London, 23 October 2014
EMA/CHMP/607459/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name Xtandi

Procedure No. EMEA/H/C/002639/II/0008

Marketing authorisation holder (MAH): Astellas Pharma Europe B.V.

Note

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

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List of abbreviations

Abbreviation	Definition
BPI	Brief Pain Inventory Short Form
Cmin	Minimum plasma concentrations
CR	Complete response
CT	Computed tomography
CRPC	Castration resistant prostate cancer
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	European Quality of Life Five Domain Scale
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy Prostate
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
M2	Major human metabolite MDPC0002 (active)
MRI	Magnetic resonance imaging
PR	Partial response
PSA	Prostate-specific antigen
PCWG2	Prostate Cancer Clinical Trials Working Group 2
QLQ C30	Core Quality of Life Questionnaire
QLQ PR25	Prostate module (of the Core Quality of Life Questionnaire)
rPFS	Radiographic progression free survival
RECIST	Response Evaluation Criteria in Solid Tumors
US	United States
vs	Versus

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Astellas Pharma Europe B.V. submitted to the European Medicines Agency on 2 April 2014 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Xtandi	enzalutamide	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication for the treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. Consequently, changes are proposed to sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC. The package leaflet is updated accordingly. The MAH also propose to update the contact details of local representatives in the package leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on 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(s) for consideration

Additional data protection / marketing exclusivity

The applicant requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

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

1.2. Steps taken for the assessment of the product

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

Rapporteur: Arantxa Sancho-Lopez Co-Rapporteur: Kristina Dunder

Submission date:	2 April 2014
Start of procedure:	25 April 2014
Rapporteur's preliminary assessment report circulated on:	24 June 2014
CoRapporteur's preliminary assessment report circulated on:	17 June 2014
Joint Rapporteur's updated assessment report circulated on:	18 July 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 July 2014
MAH's responses submitted to the CHMP on:	22 August 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	26 September 2014
PRAC Rapporteur's updated assessment report on the MAH's responses circulated on:	1 October 2014
PRAC RMP advice and assessment overview adopted by PRAC	9 October 2014
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	15 October 2014
CHMP opinion:	23 October 2014
The CHMP adopted a report on the significant clinical benefit for Xtandi in comparison with existing therapies. (Appendix 1)	23 October 2014

2. Scientific discussion

Worldwide, prostate cancer ranks second in cancer incidence and fifth in cancer mortality in men [Globocan, 2012]. Prostate cancer growth is dependent on androgens, and androgen deprivation therapy (i.e. treatment with a luteinizing hormone-releasing hormone [LHRH] analogue or bilateral orchiectomy) is the cornerstone of treatment of men with metastatic prostate cancer. Although initial response rates are high, the disease can progress despite castrate levels of testosterone at which point it is considered castration resistant. Castration Resistant Prostate Cancer (CRPC) represents a lethal transition in the natural history of prostate cancer, with most patients dying of disease progression.

While the precise mechanism through which tumours progress from being castration sensitive to castration resistant is unknown, a key step may include the development of continuous activation of androgen signalling. This activation may arise through androgen receptor gene amplification,

androgen receptor overexpression, androgen receptor mutations, and/or aberrant androgen receptor co-regulation [Scher & Sawyers, 2005]. In addition, studies have shown that tumour cells display increased sensitivity to androgen mediated cell growth and intra-tumoral production of androgens. These findings suggest that despite androgen deprivation therapy, androgen receptor signalling remains an important mediator of tumour cell growth in CRPC and as such, treatment strategies that target the androgen receptor may have important therapeutic potential.

The treatment of patients with metastatic CRPC often includes anti-androgens such as bicalutamide, nilutamide, or flutamide; however, these agents have the potential to stimulate androgen receptor signalling and can accelerate tumour cell growth [Bohl et al, 2005]. Immunotherapy with sipuleucel-T was shown to be associated with a statistically significant improvement in overall survival compared with placebo in men with asymptomatic or minimally symptomatic metastatic CRPC [Kantoff et al, 2010]; however, this therapy was not associated with improvement in other markers of disease progression such as objective radiographic response or prostate specific antigen (PSA) response. In 2012, abiraterone acetate (abiraterone) plus prednisone was shown to significantly improve radiographic progression free survival (rPFS) in asymptomatic or mildly symptomatic chemotherapy naïve patients with metastatic CRPC compared with prednisone alone. A strong trend toward improvement in overall survival was observed in that study, but results did not meet statistical significance [Ryan et al, 2013]. Recently, radium Ra 223 dichloride (radium 223) was shown to improve overall survival in the chemotherapy naïve subgroup in a study enrolling patients with metastatic CRPC and symptomatic bone metastases [Parker et al, 2013].

Over time, patients with metastatic CRPC generally experience continued disease progression, worsening pain, and become eligible for chemotherapy. Although first line chemotherapy with docetaxel plus prednisone demonstrated a survival benefit in these patients [Tannock et al, 2004], its use leads to substantial morbidity from severe neutropenia, diarrhoea, and other toxicities. Other treatment options that have demonstrated a survival improvement in patients with metastatic CRPC after docetaxel include cabazitaxel plus prednisone [de Bono et al, 2010], abiraterone plus prednisone [de Bono et al, 2011], and enzalutamide [Scher et al, 2012].

Because of its potential side effects many patients are denied chemotherapy. Recently published data from the Swedish Prostate Cancer database indicate that the majority of men younger than 70-years-old with CRPC were treated with chemotherapy. In contrast, only half as many men between 70- and 79-years-old received chemotherapy. In addition, chemotherapy was often administered shortly prior to death [Lissbrant et al, 2013].

2.1. Introduction

Enzalutamide (Xtandi) is an oral androgen receptor signalling inhibitor designed to block multiple steps in the androgen receptor signalling pathway. In non-clinical studies, enzalutamide competitively inhibited androgen induced receptor activation 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. In addition, enzalutamide treatment decreased the growth of prostate cancer cells and induced cancer cell death and tumour regression.

The clinical benefit of enzalutamide has been shown in patients with metastatic castration resistant prostate cancer (CRPC) who previously received docetaxel based chemotherapy in the phase 3 study, CRPC2 (AFFIRM). Treatment with enzalutamide 160 mg orally once daily resulted in a statistically significant and clinically relevant reduction of the risk of death (37% relative risk reduction) compared with patients receiving placebo. 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 appeared clear, robust and of clinical relevance. The safety profile was 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.

The European Commission issued a decision to grant marketing authorisation for Xtandi on 21 June 2013 for the treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy.

The present application is intended to extend the indication of enzalutamide to include the treatment of adult men with metastatic castration resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

Scientific advice was received from the CHMP on the design of the pivotal study MDV3100-03 (PREVAIL) to the present application in June 2010 (EMA/CHMP/SAWP/372658/2010). The CHMP was in general agreement with the proposed study design (e.g. placebo arm, inclusion/ exclusion criteria) and agreed with the use of overall survival and rPFS as co-primary endpoints. The study could be considered positive if one of the co-primary endpoints was positive in favour of enzalutamide, as long as the treatment effects were favourable on both endpoints. Concern was expressed that an early submission based on rPFS data alone could jeopardize the final OS analysis.

2.2. Non-clinical aspects

No new non-clinical data have been submitted within this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

The MAH has provided a justification for the absence of an ERA, which was considered acceptable (see below).

2.2.2. Discussion and conclusion on non-clinical aspects

As part of the initial marketing application, the applicant submitted an environmental risk assessment on the active ingredient enzalutamide. The ERA included a Phase I assessment. The calculation of predicted environmental concentration in surface water covered all metastatic prostate cancer including chemotherapy-naïve metastatic CRPC. The calculated $PEC_{surfacewater}$ value was 0.0084 µg/L. The CHMP considered that the new indication is covered by the existing ERA.

Further data was considered needed at the time of initial marketing authorisation to conclude definitively on the potential risk of enzalutamide to the environment. The Applicant was recommended to conduct the fish early life cycle test (OECD 210) and the fish sexual development test (OECD 234). These studies are ongoing and the final reports are expected to be available by June 2015. Until these reports are available, the more restrictive wording agreed at the time of initial marketing authorisation is kept in section 6.6 of the SmPC regarding disposal of enzalutamide.

2.3. Clinical aspects

2.3.1. 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	Number of Patients	Study Design	Population	Enzalutamide Doses (mg/day)	Efficacy Endpoints	
Phase 3 Randomized, Double-Blind, and Placebo-Controlled Studies in Patients With Metastatic CRPC						
[MDV3100-03] (PREVAIL)	1717 (intent-to-treat); 872 enzalutamide 845 placebo	Phase 3, randomized, double-blind, placebo-controlled	Chemotherapy-naïve	160	**Coprimary:** Overall survival, rPFS	**Secondary:** Time to first SRE, time to initiation of cytotoxic chemotherapy, time to PSA progression, PSA response ≥ 50%, best overall soft tissue response
Phase 2 Study in Patients With Hormone-Naïve Prostate Cancer						
[9785-CL-0321]	67 enzalutamide	Phase 2, open-label, single arm	Hormone-naïve	160	Radiographic response, PSA response, quality of life and bone turnover markers	
Phase 1 and 2 Studies in Patients With Metastatic CRPC						
[9785-CL-0111]	47 enzalutamide	Phase 1/2, open-label, dose escalation, dose expansion	4 chemotherapy-naive 43 previously received docetaxel	80, 160, 240 single dose; 80, 160 multiple dose; then 160 long-term	Radiographic response at day 85, PSA response, circulating tumor cell counts, bone turnover markers	

2.3.2. Pharmacokinetics

To date, the pharmacokinetics of enzalutamide have been evaluated in approximately 2500 patients with castration-resistant prostate cancer (CRPC), 67 patients with hormone-naïve prostate cancer, and 194 healthy male subjects, including 14 subjects with mild or moderate hepatic impairment.

Efficacy studies with clinical pharmacology data that were completed after submission of the original marketing application are summarised below.

Table 1: Clinical studies with clinical pharmacology analyses included in the current application

Study	***Population***	***Description***	***Subjects***	***Dose, Food Intake***	PK Data
MDV3100-03 (PREVAIL)	Patients with metastatic CRPC who are chemotherapy-naïve	Phase 3 efficacy study	1715 males (871 active 844 placebo)	160 mg/day (4 x 40 mg capsules) Food intake: Uncontrolled	Predose C_{min} PK samples All patients Weeks 5, 13 and 25. Enzalutamide, M1, and M2 in plasma.
9785-CL-0321	Hormone-naïve prostate cancer patients	Phase 2 efficacy study	67 males	160 mg/day (4 x 40 mg capsules) Food intake: Uncontrolled	Predose C_{min} PK samples All patients Weeks 2, 3, 4, 5, 9, 13, 21, and 25 or at early discontinuation, and at safety follow-up visit. Enzalutamide, M1, and M2 in plasma.

Analytical methods

A validated bioanalytical method based on liquid chromatography with tandem mass spectrometry (LC-MS/MS) (PRO3100NC86) was used for concentration determinations of enzalutamide, M1 (carboxylic acid derivative), and M2 (*N*-desmethyl enzalutamide) in human plasma. The employed bioanalytical method is the same as the one used in the original marketing application

Formulation

The drug product is a liquid-filled capsule of enzalutamide fully dissolved in the fill solution. The composition of the enzalutamide solution in the capsules remained unchanged throughout the clinical development and differed from the current marketed formulation only in the level of the antioxidant butylhydroxyanisole (BHA) in the fill solution (0.1% and 0.01% BHA in the clinical development and marketed formulations, respectively).

Pharmacokinetics in target population

Study 9785-CL-0321

Study 9785-CL-0321 was a multinational, phase 2, open-label, single-arm, efficacy, and safety study of oral enzalutamide at 160 mg once daily for at least 24 weeks in patients with prostate cancer who had non-castrate levels of testosterone at study entry. Patients must not have received prior or ongoing hormonal therapy with the intent to treat prostate cancer (surgical castration or other hormonal manipulation, e.g., gonadotropin-releasing hormone [GnRH] agonists or antagonists, anti-androgens, or oestrogens).

Plasma samples for determining C_{min} values of enzalutamide, M1, and M2 were obtained pre-dose at Weeks 2, 3, 4, 5, 9, 13, 21, and 25 or at early discontinuation and at the safety follow-up visit. A total of 67 patients were enrolled into the study to obtain 60 patients treated through week 24.

Results

The mean C_{min} plasma concentrations of enzalutamide, M1, M2, and the sum of enzalutamide plus M2 by visit are presented below.

