.9%
AE related to falling††	3.9%	3.8%	4.7%	0	4.0%
CV events‡‡	2.2%	7.6%	7.3%	25.0%	6.1%
Cerebrovascular events§§	0.4%	1.9%	0.5%	12.5%	1.3%
Infections¶¶	27.6%	38.2%	38.2%	37.5%	35.1%

Table summarises percentages of patients with at least 1 adverse event in each category, as defined below. Patients can have more than 1 adverse event in each category.

AE: adverse event; CNS: central nervous system; CV: cardiovascular.

†Patients with any treatment-emergent adverse event

‡Patients with a treatment-emergent adverse event leading to treatment discontinuation

§Patients with a treatment-emergent adverse event where preferred term is 1 of the following terms: Encephalopathy, Confusional state, Disorientation, Delirium and Mental status changes

¶Patients with a treatment-emergent adverse event where preferred term is 1 of the following terms: Restless legs syndrome, Dyskinesia and Akathisia. Additionally patients who have events of tremors except intention tremor

††Patients with a treatment-emergent adverse event where preferred term contains Fall

‡‡Patients who have treat-emergent events in the system organ class of Cardiac Disorders

§§Patients with a treatment-emergent adverse event that includes the preferred terms: Cerebrovascular accident, Transient ischemic attack, Cerebral haemorrhage, Embolic stroke, Haemorrhage intracranial, Haemorrhagic stroke, Ischaemic stroke and Lacunar infarction

¶¶ Percentage of patients with at least 1 treatment-emergent adverse event preferred term in the Infections and Infestations system organ class

Weight

The following AEs were notably more common in CRPC2 patients at or below the median weight (83 kg) compared to patients above the median weight: anemia (17.2% vs 11.5%), decreased appetite (31.6% vs 24.3%), asthenia (20.6% vs 14.4%) and bone pain (15.1% vs 10.1%). Grade ≥3 AEs were reported more commonly in patients ≤83 kg (49.3% vs 41.3%).

ECOG PS

In CRPC2, only 70 patients had ECOG PS 2. The largest imbalance in AEs more common in PS 2 patients were in the incidence of vomiting (15.1% PS 0–1 vs. 28.6 PS 2), weight decreased (10.7% vs. 22.9%), and decreased appetite (27.0% vs. 40.0%). Largest imbalance in AEs more common in PS 0–1 patients were in the incidence of fatigue (34.7% PS 0–1 vs. 22.9% PS 2) and hot flush (21.0% vs. 12.9%).

AE of fatigue ≥grade 3 was substantially higher in PS 2 patients (5.3% PS 0–1 vs. 15.7% PS 2).

History of cardiovascular (CV) disease

In CRCP2, diarrhoea (27.2%) and dizziness (11%) were reported more commonly in MDV3100 patients with previous CV disease than without and more commonly than in placebo patients with previous CV disease. However, no overall increase of AEs within the cardiac disorders SOC was noted in this group.

Safety related to drug-drug interactions and other interactions

(See data and discussion in the clinical aspects section)

Discontinuation due to adverse events

The frequencies of AEs as the primary reason for permanent discontinuation of study drug, AEs leading to temporary discontinuation of dosing and AEs leading to dose reduction were all lower in the experimental arm in CRPC2: 7.6% vs. 9.8% in the placebo arm, 12.8% vs. 15.3% and 2.1% vs. 2.8%, respectively. A dose-dependent pattern of increased incidence of all these AE categories was noted in the integrated safety population.

Fatigue was the only AE leading to temporary discontinuation of dosing that was more common in the MDV3100 treatment group. No AEs leading to dose reduction occurred in more than 1% of patients in either treatment group.

2.6.1. Discussion on clinical safety

In nonclinical studies, convulsions, anaemia, reproductive toxicity, endocrine reactions, and gastrointestinal reactions were identified as potential risks of MDV3100. In the clinical studies, patients at risk of seizure were excluded. Seizure was always to be reported as SAE.

The safety database encompasses a total of 1027 patients treated with MDV3100, whereof 923 with the target daily dose of 160 mg. Randomised placebo-controlled data is available for 800 patients, considered to reflect the target population, with this dose. These numbers are considered sufficient for assessment although safety remains to be addressed in several subgroups.

When looking at frequency of AEs in the CRPC2 study, despite the substantially longer treatment duration in the experimental arm, fractions of patients with any AE were roughly similar between study arms while AEs grade ≥3, SAEs, AEs leading to death, AEs as the primary reason for permanent discontinuation of study drug, AEs leading to temporary discontinuation of dosing and AEs leading to dose reduction were all consistently numerically lower in the experimental arm. Thus, in terms of frequency, these figures are reassuring from a safety point of view and also indicate that the safety profile of MDV3100 is overall acceptable.

Of note, psychiatric and nervous system disorders are special characteristics for this treatment, paying special attention to seizure. Seizures were reported in 0.9% of patients on MDV3100 in CRPC2, despite exclusion of patients with baseline factors potentially associated with increased risk of seizure (including but not limited to underlying brain injury, stroke, primary brain tumours or brain metastases, or alcoholism), and spanned from partial to generalised events and occurred without relation to treatment time. The risk of seizure may be increased in patients receiving concomitant medicinal products that lower the seizure threshold. The potential of MDV3100 to induce seizure is supported by preclinical and PK data. Given that this is an oral medicinal product, most cases would occur out of hospital.

The measures implemented to minimise the risk of seizures are considered acceptable as reflected in the RMP. The Applicant will conduct a post-authorisation safety study that will provide further information to update risk mitigation recommendations. The Applicant is recommended to consider the points mentioned in section 2.7 for the finalisation of the study protocol.

A warning regarding the risk for seizure was included in sections 4.4, 4.7, 4.8, 4.9 and 5.1 of the SmPC.

No clinically significant signals regarding, thromboembolic, hepatic and renal events or deterioration of renal or liver function tests were identified. However, taking into account the lack of data in severe renal patients and the inconclusive results with moderate hepatic impairment patients, caution is recommended in this population in section 4.4 of the SmPC. Regarding severe hepatic impairment, it should be taken into consideration that MDV3100 and its active metabolite are eliminated primarily by hepatic metabolism, the low grade of moderate impairment in the PK study (9785-CL-0009) and the absence of data in patients with severe hepatic impairment. For all the above mentioned reasons, MDV3100 is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) (see section 4.4 of the SmPC).

Enzalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicinal products. A review of concomitant medicinal products should therefore be conducted when initiating enzalutamide treatment. Concomitant use of enzalutamide with medicinal products that are sensitive substrates of many metabolising enzymes or transporters should generally be avoided if their therapeutic effect is of large importance to the patient, and if dose adjustments cannot easily be performed based on monitoring of efficacy or plasma concentrations.

Co-administration with warfarin and coumarin-like anticoagulants should be avoided. If enzalutamide is co-administered with an anticoagulant metabolised by CYP2C9 (such as warfarin or acenocoumarol), additional International Normalised Ratio (INR) monitoring should be conducted.

No data are available on the concomitant use of enzalutamide with cytotoxic chemotherapy.

CRPC2 study excluded patients with recent myocardial infarction (in the past 6 months) or unstable angina (in the past 3 months), New York Heart Association Class (NYHA) III or IV heart failure except if Left Ventricular Ejection Fraction (LVEF) ≥ 45%, long QT, QTcF > 470 ms, bradycardia or uncontrolled hypertension. This should be therefore taken into account when prescribing enzalutamide in these patients (see section 4.5 of the SmPC).

No clinical signs reflecting adrenal cortical hypertrophy with functional consequences or pituitary hyperplasia are identified.

Data on safety of MDV3100 in the treatment of patients with ECOG PS ≥2 or of non-Caucasian race is scarce. This has been reflected in the SmPC and the RMP.

The CRPC2 safety database comprising 568 patients ≥65 years and 199 patients ≥75 years is considered reasonably sufficient for assessment.

There are no human data on the use of Xtandi in pregnancy and this medicinal product is not for use in women of childbearing potential.

The imbalance seen in various adverse events within the SOC of Infections and Infestations was not considered causally related to MDV3100 but attributed to the longer duration of safety follow-up leading to observations of more common respiratory and other types of infections in the MDV3100 arm. The CHMP considers that there is insufficient evidence to include “infections” as an adverse drug reaction in section 4.8 of the SmPC.

Studies in animals have shown reproductive toxicity. It is not known whether enzalutamide or its metabolites are present in semen. A condom is therefore required during and for 3 months after treatment with enzalutamide if the patient is engaged in sexual activity with a pregnant woman. If the patient engages in sexual intercourse with a woman of childbearing potential, a condom and another form of birth control must be used during and for 3 months after treatment.