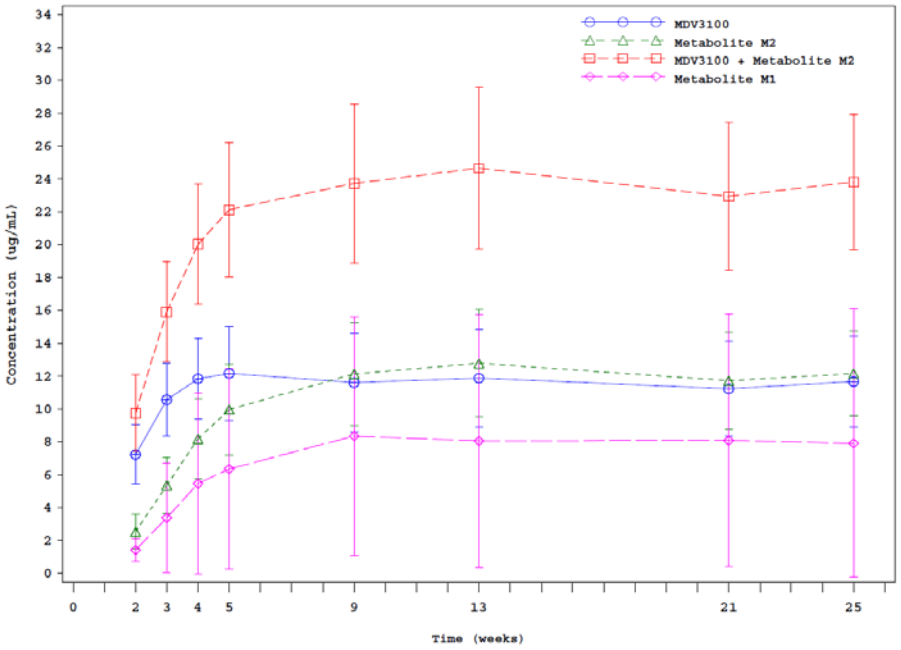


Figure 1: Mean (± SD) C_{min} versus Time Profiles for Enzalutamide, M1, M2, and the Sum of Enzalutamide Plus M2

C_{min} concentrations of enzalutamide remained relatively constant beginning at approximately Week 4 (11.8 µg/mL, CV 20.8%), indicating attainment of steady-state. C_{min} concentrations of the sum of enzalutamide plus M2 remained relatively constant beginning at approximately Week 9 (23.7 µg/mL, CV 20.4%). Similarly, C_{min} concentrations of M1 and M2 remained relatively constant beginning at approximately Week 9 (8.4 µg/mL, CV 87.1% and 12.1 µg/mL, CV 25.8%, respectively), indicating attainment of steady-state. Cmin concentrations of enzalutamide and M2 were similar at Week 9 (11.6 and 12.1 µg/mL, respectively) and at all-time points thereafter.

Study MDV3100-03

Study MDV3100-03 (PREVAIL) was a multinational, phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide administered at 160 mg/day orally to patients with metastatic CRPC who were chemotherapy-naïve. Patients had to be asymptomatic or mildly symptomatic at study entry, and not have previously received cytotoxic chemotherapy. Patients were randomly assigned 1:1 to enzalutamide or placebo. Randomization was central and stratified by investigative site.

Pre-dose C_{min} samples were collected from all patients at Weeks 5, 13, and 25, and at adverse event-related, unscheduled visits prior to Week 25. Plasma samples from enzalutamide-treated patients were analysed for enzalutamide, M1, and M2. Based on the time to reach steady state (28 days for enzalutamide and 56 days for M1 and M2), Week 13 was selected for pharmacokinetic summary statistics. For the purpose of exposure-response analyses for safety, Week 13 data were used to define steady-state C_{min} values; if a Week 13 C_{min} value was not available, then alternative qualifying C_{min} values were considered based on a systematic hierarchy.

Steady-state C_{min} data were examined for relationships with selected demographic characteristics at baseline (age, weight) and safety endpoints (common adverse events, adverse events of interest). For these analyses, C_{min} values for enzalutamide, M2, and the sum of enzalutamide plus M2 were classified into 4 categories (quartiles) by rank order for enzalutamide-treated patients and 1 category (C_{min} = 0) for placebo-treated patients. The statistical methodology was similar to the methodology used for Study CRPC2 (AFFIRM) as presented in the initial marketing application.

Results

The steady-state C_{min} values for enzalutamide, M1, and M2 at Week 13 are provided in Table 2.

Table 2: Week 13 C_{min} Concentration Values for Enzalutamide, M1, and M2 in Study MDV3100-03

Statistic	Enzalutamide	M1	M2
Number of observations	741	741	741
Mean (µg/mL)	12.8	6.56	13.0
SD (µg/mL)	3.20	4.97	3.58
%CV	25.1	75.7	27.6
Min (µg/mL)	0.142	0.196	1.50
Median (µg/mL)	12.5	5.38	12.4
Max (µg/mL)	24.0	49.0	30.9

Data are reported for patients treated with enzalutamide treatment. PK full analysis population is defined as all enrolled patients treated with enzalutamide treatment and had at least 1 plasma concentration result for enzalutamide, M1, or M2.
M1: major human metabolite (inactive); M2: major human metabolite (active); CV: coefficient of variation; CI: confidence interval; SD: standard deviation; PK: pharmacokinetic.

The total number of enzalutamide-randomized patients (871 patents) who had qualifying C_{min} data for enzalutamide, M2, and enzalutamide plus M2 exposure quartiles was 826 patients (94.8% of enrolled patients), 785 patients (90.1%), and 785 patients (90.1%), respectively. There were 844 patients in

the placebo-treated group. The exposure quartiles for enzalutamide, M2, and enzalutamide plus M2 are presented in Table 3.

Table 3: Summary statistics for enzalutamide, M2, and enzalutamide plus M2 exposure quartiles (exposure-response safety population)

	C_{min} (µg/mL) Quartile			
Exposure Variable	**Quartile 1**	**Quartile 2**	**Quartile 3**	**Quartile 4**
Enzalutamide (n)	209	204	211	202
Median (µg/mL)	9.5	11.6	13.5	16.5
Min, Max	0.0, 10.7	10.8, 12.4	12.5, 14.6	14.7, 25.8
M2 (n)	199	195	193	198
Median (µg/mL)	9.5	11.5	13.6	16.9
Min, Max	0.0, 10.6	10.7, 12.4	12.5, 14.7	14.8, 30.9
Enzalutamide + M2 (n)	196	197	195	197
Median (µg/mL)	20.1	23.7	27.2	31.9
Min, Max	0.0, 22.2	22.2, 25.5	25.6, 28.8	28.8, 43.0

Exposure-Response safety population was defined as patients who received at least 1 dose of study drug and have at least 1 qualifying C_{min} value.

C_{min}: minimum plasma concentration; M2: major human metabolite (active).
Source: Study MDV3100-03 Table 14.3.7.5

Selected demographic characteristics (age, weight) are summarised below by exposure quartiles for enzalutamide, M2, and the sum of enzalutamide plus M2.

Table 4: Baseline age and weight in the enzalutamide, M2, and enzalutamide plus M2 exposure quartiles (exposure-response safety population)

Characteristic	Enzalutamide C_{min} Quartile				Placebo (n = 844)
	Q1 (n = 209)	Q2 (n = 204)	Q3 (n = 211)	Q4 (n = 202)	
Age (years)					
n	209	204	211	202	844
Mean (SD)	69.2 (8.04)	70.9 (9.11)	72.1 (7.97)	73.0 (8.45)	71.2 (8.43)
Median	69.0	71.5	72.0	74.0	71.0
Min, Max	43.0, 89.0	44.0, 90.0	51.0, 93.0	44.0, 90.0	42.0, 93.0
Baseline weight (kg)					
n	209	203	211	202	843
Mean (SD)	92.0 (17.76)	86.5 (15.69)	82.3 (13.67)	78.7 (12.99)	84.9 (15.97)
Median	88.1	84.1	80.9	77.5	82.8
Min, Max	48.9, 162.2	49.8, 139.7	53.6, 150.2	49.9, 119.1	33.9, 160.2
	M2 C_{min} Quartile				Placebo (n = 844)
	Q1 (n = 199)	Q2 (n = 195)	Q3 (n = 193)	Q4 (n = 198)	
Age (years)					
n	199	195	193	198	844
Mean (SD)	69.3 (8.65)	70.4 (8.31)	72.2 (8.31)	72.8 (8.13)	71.2 (8.43)
Median	70.0	71.0	73.0	73.0	71.0
Min, Max	43.0, 87.0	44.0, 89.0	49.0, 90.0	48.0, 93.0	42.0, 93.0
Baseline weight (kg)					
n	199	195	193	197	843
Mean (SD)	93.7 (18.37)	86.3 (14.57)	81.5 (12.85)	78.6 (13.27)	84.9 (15.97)
Median	90.1	85.1	80.1	77.1	82.8
Min, Max	48.9, 162.2	49.8, 135.5	54.1, 123.2	49.9, 128.0	33.9, 160.2
	Enzalutamide Plus M2 C_{min} Quartile				Placebo (n = 844)
	Q1 (n = 196)	Q2 (n = 197)	Q3 (n = 195)	Q4 (n = 197)	
Age (years)					
n	196	197	195	197	844
Mean (SD)	68.9 (8.44)	70.8 (8.39)	71.7 (8.48)	73.3 (7.94)	71.2 (8.43)
Median	69.0	71.0	72.0	74.0	71.0
Min, Max	43.0, 89.0	45.0, 89.0	44.0, 90.0	49.0, 93.0	42.0, 93.0
Baseline weight (kg)					
n	196	197	194	197	843
Mean (SD)	94.4 (18.87)	85.5 (13.78)	83.2 (12.31)	77.0 (13.14)	84.9 (15.97)
Median	90.1	85.6	83.0	75.5	82.8
Min, Max	48.9, 162.2	49.8, 119.1	54.1, 121.1	49.9, 128.0	33.9, 160.2

Exposure-Response safety population was defined as patients who received at least 1 dose of study drug and have at least 1 qualifying C_{min} value.

All percentage are based on the number of patients in the Exposure-Response safety population.

C_{min}: minimum plasma concentration; M2: major human metabolite (active); SD: standard deviation.
Source: Study MDV3100-03 Tables 14.1.14.4, 14.1.14.5, and 14.1.14.6

In the exposure-response analyses for safety (treatment-emergent adverse events and adverse events of clinical interest), no clinically meaningful and statistically significant differences between exposure groups were noted for any individual adverse event. In addition, no adverse event of clinical interest had consistent statistically significant findings in pairwise odds ratio comparisons between exposure quartiles in enzalutamide, M2, and enzalutamide plus M2.

2.3.3. Discussion on clinical pharmacology

The pharmacokinetic profiles in study 9785-CL-0321 were generally consistent with those in other studies of enzalutamide. The finding that concentrations remained constant after steady state was achieved is consistent with the conclusion of time-linearity in the original marketing application.

The pharmacokinetic data from study MDV3100-03 were also generally consistent with those in other studies of enzalutamide and nearly identical to those in the original phase 3 study CRPC2 (AFFIRM),

where mean steady-state enzalutamide was 11.4 µg/mL, M1 was 8.44 µg/mL, and M2 was 13.0 µg/mL.

Results from the pivotal study (MDV3100-03), showed that the mean steady-state Cmin values were 12.8 ± 3.20 µg/mL for enzalutamide, 6.56 ± 4.97 µg/mL for M1, 13.0 ± 3.58 µg/mL for M2, and 25.7 ± 5.30 µg/mL for enzalutamide plus M2. As expected based on prior data, enzalutamide and M2 circulate at approximately the same plasma concentrations, and the coefficient of variability is low (25.1% for enzalutamide and 27.6% for M2).

Due to the use of a single dosing regimen in all patients (160 mg/day) and the low pharmacokinetic variability, the quartile ranges were narrow. For example, the median values of neighbouring quartiles never differed by more than 25%, and the overall difference in the median Cmin concentrations of lowest and highest quartiles did not exceed 1.78-fold. Narrow ranges of the exposure quartiles also occurred in Study CRPC2 (AFFIRM) and limited the ability to demonstrate clear exposure-response relationships.

The summary statistics provided from study MDV3100-03 (mean and median) suggested a positive relationship with increasing exposure in all 3 groups (enzalutamide, M2, and the sum of enzalutamide plus M2) with increasing age, and a negative relationship with increasing exposure in the 3 groups with decreasing baseline weight. For both age and weight, the ranges (min, max) were overlapping among the quartiles. The trends in the means and medians for these covariates were consistent with results in the initial marketing application; however, as shown in a population pharmacokinetic model in the initial marketing application, the impact of these covariates on enzalutamide pharmacokinetics was small and not clinically meaningful when compared to inter-individual and residual variability, and dose adjustments were not warranted for either age or weight.

Based on the exposure-response analyses for safety, no clinically meaningful and statistically significant differences between exposure groups were noted for any individual adverse event. In addition, no adverse event of clinical interest had consistent statistically significant findings in pairwise odds ratio comparisons between exposure quartiles in enzalutamide, M2, and enzalutamide plus M2.

Taken as a whole, these exposure-response analyses showed no clear or consistent exposure-response relationship between enzalutamide, M2, or enzalutamide plus M2 exposure and any single adverse event, which is identical to the results for Study CRPC2 (AFFIRM) in the original marketing application.

2.3.4. Conclusions on clinical pharmacology

Overall, the pharmacokinetics data from studies 9785-CL-0321 and MDV3100-03 were consistent with those previously described in the initial application.

No new information on the PK properties of enzalutamide is proposed to be included in the SmPC, which is acceptable.

2.4. Clinical efficacy

This application is based on one single pivotal phase III study, MDV3100-03 (PREVAIL), supported by studies CPRC2 (Phase III, AFFIRM), S-3100-1-01 (Phase I), CPRC-MDA-1 (Phase II) and 9785-CL-0111 (Phase II). In addition, supportive data from a study in hormone naive prostate cancer (9785-CL-0321) were submitted. The clinical study reports for studies CRPC2, S-3100-1-01, and CRPC-MDA-1 were provided in the initial marketing application and are summarised below.

Table 5: Clinical efficacy Studies

Study	Number of Patients	Study Design	Population	Enzalutamide Doses (mg/day)	Efficacy Endpoints	
Phase 3 Randomized, Double-Blind, and Placebo-Controlled Studies in Patients With Metastatic CRPC						
MDV3100-03 (PREVAIL)	1717 (intent-to-treat); 872 enzalutamide 845 placebo	Phase 3, randomized, double-blind, placebo-controlled	Chemotherapy-naïve	160	**Coprimary:** Overall survival, rPFS	**Secondary:** Time to first SRE, time to initiation of cytotoxic chemotherapy, time to PSA progression, PSA response ≥ 50%, best overall soft tissue response
CRPC2 (AFFIRM)	1199; 800 enzalutamide 399 placebo	Phase 3, randomized, double-blind, placebo-controlled	Previously received docetaxel	160	**Primary:** Overall survival	**Secondary:** rPFS, time to first SRE, time to PSA progression, PSA response rate, quality of life measures/pain palliation
Phase 1 and 2 Studies in Patients With Metastatic CRPC						
S-3100-1-01	140 enzalutamide	Phase 1, open-label, dose escalation, dose expansion	65 chemotherapy-naive 75 previously received docetaxel	30, 60, 150/160, 240, 360, 480, 600	PSA response, circulating tumor cell counts, radiographic response, bone turnover markers	
CRPC-MDA-1	60 enzalutamide	Phase 2, open-label, single arm	12 chemotherapy-naïve 44 previously received docetaxel; 4 received other chemotherapy	160	PSA response, bone turnover markers	
9785-CL-0111	47 enzalutamide	Phase 1/2, open-label, dose escalation, dose expansion	4 chemotherapy-naive 43 previously received docetaxel	80, 160, 240 single dose; 80, 160 multiple dose; then 160 long-term	Radiographic response at day 85, PSA response, circulating tumor cell counts, bone turnover markers	
Phase 2 Study in Patients With Hormone-Naïve Prostate Cancer						
9785-CL-0321	67 enzalutamide	Phase 2, open-label, single arm	Hormone-naïve	160	Radiographic response, PSA response, quality of life and bone turnover markers	

2.4.1. Dose response study

Study S-3100-1-01

This was a Phase I, open-label, uncontrolled, dose-escalation study with dose-expansion at the tolerated doses for patients with progressive CRPC, both with and without previous chemotherapy. The key objectives of this study were to determine the maximum tolerated dose and initial safety profile of enzalutamide, to provide data on the pharmacokinetics of enzalutamide, to identify evidence of an antitumor effect, and to determine the optimal dose to move forward into Phase III clinical evaluation.

A total of 140 patients with metastatic CRPC (whereof 65 chemotherapy-naïve patients and 75 patients who had received prior chemotherapy) were enrolled. Enzalutamide doses of 30, 60, 150, 240, 360, 480, and 600 mg/day were studied in 7 dose cohorts.

This antitumor activity was demonstrated consistently across a number of efficacy endpoints:

- 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 median time to PSA progression was not reached in patients without previous chemotherapy. The median time to PSA progression was 316 days (10.4 months) in patients with previous chemotherapy.

- In patients with measurable disease at study entry, 22/31, or 71%, of those without previous chemotherapy had partial responses or stable disease in radiographically evident soft tissue and bone lesions. In patients with previous chemotherapy and measurable disease, 23/42, or 55%, had partial responses or stable disease.

- In patients with favourable circulating tumour cell counts at baseline, MDV3100 therapy was associated with maintenance of favourable circulating tumour cell counts in almost 80% of patients. In patients with unfavourable circulating tumour cell counts at baseline, MDV3100 therapy was associated with conversion to favourable circulating tumour cell counts in 69% of patients without previous chemotherapy and in 30% of men with previous chemotherapy.

- MDV3100 therapy was associated with decreases in levels of markers of bone turnover. Of men without previous chemotherapy, 87% had decreases in bone-specific alkaline phosphatase and 71% had decreases in urinary N-telopeptide. Of men with previous chemotherapy, 66% had decreases in bone-specific alkaline phosphatase and 43% had decreases in urinary N-telopeptide.

2.4.2. Main study

Study MDV3100-03 (PREVAIL)

This is a multinational phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 in chemotherapy-naïve patients with progressive metastatic prostate cancer who have failed androgen deprivation therapy.

Methods

Study participants

Main inclusion criteria:

- Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features.
- Ongoing androgen deprivation therapy with a GnRH analogue or bilateral orchiectomy (i.e., surgical or medical castration)
- Patients who had not had a bilateral orchiectomy, must have had a plan to maintain effective GnRH analogue therapy for the duration of the trial
- Serum testosterone level ≤ 1.73 nmol/L (50 ng/dL) at the screening visit
- Patients receiving bisphosphonate therapy must have been on stable doses for at least 4 weeks

- Progressive disease at study entry defined as one or more of the following 3 criteria that occurred while the patient was on androgen deprivation therapy as defined in inclusion criterion 3:
    - PSA progression defined by a minimum of 2 rising PSA levels with an interval of ≥ 1 week between each determination. Patients who received an antiandrogen must have had progression after withdrawal (≥ 4 weeks since last flutamide or ≥ 6 weeks since last bicalutamide or nilutamide). The PSA value at the screening visit was to be ≥ 2 µg/L (2 ng/mL)
    - Soft tissue disease progression defined by RECIST 1.1
    - Bone disease progression defined by PCWG2 with 2 or more new lesions on bone scan
- Metastatic disease documented by bone lesions on bone scan or by measurable soft tissue disease by CT/MRI. Patients whose disease spread was limited to regional pelvic lymph nodes were not eligible
- No prior cytotoxic chemotherapy for prostate cancer
- Asymptomatic or mildly symptomatic from prostate cancer (ie, < 4 on BPI question 3)
- ECOG performance status 0–1
- Estimated life expectancy ≥ 6 months

Main exclusion criteria:

- Known or suspected brain metastasis or active leptomeningeal disease
- History of seizure or any condition that may predispose to seizure. Also, history of loss of consciousness or transient ischemic attack within 12 months of enrollment (day 1 visit)
- Use of opiate analgesics for pain from prostate cancer within 4 weeks of enrolment (day 1 visit)
- Radiation therapy for treatment of the primary tumor within 3 weeks of enrollment (day 1 visit)
- Radiation or radionuclide therapy for treatment of metastasis
- Treatment with flutamide within 4 weeks of enrollment (day 1 visit)
- Treatment with bicalutamide or nilutamide within 6 weeks of enrollment (day 1 visit)
- Treatment with 5-α reductase inhibitors (finasteride, dutasteride), estrogens, cyproterone within 4 weeks of enrollment (day 1 visit)
- Treatment with systemic biologic therapy for prostate cancer (other than approved bone targeted agents and GnRH analogue therapy) or other agents with antitumor activity within 4 weeks of enrollment (day 1 visit)
- History of prostate cancer progression on ketoconazole
- Prior use, or participation in a clinical trial, of an investigational agent that blocks androgen synthesis (e.g., abiraterone, TAK-700, TAK-683, TAK-448) or blocks the androgen receptor (e.g., BMS 641988)

- Use of herbal products that may have hormonal antiprostate cancer activity and/or are known to decrease PSA levels (eg, saw palmetto) or systemic corticosteroids greater than the equivalent of 10 mg of prednisone per day within 4 weeks of enrollment (day 1 visit)

Patients could withdraw their participation in this study and discontinue treatment with study drug at any time for any reason. Investigators or the medical monitor could temporarily or permanently remove patients from therapy for the following reasons:

- Any adverse event that was intolerable to the patient and that could not be ameliorated by the use of adequate medical intervention, or that led to undue risk to the patient if dosing continued in the opinion of the investigator or medical monitor
- Seizure
- Creatinine > 354 µmol/L (4.0 mg/dL)
- Liver function tests (AST, ALT, or total bilirubin) > 5 times the upper limit of normal
- Absolute neutrophil count of 750/µL
- Platelet count of < 50,000/µL
- Gross noncompliance with the protocol in the opinion of the investigator or medical monitor

Patients who experienced a grade 3 or higher toxicity that could not be ameliorated by the use of adequate medical intervention were to interrupt treatment until the toxicity improved to a grade 2 or lower severity.

In addition, patients were required to permanently discontinue treatment with study drug prior to the initiation of a cytotoxic chemotherapy or an investigational agent. Patients who permanently discontinued study drug treatment for any reason were evaluated at a safety follow-up visit 28 days after the last dose of study drug or before initiation of cytotoxic chemotherapy or an investigational agent, whichever was first. After permanent discontinuation of study drug, patients continued to be monitored in long-term follow-up for radiographic disease progression (unless disease progression was already confirmed), skeletal-related events (unless a skeletal-related event was previously documented), additional antineoplastic treatments for prostate cancer and survival.

Treatments

Patients were randomly assigned 1:1 to receive enzalutamide 160 mg or placebo, administered as four 40-mg capsules once per day by mouth. The study drug could be taken with or without food. Patients received a 28-day supply (1 bottle) of study drug at each clinic visit through week 21, and an 84-day supply (3 bottles) of study drug at week 25 and thereafter. Patients were instructed to store the study drug at room temperature out of the reach of children, and return all study drug bottles (used and unused) at each clinic visit.

Table 6: Prohibited, allowed and required concomitant medications and prostate cancer therapies

Prohibited within 4 weeks of randomization	• Flutamide (4-week washout required) • Bicalutamide or nilutamide (6 weeks washout required) • 5 α-reductase inhibitors (finasteride, dutasteride) • Estrogens • Cyproterone acetate • Biologic, or other agents with antitumor activity against prostate cancer • Systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone • Herbal medications that have known hormonal antiprostate cancer activity and/or are known to decrease prostate-specific antigen levels (ie, saw palmetto) • Androgens (testosterone, dihydroepiandrosterone [DHEA], etc) • Opiate analgesics for prostate cancer pain
Allowed throughout the study	• Blood transfusions (except within 28 days of randomization) and growth factor support (except within 7 days of randomization) per standard of care and institutional guidelines • Steroid use per standard of care up to an equivalent of a daily dose of 10 mg prednisone • Pain therapy per standard of care and institutional guidelines (except opiates for prostate cancer within 4 weeks of randomization) • Radiation therapy including external beam radiotherapy or systemic radionuclides (eg, Samarium or Strontium) • Vaccine therapy that has prior market authorization • Palliative surgical procedures to treat skeletal-related events • Bisphosphonates (except if initiating within 28 days of randomization) and other approved bone-targeting agents for the treatment of metastatic prostate cancer • Hormonal treatment for treating complications of luteinizing hormone-releasing hormone treatment (eg, hot flashes), with medical monitor approval
Allowed during the treatment period after confirmed radiographic progression or skeletal-related event	• Hormonal therapies including other antiandrogens and abiraterone acetate • Biological antitumor treatments
Required during screening and treatment periods	• Gonadotropin-releasing hormone analogues (if not surgically castrated)

Objectives

Co-primary Objectives

- To determine the benefit of enzalutamide as compared to placebo as assessed by overall survival
- To determine the benefit of enzalutamide as compared to placebo as assessed by rPFS

Secondary Objectives

- To determine the benefit of enzalutamide as compared to placebo as assessed by time to first skeletal-related event
- To determine the benefit of enzalutamide as compared to placebo as assessed by time to initiation of cytotoxic chemotherapy

- To determine the benefit of enzalutamide as compared to placebo as assessed by time to PSA progression
- To determine the benefit of enzalutamide as compared to placebo as assessed by PSA response ≥ 50%
- To determine the benefit of enzalutamide as compared to placebo as assessed by best overall soft tissue response
- To determine the safety of treatment with enzalutamide as compared to placebo

Exploratory Objectives

- To evaluate quality of life using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) and the European Quality of Life 5-Domain Scale (EQ-5D) instruments
- To evaluate emergence of pain relative to baseline at 6 months using the Brief Pain Inventory (BPI) Short Form for enzalutamide as compared to placebo
- To determine the benefit of enzalutamide as compared to placebo as assessed by time to first subsequent antineoplastic therapy (cytotoxic or hormonal)
- To determine the benefit of enzalutamide as compared to placebo as assessed by PSA response ≥ 90%
- To characterize enzalutamide exposure (e.g., minimum plasma concentration [C_{min}])
- To collect PK data to be combined with data from other studies in a population PK model

Outcomes/endpoints

Co-primary endpoints

- Overall survival was a co-primary efficacy assessment and defined as the time from randomization to death due to any cause.
- Radiographic progression-free survival was a coprimary efficacy assessment and defined as the time from randomization to the first objective evidence of radiographic disease progression assessed by independent central radiology review or death due to any cause within 168 days after treatment discontinuation, whichever was first.

Radiographic disease progression was evaluated by CT scan or MRI and radionuclide bone scans at weeks 9, 17, 25, and then every 12 weeks thereafter. Radiographic disease progression in bone (2 or more new lesions on radionuclide bone scan) observed at week 9 required 2 additional new lesions on a confirmatory scan at least 6 weeks later; radiographic disease progression in bone observed after week 9 required persistence of 2 new lesions on a confirmatory scan at least 6 weeks later. Radiographic disease progression in soft tissue did not require a confirmatory scan for purposes of analysis, although study sites were requested to obtain confirmatory soft tissue scans through week 13. Scheduled and confirmatory scans had a ± 1-week window for completion.

Radiographic disease progression was evaluated by independent central radiology review using RECIST 1.1 for soft tissue disease and the PCWG2 guidelines for bone disease as defined in a separate imaging review charter until at least the first 410 rPFS events were confirmed. Subsequently, radiographic progression was assessed by local radiology review per RECIST 1.1 and Prostate Cancer Clinical Trials Working Group 2 (PCWG2). Continued radiographic imaging was not required after radiographic progression was confirmed. Independent radiology reviewers (2 for soft tissue and 2 for nuclear medicine) read images in a blinded fashion. If there was disagreement between either the 2 independent reviewers of soft tissue or between the 2 independent reviewers of bone scans in terms of

the occurrence or time point of disease progression (confirmed or unconfirmed), a third independent reviewer would provide adjudication.