2.6.2. Conclusions on the clinical safety

The safety profile of MDV3100 160 mg daily has been sufficiently characterised in the target population. The side effects are mainly, but not exclusively, attributable to androgen blockade and certain unexpected events that potentially may constitute adverse drug reactions should be further addressed (addressed in the RMP).

The safety profile is considered acceptable and generally manageable with basic medical interventions (diuretics and antihypertensive medication). Toxicities were generally mild, and resulted in infrequent dose reductions, dose interruptions, or discontinuations.

However, the main concerns are about psychiatric and nervous system disorder, paying special attention to seizure. As it is an oral medicinal product, seizures are expected to occur out of hospital in the majority of cases. In order to prevent or minimise this risk, an effort to further characterise patients at risk should be done. In this sense, the measures implemented to minimise the risk of seizures are considered acceptable (as reflected in section 4.4 and 4.8 of the SmPC and in the RMP). The post-authorisation safety study as detailed in the RMP will provide further information to update risk mitigation recommendations. The submitted draft protocol synopsis of this study was reviewed (see RMP for further information).

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfills the legislative requirements.

Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 3.0, the PRAC considers by consensus that the risk management system for enzalutamide (Xtandi) in the treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy is acceptable.

The following point should be taken into account in the next update:

The clinical trial in patients with moderate hepatic impairment should be included in all the applicable sections of the RMP (III.1 Safety concerns and overview of planned pharmacovigilance actions, and VI.1.2 Ongoing and planned additional pharmacovigilance studies/activities in the pharmacovigilance plan).

This advice is based on the following content of the Risk Management Plan:

- Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 25: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	- Seizures

Summary of safety concerns	
	- Hypertension - Falls - Hallucination - Neutrophil count decreased - Non-pathologic fracture - Interactions with strong inhibitors or inducers of CYP2C8 - Interactions with medicinal products that are substrates of CYP3A4, CYP2C9 or CYP2C19
Important potential risks	- Cognitive/memory impairment
Important missing information	- Patients with severe renal impairment - Patients with moderate or severe hepatic impairment - Reproduction/fertility - Patients of non-White race - Patients with ECOG PS ≥ 2 - Patients with severe cardiovascular disease - Patients with brain metastases or with baseline factors predisposing for seizure

The PRAC agreed.

- Pharmacovigilance plans

Safety concern	**Description of activity**	**Milestone(s)**	**Due Date(s)**
Seizures	Post-authorisation safety study to assess the risk of seizure with enzalutamide 160 mg/day in patients with metastatic CRPC who are at increased risk for seizure. A harmonised approach to the post-marketing requirement 1918-2 requested by the FDA will be taken by the applicant.	Final protocol submission	June 2013
		Trial completion date	June 2018
		Final report submission	March 2019
Patients with severe hepatic impairment	Clinical trial in subjects with normal hepatic function and patients with preexisting **severe** hepatic impairment, to assess the effect of severe hepatic impairment on the pharmacokinetics of enzalutamide and N-desmethyl enzalutamide, following the post-marketing requirement 1918-3 request by the FDA.	Final protocol submission†	31 March 2013
		Trial completion date	May 2014
		Final report submission	November 2014
Patients with moderate hepatic impairment	Clinical trial in subjects with normal hepatic function and patients with preexisting **moderate** hepatic impairment, to assess the effect of moderate hepatic impairment on the pharmacokinetics of enzalutamide and N-desmethyl enzalutamide.	Final protocol submission	February 2014
		Final report submission	December 2015

CRPC: castration-resistant prostate cancer
†Draft protocol was included with the submission of the RMP.

The PRAC, having considered the data submitted, was of the opinion that the additional pharmacovigilance activities are acceptable, provided that the clinical trial in patients with moderate hepatic impairment is included in all the applicable sections of the RMP (III.1 Safety concerns and

overview of planned pharmacovigilance actions, and VI.1.2 Ongoing and planned additional pharmacovigilance studies/activities in the pharmacovigilance plan) at the next RMP update.

A full assessment of the proposed study to assess the safety of enzalutamide in patients excluded from the pivotal study due to certain baseline factors considered predisposing for seizure will take place when the final protocol is available. The Applicant is recommended to consider the points mentioned below:

- First, the selected study population is critical in relation to presently proposed as well as potential future wordings of SmPC 4.3 and 4.4. It is noted that "Patients with a history of seizures should not have had a seizure within 12 months of Screening and must have had no anticonvulsants for 12 months prior to Screening" to be eligible for study participation. However, it is not clear whether this constitutes a safety precaution or whether it serves to increase the sensitivity of the study. Anyway, exclusion of this patient category may impact on the wording of the SmPC.
- Second, considering that a substantial fraction of seizures in the previous experience have occurred at time points later than 4 months of treatment, it could be discussed whether the proposed 4-month treatment period is sufficient.
- Third, a plan for putting study data into perspective and so allowing its interpretation is lacking.

- Risk minimisation measures

Table 26: Summary table of Risk Minimisation Measures

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Seizures	SmPC Section 4.4 (Special warnings and precautions for use) will include: *Risk of seizure* *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.* SmPC Section 4.8 (undesirable effects): Listed as undesirable effects Description of selected adverse reactions *Seizures* *In the phase 3 clinical trial (AFFIRM), six patients (0.8%) experienced a seizure out of 800 patients treated with a daily dose of 160 mg enzalutamide, whereas no seizures occurred in patients receiving placebo. Potentially contributing factors were present in several of these patients that may have independently increased their risk of seizure. The AFFIRM trial excluded patients with prior seizure or risk factors for seizure. Dose appears to be an important predictor of the risk of seizure, as reflected by preclinical data, and data from a dose-escalation study. The mechanism by which enzalutamide may lower the seizure threshold is not known, but could be related to data from in vitro studies showing that enzalutamide and its active metabolite bind to and can inhibit the activity of the GABA-gated chloride channel.*	None

Hypertension **Hallucination** **Falls** **Cognitive / Memory Impairment** **Neutrophil count decreased** **Non-pathological fracture**	SmPC Section 4.8 (Undesirable effects) • Listed as undesirable effects	None
Patients with severe renal impairment	SmPC Section 4.2 (Posology and method of administration) include: Renal impairment No dose adjustment is necessary for patients with mild or moderate renal impairment (see section 5.2). Caution is advised in patients with severe renal impairment or end-stage renal disease (see section 4.4). SmPC Section 4.4 (Special warnings and precautions for use) will include: Renal impairment Caution is required in patients with severe renal impairment as enzalutamide has not been studied in this patient population.	None
Patients with severe hepatic impairment	SmPC Section 4.2 (Posology and method of administration) include: Hepatic impairment No dose adjustment is necessary for patients with mild or moderate hepatic impairment (Child-Pugh Class A or B; see section 5.2). Caution is advised in patients with severe hepatic impairment (Child-Pugh Class C;see section 4.4). SmPC Section 4.4 (Special warnings and precautions for use) will include: Hepatic impairment Caution is required in patients with severe hepatic impairment as enzalutamide has not been studied in this patient population.	None
Reproduction / Fertility	SmPC Section 4.6 (Fertility, pregnancy and lactation) will include: Contraception in males and females It is not known whether enzalutamide or its metabolites are present in semen. A condom is required during and for 3 months after treatment with enzalutamide if the patient is engaged in sexual activity with a pregnant woman. If the patient engages in sexual intercourse with a woman of childbearing potential, a condom and another form of birth control must be used during and for 3 months after treatment. Pregnancy Enzalutamide is not for use in women. Enzalutamide is contraindicated in women who are or may become pregnant (see section 4.3 and 5.3). There are no human data on the use of enzalutamide in pregnancy. Considering the pharmacological consequences of AR signalling inhibition, maternal use of enzalutamide is expected to produce changes in hormone levels that could affect development of the foetus. Breast-feeding Enzalutamide is not for use in women. It is unknown whether enzalutamide and its metabolites are excreted in human milk.	None