Secondary endpoints

- Time to First Skeletal-Related Event

Time to first skeletal-related event was defined as the time from randomization to the date of the first occurrence of a skeletal-related event for each patient. A skeletal-related event was defined as radiation therapy or surgery to bone for prostate cancer, pathological bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain from prostate cancer. An alteration of analgesic medication for bone pain or the initiation of bisphosphonates or denosumab was not considered a skeletal-related event. Skeletal-related events were recorded at each scheduled and unscheduled study visit and during long-term follow-up if a skeletal-related event was not documented previously.

- Time to Initiation of Cytotoxic Chemotherapy

The time from randomization to the date of initiation of cytotoxic chemotherapy was used for this assessment.

- Time to PSA Progression

The time to PSA progression was defined according to the PCWG2 guidelines. For patients with PSA declines 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 nadir was documented, and confirmed by a second consecutive value obtained 3 or more 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 baseline is documented, and confirmed by a second consecutive value 3 or more weeks later. PSA assessments were performed locally at screening, day 1, weeks 13, 17, 21, 25, and every 12 weeks thereafter, and at the safety follow-up visit.

- PSA Response ≥ 50%

PSA response was defined as a ≥ 50% reduction in PSA from baseline to the lowest postbaseline PSA value and required confirmation by a consecutive assessment at least 3 weeks later

- Best Overall Soft Tissue Response

Table 7: Soft tissue assessment (RECIST 1.1)

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; Jan 45(2):228-47 [Eisenhauer et al, 2009].
CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Exploratory Efficacy Assessments

- Functional Assessment of Cancer Therapy – Prostate

The FACT-P quality of life questionnaire is a multidimensional, self-reported quality of life instrument specifically designed for use in patients with prostate cancer. It consists of 27 core items that assess patient function in 4 domains (FACT-G [General] score): physical, social/family, emotional, and functional well-being, followed by a domain of 12 items that assess disease-related symptoms. The sum of scores in all 5 domains constitutes the FACT-P. Each item is rated on a 0 to 4 Likert-type scale, and then combined to produce scores for each domain, as well as a total quality-of-life score with higher scores representing better quality of life. A validated version of the questionnaire was provided to each patient in the local language and completed by the patient on day 1, at weeks 5, 13, and every 12 weeks thereafter

- Time to Degradation of the Functional Assessment of Cancer Therapy-Prostate

The time from randomization to date of degradation of FACT-P was evaluated based on completion of the FACT-P on day 1, at weeks 5, 13, and every 12 weeks thereafter. Degradation on the FACT-P was defined as at least a 10-point decrease from baseline in the total score. Degradation on individual domains of the FACT-P was defined as at least a 3-point decrease from baseline score for that domain.

- European Quality of Life 5-Domain Scale

The EQ-5D is a standardized instrument that measures health outcome. Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each assessed on a 3-point categorical scale ranging from “no problem” to “extreme problem.” The EQ-5D questionnaire was administered by study site staff directly to the patient on day 1, at week 13, and every 12 weeks thereafter. A validated version of the questionnaire was available for use with each patient in the local language

- Brief Pain Inventory

The BPI Short Form (referred to as BPI throughout this report) is a validated self-administered instrument designed to measure the level of pain and effect of pain on daily activities. The form contains 9 questions and patients were instructed to use the instrument to assess pain related to prostate cancer only. A validated version of the questionnaire was provided to each patient in the local language

- Time to First Post-baseline Antineoplastic Therapy

Antineoplastic therapies, including cytotoxic, investigational, and hormonal therapies for prostate cancer, were considered for this assessment. Time to first post-baseline antineoplastic therapy was defined as time from randomization to date of first use of antineoplastic therapy. Such therapies included cytotoxic chemotherapy, noncytotoxic chemotherapy, antiandrogen therapy (ie, bicalutamide, nilutamide, flutamide, and enzalutamide), approved immunotherapy, estrogen, abiraterone, and investigational agents for prostate cancer. The first new post-baseline antineoplastic therapy could have been initiated before the discontinuation of study drug.

Sample size

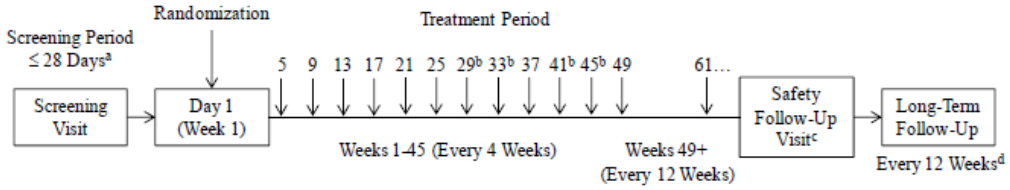
This study was powered to evaluate overall survival and rPFS. The overall type I error rate (2-sided) for the study is 0.05 with 0.049 allocated to overall survival and 0.001 allocated to rPFS. The desired operating characteristics for the overall survival endpoint were used to determine the total sample size for the study and its overall duration.

The final analysis of overall survival was planned when at least 765 deaths were reported. A prespecified interim analysis of overall survival was planned when approximately 516 deaths (or 67% of the total number of deaths for the final overall survival analysis) occurred. The final prespecified

analysis of rPFS was based on a minimum of 410 centrally determined rPFS events and conducted at the time of interim analysis of overall survival.

Randomisation

After a patient was screened and the investigator determined that the patient was eligible for enrolment, the study site staff completed the Randomization Authorization Form and faxed it to Medivation. The medical monitor reviewed the form and, if appropriate, approved the enrolment of the patient in writing. Once the study site had approval, the patient could proceed with the day 1 visit. If all inclusion criteria were met and no exclusion criteria applied, patients were assigned 1:1 to enzalutamide or placebo using a centrally administered, randomized, permuted-block method and stratified by study site. An IVRS/IWRS assigned the patient a study drug bottle number according to the randomization code on day 1.



[a] Informed consent, abdominopelvic computed tomography (CT) scan or magnetic resonance imaging (MRI), bone scan, and chest x-ray or chest CT must have occurred within 6 weeks before randomization.
[b] Assessments may have been conducted by telephone.
[c] 28 days after the last dose of study drug or before initiation of cytotoxic chemotherapy or an investigational agent, whichever was first.
[d] After study drug discontinuation.

Figure 2: Study schematic

Blinding (masking)

This study was blinded and placebo-controlled. Placebo capsules were identical in appearance to the enzalutamide capsules. All patients, investigators, site personnel, and sponsor personnel involved in the conduct of the study were blinded to treatment assignment. Unblinding was to occur only if the knowledge of treatment assignment would materially change the planned management of a medical emergency. In addition, some patients who had disease progression and previously discontinued study drug were unblinded in order to determine eligibility for a subsequent clinical study when this study was determined by the investigator to be the best (or only) available treatment option.

Statistical methods

The statistical analyses for the study are described in the statistical analysis plan finalised on 9 October 2013 before unblinding of any data. The data cut-off date was 16 September 2013 for all analyses summarised in this report unless otherwise specified. The analysis populations are described in Table 8.

Table 8: Analysis populations

Population	Definition	Analyses	Comment on Analyses
Intent-to-treat	All patients randomly assigned to treatment	Disposition Demographics Protocol deviations Disease characteristics Prior therapies Coprimary efficacy endpoints Secondary and exploratory efficacy endpoints (except PSA response rate)	Based on treatment group as randomized (not actual treatment received)
Evaluable intent-to treat	All patients randomly assigned to treatment with PSA values at baseline and at least 1 postbaseline assessment	PSA response rate ≥ 50% PSA response rate ≥ 90%	As above
Measurable disease	All patients with at least 1 soft tissue target lesion per RECIST 1.1	Best overall soft tissue response	As above
Safety	All patients randomly assigned to treatment who received at least 1 dose or partial dose of study drug (enzalutamide or placebo)	Concomitant medications Exposure Adverse events Laboratory Evaluations Vital signs Electrocardiograms	Based on actual treatment received (not assigned treatment). For patients who inadvertently received more than 1 treatment, analyses were based on the treatment received for the greatest length of time.
Exposure-response safety population	All patients randomly assigned to treatment who received at least 1 dose of study drug (enzalutamide or placebo) and had at least 1 qualifying steady-state C_{min} value (for enzalutamide-treated patients only)	Disposition Demographics Exposure Exposure quartiles C_{min} values Adverse events	As above

C_{min}, minimum plasma concentration; PSA, prostate-specific antigen, RECIST, Response Evaluation Criteria in Solid Tumors.

OS

The ITT population was used for coprimary efficacy evaluations (overall survival and rPFS). The type I error rate of 0.05 was allocated between the 2 coprimary efficacy endpoints: 0.049 (2-sided) for overall survival and 0.001 (2-sided) for rPFS. A prespecified interim analysis of overall survival was planned when approximately 516 deaths (or 67% of the total number of deaths for the final analysis) occurred and was evaluated using a 2-sided type I error rate of 0.012. A 2-stage group sequential design with Lan-DeMets alpha-spending function determined by the O'Brien-Fleming approach was used to allocate the overall type I error rate, 0.049 (2-sided), between the single interim analysis and the final analysis of overall survival. An unstratified log-rank test was used to compare the enzalutamide and placebo groups for the interim and final analyses of overall survival. The interim analysis of overall survival was prepared by an independent statistical unit, and presented by the independent statistician to the independent DMC during the closed session on 21 Oct 2013.

During the initial development of the design of this study, OS would be looked at using the P = 0.0029 level, with around 444 deaths by the interim analysis. The final analysis would be for OS at the P = 0.048 level, scheduled for when 888 deaths had occurred. Nevertheless, based upon the results of the

COU-AA-302 study with abiraterone acetate in chemotherapy-naïve patients and the activity of enzalutamide seen in CRPC2 (AFFIRM), the target hazard ratio was reduced from 0.83 to 0.815, which reduced the required number of targeted death events from 888 to 765 for a type I error rate of 0.049. The number of death events required for the interim analysis of OS was increased from 444 to 516 (67% of events).

rPFS

The primary (final) rPFS analysis was conducted at the time of the interim overall survival analysis, when a minimum of 410 centrally confirmed rPFS events occurred. Radiographic PFS was compared between the 2 treatment groups using a 2-sided unstratified log-rank test. The rPFS analysis was prepared by the independent statistical unit and presented to the DMC at the time of the interim analysis of overall survival.

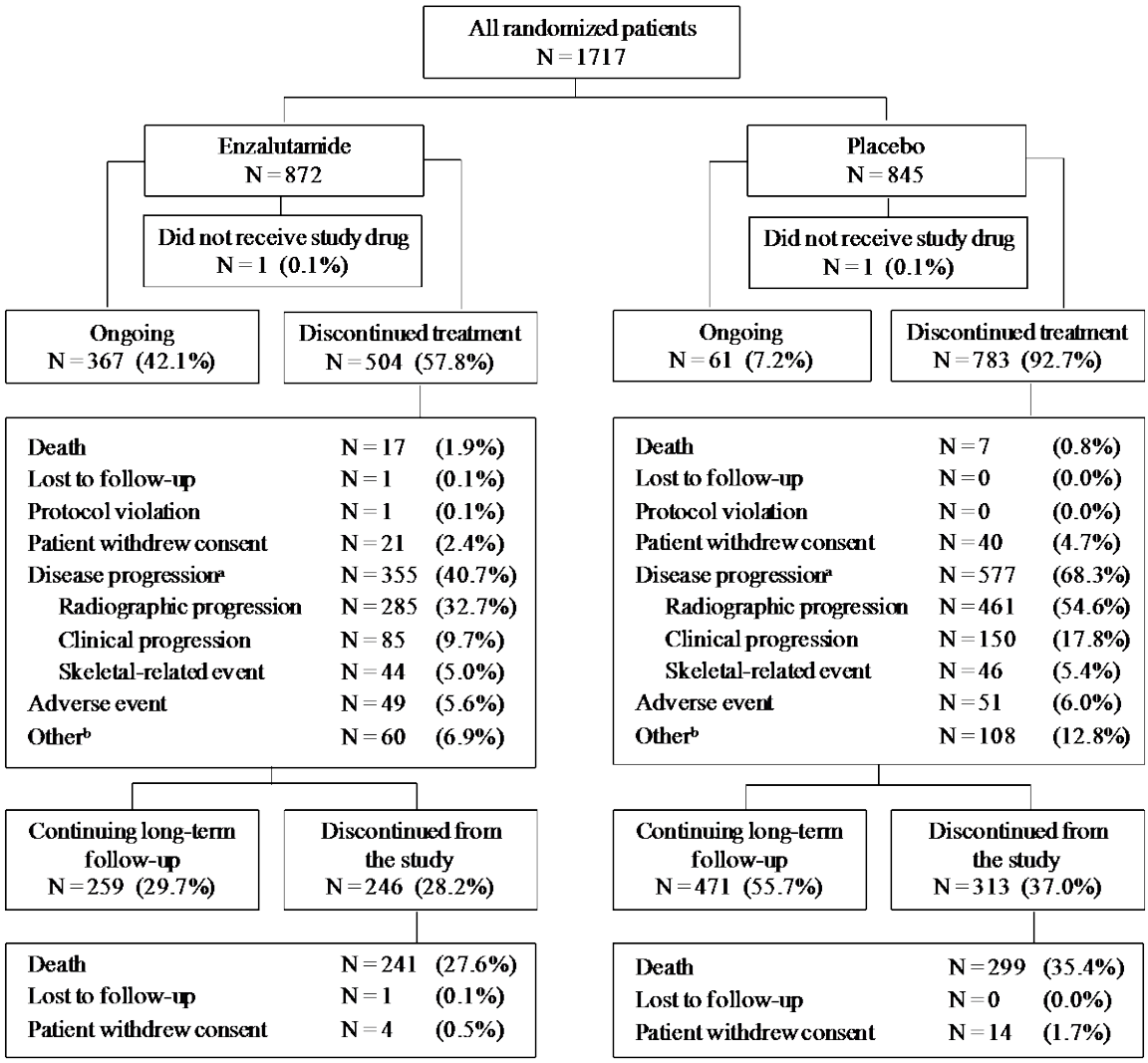
The censoring rules and sensitivity analyses for rPFS are acceptable.

Secondary endpoints

The ITT population was used for secondary efficacy evaluations. To maintain a study-wide type I error of 5%, the Holm step-down procedure was applied to secondary endpoint analyses.

Results

Participant flow



Source: [Table 14.1.3]
Percentages are based on total number of randomized patients in each treatment group and overall.
[a] Patients discontinued due to disease progression could be counted in more than 1 subcategory.
[b] The most common reason was rising prostate-specific antigen.
ITT, intent-to-treat.

Figure 3: Patient disposition flowchart as of 16 September 2013 (ITT population)

Recruitment

Between 28 September 2010 and 07 September 2012, 1717 patients were randomly assigned 1:1 to treatment with enzalutamide (872 patients) or placebo (845 patients); 1715 patients received at least 1 dose of enzalutamide (871 patients) or placebo (844 patients). A total of 207 study sites in 22 countries in North America, Europe, Australia, and Asia randomized patients in this study. The highest enrolling countries were the US (247 patients, 14.4%), Australia (232 patients, 13.5%), Canada (179 patients, 10.4%), France (175 patients, 10.2%), and the United Kingdom (153 patients, 8.9%). Enrollment by site ranged from 1 to 35 patients. The highest enrolling sites were the Institut Gustave-

Roussy (France, site 300, 35 patients, 2.0%), Memorial Sloan-Kettering (US, site 001, 32 patients, 1.9%), and The Royal Marsden Hospital (United Kingdom, site 650, 29 patients, 1.7%).

At weeks 25, 49, and 85 (approximately 6, 12, and 18 months, respectively), the number of patients in the treatment phase in the enzalutamide group was 777 (89.1%), 643 (73.7%), and 287 (32.9%) versus 387 (45.8%), 185 (21.9%), and 48 (5.7%), respectively, for the placebo group.

As of the data cut-off date, 246 patients (28.2%) in the enzalutamide group and 313 patients (37.0%) in the placebo group permanently discontinued from the study. The primary reason for discontinuation from the study was death: 540 patients (241 enzalutamide, 27.6% vs 299 placebo, 35.4%). Only 19 patients (1.1%) withdrew consent for survival follow-up or were lost to survival follow-up prior to death.

Conduct of the study

The original study protocol was dated 9 June 2010. The protocol was amended 4 times during the blinded study period. A subsequent amendment added an open-label extension period based on the recommendation of the DMC to halt the study and allow placebo-treated patients access to enzalutamide.

Major changes to the controlled portion of the study (amendments 1 through 4) are summarized below.

Amendment 1 (27 Aug 2010, prior to first randomization) made the following major changes:

- Replaced the original primary efficacy variables (time to first skeletal-related event and time to initiation of cytotoxic chemotherapy) with new primary efficacy variables (overall survival and progression-free survival [PFS]).
- Added that the primary analysis of overall survival was to be performed when 888 deaths were reported.
- Specified that the study would not be discontinued based on the primary analysis of PFS; the study was to continue until the primary analysis of overall survival was complete.

Amendment 2 (29 Mar 2011, after 153 patients were randomized) made the following major changes:

- Clarified that informed consent must be signed, and abdominopelvic CT scan or MRI, bone scan, chest x-ray or chest CT must occur within 6 weeks of randomization, otherwise the screening visit had to be repeated.
- Clarified that chest CT should be performed at the time of radiographic assessments if screening scan demonstrated metastatic chest disease.
- Added that determination of radiographic progression had to be confirmed by the independent central radiology review before stopping radiographic imaging.
- Clarified that the BPI was to assess prostate cancer-related pain only.

Amendment 3 (23 Jul 2012, after 1696 patients were randomized) made the following major changes:

- Specified that the primary analysis of rPFS was to be based on the first 410 rPFS events and conducted at the time of the formal interim analysis of overall survival.
- Clarified that the prespecified interim analysis for overall survival was to be performed at approximately 50% of the required total number of death events (444 of 888) for the primary overall survival analysis and not at the end of the enrollment period.

Amendment 4 (14 Mar 2013, after all 1717 patients were randomized) made the following major changes:

- Added secondary objectives (time to PSA progression, PSA response 50%, best overall soft tissue response, and safety of enzalutamide compared to placebo). Time to PSA progression and safety were formerly other secondary objectives.
- Clarified that rPFS was to be analyzed from randomization to radiographic progression or death within 168 days after treatment discontinuation (whichever was first).
- Clarified that a minimum of the first 410 rPFS events were required for the primary PFS analysis. After the required 410 rPFS events, radiographic progression should be confirmed by the local radiology review before stopping radiographic imaging.
- Changed the assumed target hazard ratio for benefit of enzalutamide over placebo in overall survival from 0.83 to 0.815. The minimum target number of deaths required for the primary analysis of overall survival changed from 888 to 765 due to increased assumed effect size.
- Updated statistical endpoints and methods to be consistent with new objectives and the statistical analysis plan.

Protocol deviations

Table 9: Major protocol deviations (ITT population)

	Enzalutamide (N = 872)	Placebo (N = 845)	Total (N = 1717)
Patients with at least 1 major protocol deviation	104 (11.9%)	97 (11.5%)	201 (11.7%)
Major deviation			
Eligibility criteria not met	94 (10.8%)	92 (10.9%)	186 (10.8%)
Expected to interrupt/discontinue study drug but did not	1 (0.1%)	0 (0.0%)	1 (< 0.1%)
Received excluded concomitant medication	0 (0.0%)	1 (0.1%)	1 (< 0.1%)
Received the wrong treatment	4 (0.5%)	3 (0.4%)	7 (0.4%)
Received incorrect dose	6 (0.7%)	3 (0.4%)	9 (0.5%)

Source: [Table 14.1.13.1]
Patients may have had more than 1 protocol deviation.
ITT, intent-to-treat.

Table 10: Protocol deviations of inclusion / exclusion criteria (ITT population)

Criteria	Enzalutamide (N = 872)	Placebo (N = 845)	Total (N = 1717)
Inclusion			
7 Progressive disease at study entry defined as PSA, soft tissue disease, or bone disease progression while on androgen deprivation therapy (PSA progression required at least a 4-week washout from flutamide and at least a 6-week washout from bicalutamide or nilutamide)	22 (2.5%)	25 (3.0%)	47 (2.7%)
10 Asymptomatic or mildly symptomatic due to prostate cancer (score must be < 4 on BPI question 3)	26 (3.0%)	15 (1.8%)	41 (2.4%)
8 Metastatic disease documented by bone lesions on bone scan or measurable soft tissue disease by CT/MRI	8 (0.9%)	11 (1.3%)	19 (1.1%)
6 Patients receiving bisphosphonate therapy must have been on stable doses for at least 4 weeks	2 (0.2%)	4 (0.5%)	6 (0.3%)
9 No prior cytotoxic chemotherapy for prostate cancer	1 (0.1%)	4 (0.5%)	5 (0.3%)
2 Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features	0 (0.0%)	1 (0.1%)	1 (< 0.1%)
Exclusion			
14 Radiation or radionuclide therapy for treatment of metastasis	15 (1.7%)	15 (1.8%)	30 (1.7%)
9 Clinically significant cardiovascular disease	10 (1.1%)	7 (0.8%)	17 (1.0%)
16 Treatment with bicalutamide or nilutamide within 6 weeks of enrollment	5 (0.6%)	6 (0.7%)	11 (0.6%)
17 Treatment with 5-α reductase inhibitors (finasteride, dutasteride), estrogens, cyproterone within 4 weeks of enrollment	4 (0.5%)	5 (0.6%)	9 (0.5%)
8 History of seizure or any condition that may predispose to seizure; history of loss of consciousness or TIA within 12 months of enrollment	4 (0.5%)	4 (0.5%)	8 (0.5%)
12 Use of opiate analgesics for pain from prostate cancer within 4 weeks of enrollment	3 (0.3%)	3 (0.4%)	6 (0.3%)
3 History of another malignancy within 5 years other than curatively treated nonmelanomatous skin cancer	2 (0.2%)	3 (0.4%)	5 (0.3%)
23 Use of herbal products that may have hormonal antiprostate cancer activity and/or are known to decrease PSA levels or systemic corticosteroids greater than the equivalent of 10 mg of prednisone per day within 4 weeks of enrollment	2 (0.2%)	1 (0.1%)	3 (0.2%)
18 Treatment with systemic biologic therapy for prostate cancer (other than approved bone targeted agents and GnRH-analogue therapy) or other agents with antitumor activity within 4 weeks of enrollment	1 (0.1%)	0 (0.0%)	1 (< 0.1%)

Source: [Listing 16.2.2.1]
BPI, Brief Pain Inventory; CT, computed tomography; GnRH, gonadotropin-releasing hormone; ITT, intent-to-treat; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; TIA, transient ischemic attack.

Baseline data

Table 11: MDV3100-03 Demographic and Baseline Characteristics (ITT Population)

Baseline Characteristic	Enzalutamide (N = 872)	Placebo (N = 845)
Age		
Mean (SD)	71.3 (8.51)	71.2 (8.42)
Median	72.0	71.0
Min, max	43.0, 93.0	42.0, 93.0
Age category (years)		
< 65	179 (20.5%)	179 (21.2%)
65 to 74	376 (43.1%)	374 (44.3%)
≥ 75 to 84	274 (31.4%)	240 (28.4%)
≥ 85	43 (4.9%)	52 (6.2%)
Race		
American Indian or Alaska Native	1 (0.1%)	0 (0.0%)
Asian	85 (9.7%)	82 (9.7%)
Black or African American	21 (2.4%)	13 (1.5%)
Native Hawaiian or other Pacific Islander	1 (0.1%)	1 (0.1%)
White	669 (76.7%)	655 (77.5%)
Other, multiple, unknown	95 (10.9%)	94 (11.1)
Ethnicity		
Not Hispanic or Latino	784 (89.9%)	743 (87.9%)
Hispanic or Latino	16 (1.8%)	22 (2.6%)
Not reported, unknown	72 (8.3%)	80 (9.5%)
Baseline weight (kg)		
N	870	844
Mean (SD)	85.0 (16.01)	85.0 (16.02)
Median	83.1	82.8
Min, max	48.9, 162.2	33.9, 160.2
Body mass index (kg/m^2)		
N	870	843
Mean (SD)	28.3 (4.62)	28.1 (4.59)
Median	27.5	27.5
Min, max	17.5, 46.8	15.3, 50.6
Baseline ECOG performance status		
0	584 (67.0%)	585 (69.2%)
1	288 (33.0%)	260 (30.8%)
≥ 2	0 (0.0%)	0 (0.0%)
Baseline mean pain score (BPI question 3)		
N	859	840
0 to 1	569 (66.2%)	567 (67.5%)
2 to 3	275 (32.0%)	262 (31.2%)
> 3	15 (1.7%)	11 (1.3%)
Baseline haemoglobin (g/L)		
Mean (SD)	129.5 (12.81)	129.8 (12.30)
Median	130.0	131.0
Min, max	82.0, 168.0	74.0, 167.0
Baseline alkaline phosphatase (U/L)		
Mean (SD)	151.6 (271.99)	142.6 (200.26)
Median	94.0	86.0
Min, max	34.0, 4485.0	27.0, 2350.0
Baseline lactate dehydrogenase (U/L)		
N	871	844
Mean (SD)	207.2 (113.66)	206.5 (111.03)
Median	185.0	185.0

Baseline Characteristic	Enzalutamide (N = 872)	Placebo (N = 845)
Min, max	52.0, 1861.0	67.0, 2321.0
Baseline serum albumin (g/L)		
Mean (SD)	38.3 (3.37)	38.3 (3.23)
Median	38.0	39.0
Min, max	25.0, 48.0	28.0, 49.0
Baseline serum PSA (µg/L)		
N	872	844
Mean (SD)	140.7 (284.22)	137.9 (298.61)
Median	54.1	44.2
Min, max	0.1, 3182.0	0.3, 3637.0
Baseline creatinine (µmol/L)		
Mean (SD)	89.9 (23.22)	90.5 (23.31)
Median	85.0	87.0
Min, max	29.0, 207.0	41.0, 218.0
Baseline use of corticosteroids > 7 days[a]	35 (4.0%)	36 (4.3%)
History of cardiovascular disease	179 (20.5%)	168 (19.9%)

Source: [MDV3100-03 Table 14.1.4.1]
[a] Includes all oral steroid use for prostate cancer on the date of first dose of study drug and with continuous exposure for at least 7 days. Excludes steroids taken for indications not associated with prostate cancer.
BPI, Brief Pain Inventory Short Form; ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; PSA, prostate-specific antigen.