	Fertility Animal studies showed that enzalutamide affected the reproductive system in male rats and dogs (see section 5.3). Considering the pharmacological activity of AR signalling inhibitors, an effect on male fertility cannot be excluded in humans.	
Patients of non-White race	SmPC Section 5.1 (Pharmacodynamic properties) will include: Clinical efficacy and safety The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 41-92) and the racial distribution was 92.7% Caucasian, 3.9% Black, 1.1% Asian, and 2.1% Other. SmPC Section 5.2 (Pharmacokinetic properties) will include: Race Most patients in the clinical trials (>92%) were Caucasian, thus no conclusions on the impact of race on enzalutamide pharmacokinetics can be drawn.	None
Patients with ECOG PS ≥ 2	SmPC Section 5.1 (Pharmacodynamic properties) will include: Clinical efficacy and safety The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 41-92) and the racial distribution was 92.7% Caucasian, 3.9% Black, 1.1% Asian, and 2.1% Other. The ECOG performance score was 0-1 in 91.5% of patients and 2 in 8.5% of patients.	None
Patients with severe cardiovascular disease	SmPC Section 5.1 (Pharmacodynamic properties) will include: Clinical efficacy and safety The phase 3 study excluded patients with medical conditions that may predispose them to seizures (see section 4.8) and medications known to decrease the seizure threshold, as well as clinically significant cardiovascular disease such as uncontrolled hypertension, recent history of myocardial infarction or unstable angina, New York Heart Association class III or IV heart failure (unless ejection fraction was ≥ 45%), clinically significant ventricular arrhythmias or AV block (without permanent pacemaker).	None
Patients with brain metastases or baseline factors predisposing for seizure	SmPC Section 4.4 (Special warnings and precautions for use) will include: Risk of seizure 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. SmPC Section 4.8 (undesirable effects): Listed as undesirable effects Description of selected adverse reactions Seizures In the phase 3 clinical trial (AFFIRM), six patients (0.8%) experienced a seizure out of 800 patients treated with a daily dose of 160 mg enzalutamide, whereas no seizures occurred in patients receiving placebo. Potentially contributing factors were present in several of these patients that may have independently increased their risk of seizure. The AFFIRM trial excluded patients with prior seizure or risk factors for	None

	seizure. Dose appears to be an important predictor of the risk of seizure, as reflected by preclinical data, and data from a dose-escalation study. The mechanism by which enzalutamide may lower the seizure threshold is not known, but could be related to data from in vitro studies showing that enzalutamide and its active metabolite bind to and can inhibit the activity of the GABA-gated chloride channel.	
Patients with brain metastases or baseline factors predisposing for seizure	SmPC Section 5.1 (pharmacodynamic properties) The phase 3 study excluded patients with medical conditions that may predispose them to seizures (see section 4.8) and medications known to decrease the seizure threshold.	

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice. However in order to address the uncertainties regarding the benefit of enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with abiraterone acetate, the CHMP requested the Applicant to include this as 'missing information' into the RMP. Additional pharmacovigilance activity and routine risk minimisation measures are described in the RMP 4.0 in order to address this missing information.

- Safety concerns

Summary of safety concerns	
Important missing information	Patients with metastatic castration-resistant prostate cancer previously treated with abiraterone acetate

- Pharmacovigilance plan

Safety concern	Description of activity	Milestone(s)	Due Date(s)
Patients with metastatic castration-resistant prostate cancer previously treated with abiraterone acetate	Collect efficacy data for enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with abiraterone acetate.	Final protocol submission: Report of interim analysis: Final report submission:	June 2013 June 2015 December 2016

- Risk minimisation measure

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Patients with metastatic castration-resistant prostate cancer previously treated with	SmPC Section 5.1 (Pharmacodynamic properties) will include: *Clinical efficacy and safety*	None

abiraterone acetate	*The efficacy of enzalutamide in patients who previously received abiraterone acetate has not been studied*	

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Study CRPC2 enrolled 1199 patients who were randomised 2:1, 800 patients into the MDV3100 arm and 399 into the placebo arm.

At the time of data cut-off of the pre-planned interim analysis (25 September 2011; date of the 520th death event) results showed a significant improvement in terms of the primary endpoint OS: a benefit of 4.8 months compared to placebo with a hazard ratio of 0.631 (95 % CI: 0.529; 0.752). A survival benefit of this magnitude is rightfully deemed clinically meaningful considering the population consisting of patients with late stage disease.

Analyses with respect to whether post-progression therapies could have had any influence on the survival results revealed that a higher frequency of subsequent therapies were received by patients in the placebo group and was mainly consistent across all the different post-progression regimens administered. This supports the assumption that the treatment benefit is attributable to the study drug.

Results are robust after adjusting by stratification factors (pain by BPI-SF at baseline and ECOG-PS) and when taking into account an updated analysis performed at the time of database lock (16 December 2011; 576 death events).

Treatment effect on OS was also consistently favourable in several subgroups based on prognostic factors for prostate cancer; demographic features of interest or representing different regional practice patterns.

The key secondary endpoints further supports the efficacy results even though the magnitude of the MDV3100 benefit with respect to Time to PSA progression might be somewhat overestimated and although rate of censored patients is remarkably high concerns pertaining this issue were clarified.