Table 12: MDV3100-03 Baseline Disease Characteristics (ITT Population)

Baseline Characteristic	Enzalutamide (N = 872)	Placebo (N = 845)
Time (months) from initial diagnosis or first treatment of prostate cancer to randomization		
N	872	844
Mean (SD)	78.6 (59.12)	76.2 (55.73)
Median	62.7	64.6
Min, max	0.2, 326.6	0.1, 275.4
Total Gleason score category		
N	838	808
Low (2-4)	7 (0.8%)	7 (0.9%)
Medium (5-7)	407 (48.6%)	378 (46.8%)
High (8-10)	424 (50.6%)	423 (52.4%)
Type of disease progression at study entry		
PSA progression only	375 (43.0%)	369 (43.7%)
Radiographic progression with PSA	349 (40.0%)	344 (40.7%)
Radiographic progression without PSA	126 (14.4%)	107 (12.7%)
No disease progression per protocol	22 (2.5%)	25 (3.0%)
Disease localization at screening[a]		
Bone only	348 (39.9%)	335 (39.6%)
Soft tissue only	124 (14.2%)	149 (17.6%)
Both bone and soft tissue	393 (45.1%)	355 (42.0%)
None	7 (0.8%)	6 (0.7%)
Target or nontarget soft tissue disease at screening		
Target only	124 (14.2%)	104 (12.3%)
Nontarget only	122 (14.0%)	123 (14.6%)
Measurable disease[b]	396 (45.4%)	381 (45.1%)
Distribution of disease at screening[c]		
Bone	741 (85.0%)	690 (81.7%)
Lymph node	437 (50.1%)	434 (51.4%)
Visceral disease (lung or liver)	98 (11.2%)	106 (12.5%)
Visceral liver	40 (4.6%)	34 (4.0%)
Visceral lung	64 (7.3%)	75 (8.9%)

Baseline Characteristic	Enzalutamide (N = 872)	Placebo (N = 845)
Visceral lung and liver	6 (0.7%)	3 (0.4%)
Other soft tissue	113 (13.0%)	105 (12.4%)
Number of bone metastases at screening		
0	131 (15.0%)	155 (18.3%)
1	97 (11.1%)	85 (10.1%)
2 to 4	213 (24.4%)	186 (22.0%)
5 to 9	146 (16.7%)	147 (17.4%)
10 to 20	140 (16.1%)	122 (14.4%)
> 20	145 (16.6%)	150 (17.8%)

Source: [MDV3100-03 Table 14.1.5]
[a] Disease localization is based on the target lesion, nontarget lesion, and bone scan case report forms.
[b] Measurable soft tissue disease is defined as at least 1 target lesion identified per RECIST 1.1.
[c] Patients can be summarized for more than 1 category but are counted only once for each category.
ITT, intent-to-treat; PSA, prostate-specific antigen.

Table 13: MDV3100-03 Prior Therapy for Prostate Cancer (ITT Population)

Prior Treatments of Prostate Cancer	Enzalutamide (N = 872)	Placebo (N = 845)
Number of unique prior prostate cancer therapies		
0	4 (0.5%)	4 (0.5%)
1	74 (8.5%)	73 (8.6%)
2	292 (33.5%)	299 (35.4%)
3	249 (28.6%)	235 (27.8%)
≥ 4	253 (29.0%)	234 (27.7%)
Number of unique prior hormonal therapies		
0	7 (0.8%)	7 (0.8%)
1	89 (10.2%)	94 (11.1%)
2	373 (42.8%)	360 (42.6%)
3	239 (27.4%)	237 (28.0%)
≥ 4	164 (18.8%)	147 (17.4%)
Prior antiandrogen therapy use	760 (87.2%)	730 (86.4%)
Number of prior antiandrogen therapies		
0	112 (12.8%)	115 (13.6%)
1	573 (65.7%)	561 (66.4%)
2	165 (18.9%)	151 (17.9%)
3	21 (2.4%)	15 (1.8%)
≥ 4	1 (0.1%)	3 (0.4%)
Prior ketoconazole use	8 (0.9%)	8 (0.9%)
Bisphosphonate or denosumab use at baseline	223 (25.6%)	230 (27.2%)
History of radiotherapy	392 (45.0%)	380 (45.0%)
Prior radiotherapy[a]		
External beam only	373 (42.8%)	351 (41.5%)
Brachytherapy only	29 (3.3%)	32 (3.8%)
Both external beam and brachytherapy	19 (2.2%)	17 (2.0%)
Systemic	15 (1.7%)	16 (1.9%)
Type of prior radiotherapy[b]		
Primary	340 (39.0%)	330 (39.1%)
Palliative	61 (7.0%)	57 (6.7%)
Salvage	7 (0.8%)	6 (0.7%)
History of surgical prostate cancer procedure	453 (51.9%)	419 (49.6%)

Prior Treatments of Prostate Cancer	Enzalutamide (N = 872)	Placebo (N = 845)
Type of prior surgical prostate cancer procedure[c]		
Prostatectomy	226 (25.9%)	225 (26.6%)
Orchiectomy	40 (4.6%)	42 (5.0%)
Transurethral resection of the prostate	124 (14.2%)	88 (10.4%)
Cryoablation	7 (0.8%)	6 (0.7%)
Other	152 (17.4%)	140 (16.6%)

Source: [MDV3100-03 Table 14.1.6]
[a] Patients who had more than 1 prior radiotherapy are counted only once in each given category.
[b] Patients who had more than 1 type of prior radiotherapy are counted only once in each given category.
[c] Patients who had more than 1 type of prior surgery for prostate cancer are counted only once in each given category.
ITT, intent-to-treat.

Table 14: Patients with selected concomitant treatments while on study drug intent-to-treat population

	Enzalutamide 160 mg (N=872)	Placebo (N=845)	Total (N=1717)
No. patients with at least 1 of the 6 therapies below while on study drug	479 (54.9%)	473 (56.0%)	952 (55.4%)
Sipuleucel-T	4 (0.5%)	5 (0.6%)	9 (0.5%)
Abiraterone	7 (0.8%)	6 (0.7%)	13 (0.8%)
Corticosteroids > 7 Days [1]	32 (3.7%)	51 (6.0%)	83 (4.8%)
Bisphosphonates	237 (27.2%)	247 (29.2%)	484 (28.2%)
Radiation Therapy	120 (13.8%)	83 (9.8%)	203 (11.8%)
Opiate Analgesics	297 (34.1%)	277 (32.8%)	574 (33.4%)

The analysis data cutoff date is 2013-09-16.
Note: Concomitant treatments while on study drug is defined as treatments taken during first dose date and last dose date of study drug.
[1] Includes all oral steroid use started between the first dose date and last dose date of study drug. Steroids taken for indications not associated with prostate cancer are excluded. Continuous steroid exposures less than 7 days are excluded.

Numbers analysed

The pre-specified interim analysis of overall survival and final analysis of rPFS occurred on 21 October 2013. Based on these analyses, the DMC recommended halting the blinded portion of the study and allowing patients randomized to placebo access to open-label enzalutamide. The data cut-off date for all analyses was 16 September 2013, except the data cut-off date of 06 May 2012 which was used for the analyses of rPFS.

Table 15: Efficacy Analysis Populations

Patient Population	Enzalutamide (N = 872)	Placebo (N = 845)	Total (N = 1717)
ITT population	872 (100.0%)	845 (100.0%)	1717 (100.0%)
rPFS ITT population	832 (95.4%)	801 (94.8%)	1633 (95.1%)
Evaluable ITT population for PSA response rate	854 (97.9%)	777 (92.0%)	1631 (95.0%)
Measurable disease population for best overall soft tissue response	396 (45.4%)	381 (45.1%)	777 (45.3%)
Evaluable ITT population for pain progression	698 (80.0%)	358 (42.4%)	1056 (61.5%)

Source: [Table 14.1.1, Table 14.2.2.1, Table 14.2.3.7, Table 14.2.3.8.1, Table 14.2.4.3.2]
ITT, intent-to-treat; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.

The endpoint of rPFS excluded the 84 patients who were not randomised before the rPFS data cut-off date of 06 May 2012. Hence the ITT population for rPFS constitutes 1633 subjects.

Outcomes and estimation

Co-primary endpoint OS

Table 16: MDV3100-03 Duration of Overall Survival – Coprimary Analysis (ITT Population, cut-off date of 16 Sep 2013)

Overall Survival at Data Analysis Cutoff Date	Enzalutamide (N = 872)	Placebo (N = 845)	Enzalutamide vs Placebo
Survival status			
Death	241 (27.6%)	299 (35.4%)	
Censored[a]	631 (72.4%)	546 (64.6%)	
Alive at data analysis cutoff date	626 (71.8%)	532 (63.0%)	
Lost to follow-up	5 (0.6%)	14 (1.7%)	
Duration of overall survival (months)[a,b]			
N	872	845	
Censored	631 (72.4%)	546 (64.6%)	
25th percentile	22.0	17.2	
Median (95% CI)	32.4 (30.1, NYR)	30.2 (28.0, NYR)	
75th percentile	NYR	NYR	
P-value (unstratified)			< 0.0001
Hazard ratio (95% CI)[c]			0.706 (0.596, 0.837)
Median follow-up time based on reverse Kaplan-Meier estimates – all patients (months)	22.2	22.4	

Source: [MDV3100-03 Table 14.2.1.1]
[a] Patients who were not known to have died at the analysis date are censored at date last known alive or data analysis cutoff date, whichever occurs first.
[b] Based on Kaplan-Meier estimates.
[c] The hazard ratio is based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favoring enzalutamide.
ITT, intent-to-treat; NYR, not yet reached.

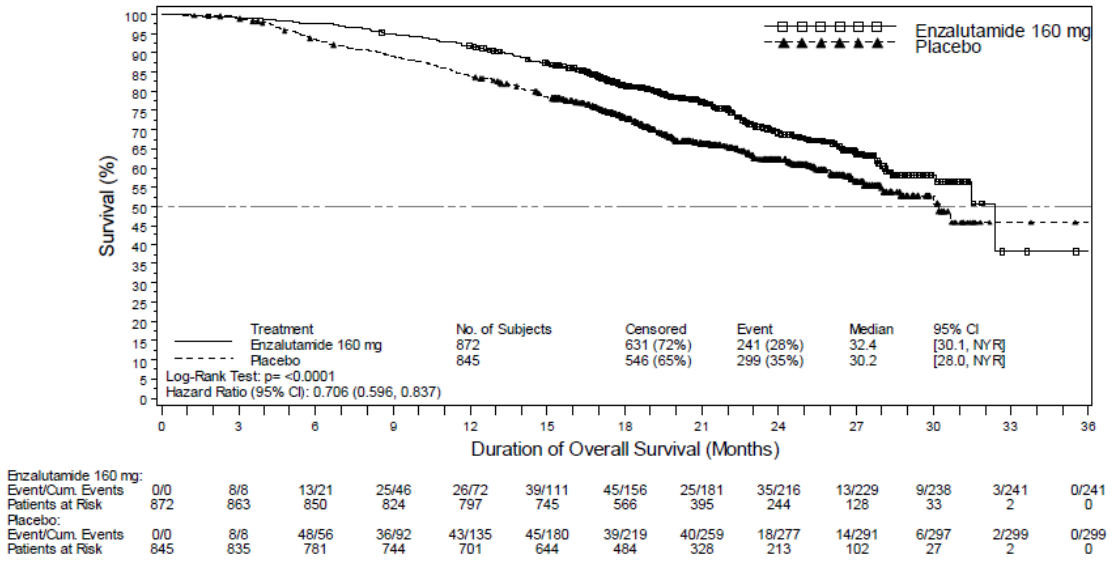


Figure 3: Duration of Overall Survival – Co-primary Analysis (ITT Population, cut-off date of 16 Sep 2013)

The MAH also conducted an updated OS analysis which used a data cut-off date of 15 January 2014. This information was not submitted in the initial application. Study sites were instructed to update survival status and a formal survival sweep was not conducted. Information was available for the majority of patients remaining in the study.

These updated survival data include the following:

- Approximately 4 additional months of survival follow-up data;

- 116 additional deaths (58 deaths in each group);
- 6 additional lost to follow-up patients;
- Remaining 1037 censored patients have their last known alive date within 30 days from the data cut-off date of 15 Jan 2014.

Using the data cut-off date of 15 January 2014, a total of 656 deaths were available for analysis, including 299/872 deaths (34.3%) in the enzalutamide group and 357/845 (42.2%) in the placebo group. Patients who were alive at the time of the data cut-off date were censored at the last date known to be alive. For patients with any data (e.g., adverse events, laboratory values, concomitant medications, vital signs, etc.) in the clinical database after the 15 Jan 2014 data cut-off date, the last date known alive was set to 15 January 2014.

Table 17: Updated Duration of Overall Survival (ITT Population)

Overall Survival at Data Analysis Cutoff Date	Enzalutamide (N = 872)	Placebo (N = 845)	Enzalutamide vs Placebo
Survival status			
Death	299 (34.3%)	357 (42.2%)	
Censored[a]	573 (65.7%)	488 (57.8%)	
Alive at data analysis cutoff date	564 (64.7%)	473 (56.0%)	
Lost to follow-up	9 (1.0%)	15 (1.8%)	
Duration of overall survival (months)[a,b]			
N	872	845	
Censored	573 (65.7%)	488 (57.8%)	
25th percentile	22.1	17.4	
Median (95% CI)	NYR (31.7, NYR)	31.0 (28.9, NYR)	
75th percentile	NYR	NYR	
Hazard ratio (95% CI)[c]			0.730 (0.626, 0.852)
Median follow-up time based on reverse Kaplan-Meier estimates - all patients (months)	26.2	26.5	

Source: [Table 14.2.1.1]
The data cutoff date is 15 Jan 2014.
[a] Patients who were not known to have died at the analysis date are censored at date last known alive or data analysis cutoff date, whichever occurs first.
[b] Based on Kaplan-Meier estimates.
[c] The hazard ratio is based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favoring enzalutamide.
ITT, intent-to-treat; NYR, not yet reached.

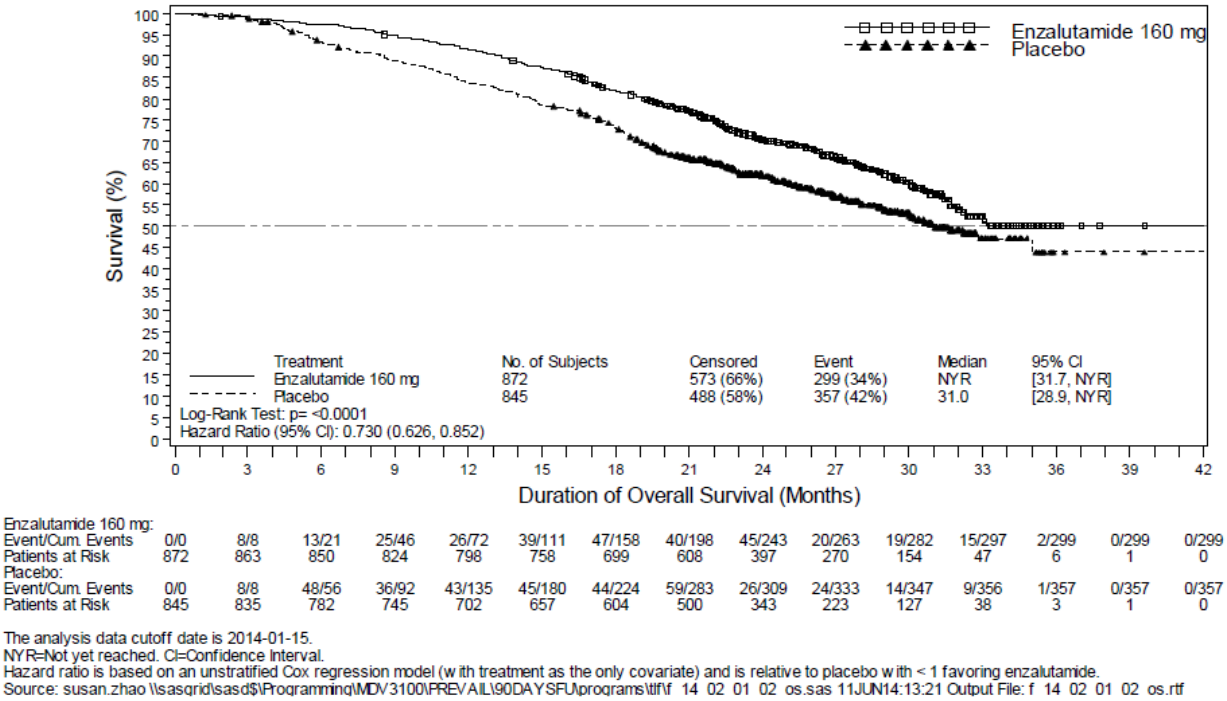


Figure 4: Kaplan-Meier Curves for Duration of Overall Survival – Co-Primary Analysis (updated) - ITT population)

Table 18: MDV3100-03 Post-baseline Antineoplastic Therapy Use (ITT Population, data cut-off date 16 September 2013)

Postbaseline Antineoplastic Therapy Use	Enzalutamide (N = 872)	Placebo (N = 845)
Patients taking any postbaseline antineoplastic therapy	382 (43.8%)	642 (76.0%)
Patients taking any of the following postbaseline antineoplastic therapies with demonstrated overall survival benefit	351 (40.3%)	594 (70.3%)
Docetaxel	286 (32.8%)	479 (56.7%)
Abiraterone acetate[a]	179 (20.5%)	385 (45.6%)
Cabazitaxel	51 (5.8%)	110 (13.0%)
Sipuleucel-T	12 (1.4%)	10 (1.2%)
Enzalutamide	9 (1.0%)	37 (4.4%)

Source: [MDV3100-03 Table 14.1.12]
[a] Concomitant use was allowed before study drug discontinuation in patients with confirmed radiographic progression or a skeletal-related event.
ITT, intent-to-treat.

Co-primary endpoint rPFS

The data cut-off date for the primary rPFS analysis was 6 May 2012, at which time 439 rPFS centrally determined events were reported. Patients randomized after the data cut-off date (N = 84) were not included in the analysis. Overall compliance with submission of radiographic scans to the central reader was > 98% (percentage of all scans performed that were received for central review) and the median time to each scheduled tumour assessment time point was nearly identical between treatment groups.

Table 19: MDV3100-03 Duration of rPFS - Coprimary Analysis Based on Independent Central Review (ITT Population)

Radiographic Progression-Free Survival Follow-Up	Enzalutamide (N = 832)	Placebo (N = 801)	Enzalutamide vs Placebo
rPFS status			
Events[a]	118 (14.2%)	321 (40.1%)	
Radiographic progression	105 (12.6%)	295 (36.8%)	
Bone progression first	36 (4.3%)	111 (13.9%)	
Soft tissue progression first	66 (7.9%)	168 (21.0%)	
Concurrent bone and soft tissue progression	3 (0.4%)	16 (2.0%)	
Death without documented radiographic progression	13 (1.6%)	26 (3.2%)	
Censored[b]	714 (85.8%)	480 (59.9%)	
Duration of rPFS (months)[b,c]			
Censored	714 (85.8%)	480 (59.9%)	
25th percentile	9.5	1.9	
Median (95% CI)	NYR (13.8, NYR)	3.9 (3.7, 5.4)	
75th percentile	NYR	8.3	
P-value (unstratified)			< 0.0001
Hazard ratio (95% CI)[d]			0.186 (0.149, 0.231)
Median follow-up time based on reverse Kaplan-Meier estimates – all patients (months)	5.4	3.6	

Source: [Module 2.7.3, Table 2.7.3.3.1.3.2.2-1]
The analysis data cutoff date is 06 May 2012. Patients randomized after the data cutoff date are not included in the analysis.
[a] Based on the earliest contributing event (radiographic progression or death due to any cause within 168 days after treatment discontinuation).
[b] Patients who were not known to have had an rPFS event at the time of analysis data cutoff are censored at date of last assessment showing no objective evidence of radiographic progression prior to scan modality change, new antineoplastic treatment, initiation of radiation therapy for prostate cancer, skeletal-related event, treatment discontinuation, and 2 or more consecutive missed tumor assessments.
[c] Based on Kaplan-Meier estimates.
[d] The hazard ratio is based on a Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favoring enzalutamide.
ITT, intent-to-treat; NYR, not yet reached; rPFS, radiographic progression-free survival.

Figure 5: Duration of rPFS – Co-primary Analysis Based on Independent Central Review (ITT Population)

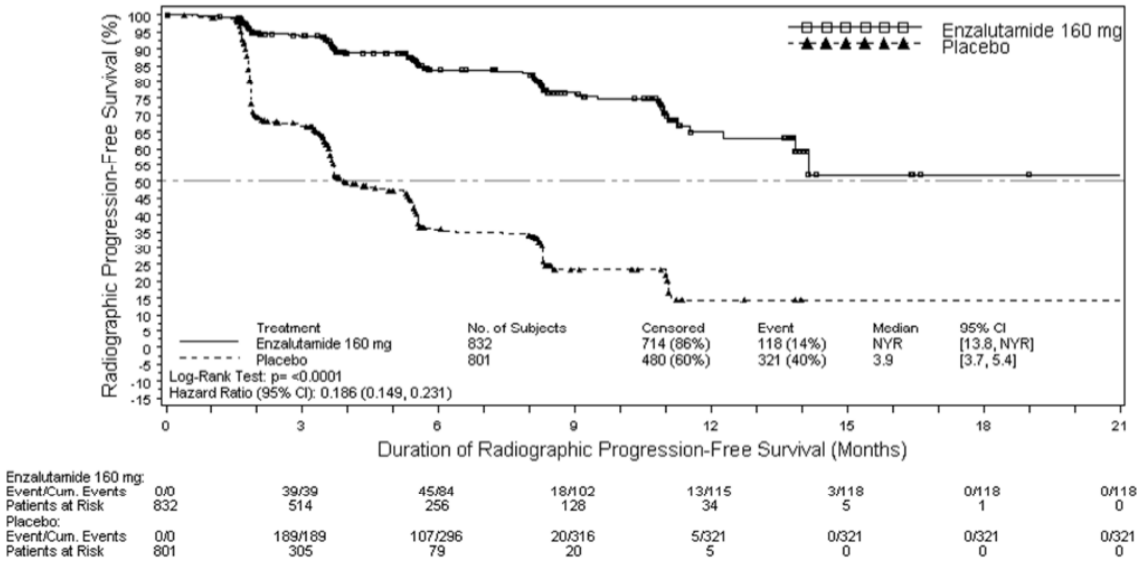


Table 20: MDV3100-03 Concordance between Independent Central Review and Investigator Assessment (ITT Population)

Investigator Assessments	Independent Central Review	
	Progressive Disease (N = 483)	Nonprogressive Disease (N = 1150)
Overall total (N = 1633)		
Progressive disease (N = 451)	365 (22.4%)	86 (5.3%)
Nonprogressive disease (N = 1182)	118 (7.2%)	1064 (65.2%)
Overall concordance with central assessments	87.6%	
Enzalutamide (N = 832)		
Progressive disease (N = 126)	88 (10.6%)	38 (4.6%)
Nonprogressive disease (N = 706)	38 (4.6%)	668 (80.3%)
Overall concordance with central assessments	90.9%	
Placebo (N = 801)		
Progressive disease (N = 325)	277 (34.6%)	48 (6.0%)
Nonprogressive disease (N = 476)	80 (10.0%)	396 (49.4%)
Overall concordance with central assessments	84.0%	

Source: [Table 14.2.3.10]
The analysis data cutoff date is 06 May 2012. Patients randomized after the data cutoff date are not included in the analysis.
Overall concordance was calculated as (concordance for progressive disease) + (concordance for nonprogressive disease).
ITT, intent-to-treat.

The primary rPFS results were shown to be robust through pre-specified sensitivity analyses evaluating the effect of various censoring rules, such as inclusion of all deaths rather than deaths within 168 days of treatment discontinuation, requirement for soft tissue confirmation before week 13, and other analyses censoring for clinical progression events (hazard ratios ranging from 0.174-0.234, all $p < 0.0001$). In addition, an analysis of rPFS using investigator assessments through the overall survival data cut-off date (16 Sep 2013) and including all randomized patients showed consistent findings in favour of enzalutamide treatment (HR = 0.307, 95% CI: 0.267, 0.353, $p < 0.0001$). In this more mature analysis, the median duration of rPFS was 19.7 months for patients receiving enzalutamide (95% CI: 18.1, 22.3) compared with 5.4 months (95% CI: 4.2, 5.6) for patients receiving placebo.

Secondary efficacy results

- Time to first skeletal-related event

Table 21: MDV3100-03 Incidence and Time to First Skeletal-Related Event - Secondary Efficacy Analysis (ITT Population)

Skeletal-Related Event Follow-Up	Enzalutamide (N = 872)	Placebo (N = 845)	Enzalutamide vs Placebo
Skeletal-related event status			
Events[a]	278 (31.9%)	309 (36.6%)	
Radiation to bone	181 (65.1%)	208 (67.3%)	
Surgery to bone	11 (4.0%)	11 (3.6%)	
Pathological bone fracture	39 (14.0%)	31 (10.0%)	
Spinal cord compression	39 (14.0%)	40 (12.9%)	
An initiation/change of antineoplastic therapy required to treat bone pain from prostate cancer	16 (5.8%)	29 (9.4%)	
Censored[b]	594 (68.1%)	536 (63.4%)	
Time to first skeletal-related event (months)[b,c]			
Censored	594 (68.1%)	536 (63.4%)	
25th percentile	16.6	10.1	
Median (95% CI)	31.1 (29.5, NYR)	31.3 (23.9, NYR)	
75th percentile	NYR	NYR	
P-value (unstratified)			< 0.0001
Hazard ratio (95% CI)[d]			0.718 (0.610, 0.844)
Median follow-up time based on reverse Kaplan-Meier estimates (months)	20.8	19.3	

Source: [Table 14.2.3.1]

[a] Based on the earliest contributing event. Patients can be summarized for more than 1 type of event but are counted only once for each type of event.

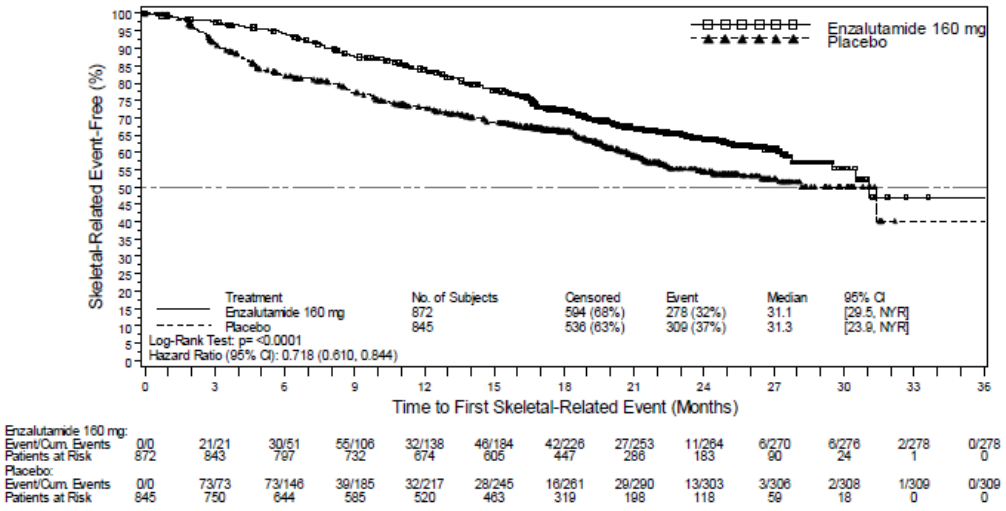
[b] Patients who have not had skeletal-related event at the time of analysis data cutoff are censored at date of last assessment indicating no evidence of skeletal-related event.