Overall, a clinically relevant effect of MDV3100 in patients with progressive CRPC that have failed 1 or 2 prior chemotherapies at least one containing docetaxel has been demonstrated.

Uncertainty in the knowledge about the beneficial effects.

Very little data are available on the optimal sequence for newer agents approved to treat CRPC. In the pivotal study for enzalutamide, only very few patients (0.5%) were treated with abiraterone. This is currently reflected in the SmPC (see section 5.1). Optimal sequencing for these agents, a possible synergistic mechanism of action or cross-resistance are currently unknown. In order to address this risk, the applicant will provide further data from a single-arm study to assess efficacy and safety of enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with abiraterone acetate, as detailed in the RMP.

Risks

Unfavourable effects

The safety profile of MDV3100 is characterised by secondary effects to androgen receptor inhibition but also by events not intuitively attributable to that mechanism, such as hypertension, decreased neutrophils/leukocytes and seizure.

In CRPC2 study, the most frequent ADRs in the MDV3100 arm were hot flush (20.3%), headache (11.6%), anxiety (6.4%), hypertension (6.1%), falls (4.0%), pruritus (3.6%), dry skin (3.5%) and non-pathological fractures (3.5%).

In addition, the assessment of the safety profile concluded to the following adverse drug reactions: seizure, neutropenia, leucopenia, visual hallucinations, cognitive disorder, memory impairment, amnesia, disturbance in attention.

The major safety concern identified is the risk of seizure with its clinical relevance supported by preclinical and PK data. The applicant will conduct a post authorisation safety study in order to further investigate this risk (see section 2.7), as detailed in the RMP.

Finally, MDV3100 has inducing effects on several metabolic enzymes and possibly also transporters, studies have shown strong induction of CYP3A4 and moderate induction of CYP2C9 and CYP2C19. Additional clinical study to investigate the effect of enzalutamide on a specific CYP1A2-substrate will be performed. This needs to be taken into account when co-administering MDV3100 with other drugs since prostate cancer patients should be treated with concomitant therapies. These recommendations are reflected adequately in the SmPC.

Uncertainty in the knowledge about the unfavourable effects

The major safety uncertainty related to MDV3100 is considered so far to be the unknown incidence of seizure in patients with certain baseline factors potentially predisposing to this event, i.e. patients that, considering the age of the target population, inevitably will be encountered in the real-life situation. Therefore, measures have been included in the RMP in order to address this risk.

Benefit-risk balance

Importance of favourable and unfavourable effects

Treatment with MDV3100 resulted in a statistically significant and clinically relevant reduction of the risk of death (37% relative risk reduction). An improvement in the median overall survival of 4.8 months was observed. Time to PSA progression and radiologic progression free survival were also significantly improved in favour of active treatment and time to first skeletal-related event also favoured MDV3100.

Overall, the benefits of MDV3100 in mCRPC patients who had progressed after 1 or 2 chemotherapy regimens at least one containing docetaxel appear clear, robust and of clinical relevance.

The safety profile is considered acceptable and generally manageable with basic medical interventions (diuretics and antihypertensive medication). Toxicities were generally mild, and resulted in infrequent dose reductions, dose interruptions, or discontinuations.

All identified risks, potential risks and missing information are adequately reflected and addressed in the RMP.

Benefit-risk balance

The antitumor effect of MDV3100 has been clearly demonstrated, leading to an increase in the life expectancy with a safety profile overall acceptable and generally manageable.

Discussion on the benefit-risk balance

The benefit-risk balance of MDV3100 in the treatment of metastatic castration-resistant prostate cancer in adult patients whose disease has progressed after 1 or 2 prior chemotherapy regimens at least one containing docetaxel, is considered positive.

Cabazitaxel and Abiraterone acetate were granted an indication in castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen. Prednisone 10 mg was used in both experimental and comparator arms in both studies. Currently, there are no direct comparative data about the relative efficacy or safety of these agents and enzalutamide.

MDV3100 opens the door to new possibilities regarding the possible synergic effect of both MDV3100 and Abiraterone acetate in combination for the treatment of metastatic castration resistant prostate cancer. In this regard, a phase 2 study determining safety and tolerability of enzalutamide in combination with abiraterone acetate in mCRPC patients is currently ongoing (NCT01650194).

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Xtandi in the treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy, is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 8 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the

same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that enzalutamide is qualified as a new active substance.