[c] Based on Kaplan-Meier estimates.

[d] Based on a Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favoring enzalutamide.

ITT, intent-to-treat; NYR, not yet reached.

Figure 6: Time to first skeletal-related event - Secondary Efficacy Analysis (ITT Population)



- Time to Initiation of Cytotoxic Chemotherapy

Table 22: MDV3100-03 Time to Initiation of Cytotoxic Chemotherapy - Secondary Efficacy Analysis (ITT Population)

Time to Initiation of Cytotoxic Chemotherapy	Enzalutamide (N = 872)	Placebo (N = 845)	Enzalutamide vs Placebo
Initiation of cytotoxic chemotherapy status			
Events	308 (35.3%)	515 (60.9%)	
Docetaxel first	276 (31.7%)	469 (55.5%)	
Cabazitaxel first	15 (1.7%)	27 (3.2%)	
Other chemo first	19 (2.2%)	21 (2.5%)	
Censored[a]	564 (64.7%)	330 (39.1%)	
Time to initiation of cytotoxic chemotherapy (months)[a,b]			
Censored	564 (64.7%)	330 (39.1%)	
25th percentile	15.3	4.9	
Median (95% CI)	28.0 (25.8, NYR)	10.8 (9.7, 12.2)	
75th percentile	NYR	28.8	
P-value (unstratified)			< 0.0001
Hazard ratio (95% CI)[c]			0.349 (0.303, 0.403)
Median follow-up time based on reverse Kaplan-Meier estimates (months)	19.6	19.4	

Source: [Table 14.2.3.3]

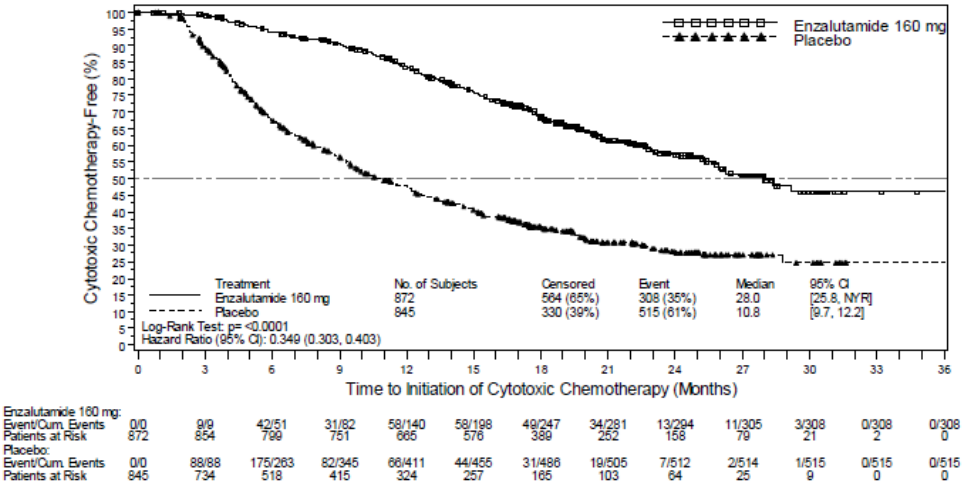
[a] Patients who did not start cytotoxic chemotherapy at the time of analysis data cutoff are censored at date of last assessment indicating no evidence of cytotoxic chemotherapy usage.

[b] Based on Kaplan-Meier estimates.

[c] Based on a Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favoring enzalutamide.

ITT, intent-to-treat; NYR, not yet reached.

Figure 7: Time to initiation of cytotoxic chemotherapy – secondary efficacy analysis (ITT population)



- Time to PSA Progression

Table 23: MDV3100-03 Time to PSA Progression - Secondary Efficacy Analysis (ITT Population)

Time to Prostate-Specific Antigen Progression	Enzalutamide (N = 872)	Placebo (N = 845)	Enzalutamide vs Placebo
PSA progression status			
Events[a]	532 (61.0%)	548 (64.9%)	
Censored[b]	340 (39.0%)	297 (35.1%)	
Time to PSA progression (months)[b,c]			
Censored	340 (39.0%)	297 (35.1%)	
25th percentile	5.7	2.8	
Median (95% CI)	11.2 (11.1, 13.7)	2.8 (2.8, 2.9)	
75th percentile	NYR	4.6	
P-value (unstratified)			< 0.0001
Hazard ratio (95% CI)[d]			0.169 (0.147, 0.195)
Median follow-up time based on reverse Kaplan-Meier estimates (months)	19.4	5.5	

Source: [Table 14.2.3.5]

[a] Based on PSA progression compliant with Prostate Cancer Clinical Trials Working Group 2 criteria. For patients with PSA declines at week 13, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained at least 3 weeks later. For patients without PSA decline at week 13, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above baseline is documented, which is confirmed by a second consecutive value at least 3 weeks later. PSA progression can only be declared on or after the week 13 assessment.

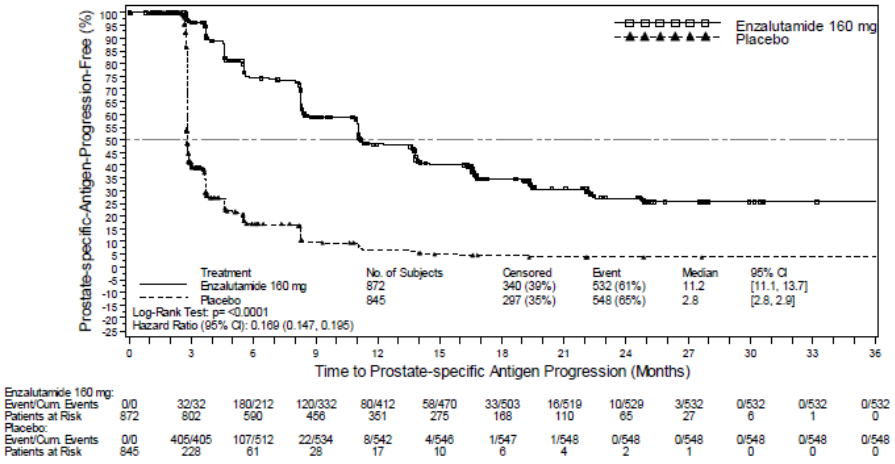
[b] Patients who did not have confirmed PSA progression at the time of analysis data cutoff are censored at date of last assessment indicating no evidence of confirmed PSA progression.

[c] Based on Kaplan-Meier estimates.

[d] Based on a Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favoring enzalutamide.

ITT, intent-to-treat; NYR, not yet reached; PSA, prostate-specific antigen.

Figure 8: MDV3100-03 Time to PSA Progression - Secondary Efficacy Analysis (ITT Population)



- PSA Response ≥ 50%

Table 24: MDV3100-03 PSA Response ≥ 50% - Secondary Efficacy Analysis (Evaluable ITT Population)

Prostate-Specific Antigen Response	Enzalutamide (N = 872)	Placebo (N = 845)	Enzalutamide vs Placebo
Patients with PSA values at baseline	872 (100.0%)	844 (99.9%)	
With at least 1 postbaseline PSA assessment	854 (97.9%)	777 (92.0%)	
No postbaseline assessment	18 (2.1%)	67 (7.9%)	
Change in PSA from baseline to PSA nadir (confirmed)[a]			
N	854	777	
Responders (≥ 50% reduction)	666 (78.0%)	27 (3.5%)	
Nonresponders	188 (22.0%)	750 (96.5%)	
95% CI for response rate[b]	75.1%-80.7%	2.3%-5.0%	
Difference in response rate (95% CI)[c]			74.51% (71.45, 77.57%)
P-value[d]			< 0.0001

Source: [Table 14.2.3.7]
Evaluable ITT population includes all patients randomly assigned to treatment with PSA values at baseline and at least 1 postbaseline assessment.
[a] Confirmation required a subsequent assessment that was consecutive and conducted at least 3 weeks later.
[b] Based on exact binomial 95% CI (Clopper-Pearson).
[c] Enzalutamide minus placebo, CI based on standard normal approximation.
[d] Based on unstratified Cochran-Mantel-Haenszel score test.
ITT, intent-to-treat; PSA, prostate-specific antigen.

- Best Overall Soft Tissue Response

Table 25: MDV3100-03 Best Overall Soft Tissue Response as Assessed by Investigators per RECIST 1.1 – Secondary Efficacy Analysis (ITT Population with Measurable Disease)

Best Overall Soft Tissue Response for Study	Enzalutamide (N = 396)	Placebo (N = 381)	Enzalutamide vs Placebo
Patients with any postbaseline soft tissue assessment	382 (96.5%)	353 (92.7%)	
Patients with no postbaseline assessment	14 (3.5%)	28 (7.3%)	
Best overall response for the study[a]			
Complete response (CR)	78 (19.7%)	4 (1.0%)	
Partial response (PR)	155 (39.1%)	15 (3.9%)	
Stable disease (SD)	128 (32.3%)	210 (55.1%)	
Progressive disease (PD)	21 (5.3%)	124 (32.5%)	
Nonevaluable (NE)	14 (3.5%)	28 (7.3%)	
Best objective response (CR or PR)[b]	233 (58.8%)	19 (5.0%)	
95% CI for objective response rate[c]	53.81-63.73%	3.03-7.68%	
Difference in objective response rate (95% CI)[d]			53.85% (48.53, 59.17%)
P-value[e]			< 0.0001

Source: [Table 14.2.3.8.1]
Only patients with measurable soft tissue disease (ie, at least 1 target lesion identified per RECIST 1.1) at screening are included in this analysis. All percentages are based on number of patients with measurable soft tissue disease at screening in each treatment group.
[a] Response categories are based on target, nontarget, and new lesions. No confirmation is required. Patients with no postbaseline assessment are included in the category of nonevaluable.
[b] The best overall soft tissue objective response is defined as PR or CR based on investigator assessments of target, nontarget, and new lesions while on study treatment.
[c] Enzalutamide minus placebo, based on exact binomial 95% CI (Clopper-Pearson).
[d] Based on standard normal approximation.
[e] Based on unstratified Cochran-Mantel-Haenszel score test.
ITT, intent-to-treat; RECIST, Response Evaluation Criteria in Solid Tumors.

Exploratory Efficacy Results

- PSA Response ≥ 90%

Table 26: Best PSA Reduction Rate (Decrease From Baseline ≥ 90%) (Evaluable ITT Population)

Best Prostate-Specific Antigen Response	Enzalutamide (N = 872)	Placebo (N = 845)	Enzalutamide vs Placebo
Patients with PSA values at baseline	872 (100.0%)	844 (99.9%)	
With any postbaseline PSA assessment	854 (97.9%)	777 (92.0%)	
No postbaseline assessment	18 (2.1%)	67 (7.9%)	
Change in PSA from baseline to PSA nadir (confirmed)[a]			
N	854	777	
Responders (≥ 90% reduction)	400 (46.8%)	9 (1.2%)	
Nonresponders	454 (53.2%)	768 (98.8%)	
95% CI for response rate[b]	43.4-50.2%	0.5-2.2%	
Difference in response rate (95% CI)[c]			45.68% (42.25, 49.11%)
P-value[d]			< 0.0001

Source: [MDV3100-03 Table 14.2.4.6]
Evaluable ITT population includes all patients randomly assigned to treatment with PSA values at baseline and at least 1 postbaseline assessment.
[a] Confirmation required a subsequent consecutive assessment conducted at least 3 weeks later.
[b] Based on exact binomial 95% CI (Clopper-Pearson).
[c] Enzalutamide minus placebo, CI based on standard normal approximation.
[d] Based on unstratified Cochran-Mantel-Haenszel score test.
ITT, intent-to-treat; PSA, prostate-specific antigen.

- Time to First Post-baseline Antineoplastic Therapy

Table 27: Time to First Post-baseline Antineoplastic Therapy - Exploratory Efficacy Analysis (ITT Population)

Follow-Up of Postbaseline Antineoplastic Therapy	Enzalutamide (N = 872)	Placebo (N = 845)	Enzalutamide vs Placebo
Postbaseline antineoplastic therapy status			
Events	382 (43.8%)	642 (76.0%)	
Censored[a]	490 (56.2%)	203 (24.0%)	
Time to postbaseline antineoplastic therapy (months)[a,b]			
Censored	490 (56.2%)	203 (24.0%)	
25th percentile	13.6	4.1	
Median (95% CI)	22.8 (20.5, 25.2)	7.4 (6.6, 8.2)	
75th percentile	NYR	14.6	
P-value (unstratified)			< 0.0001
Hazard ratio (95% CI)[c]			0.273 (0.240, 0.311)
Median follow-up time based on reverse Kaplan-Meier estimates – all patients (months)	19.8	19.4	

Source: [MDV3100-03 Table 14.2.4.4]
Postbaseline antineoplastic therapy consists of cytotoxic, hormonal, or investigational therapy.
[a] Patients who had no postbaseline antineoplastic therapy at the time of analysis data cutoff are censored at date of last assessment with no use of postbaseline antineoplastic therapy.
[b] Based on Kaplan-Meier estimates.
[c] Based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favoring enzalutamide.
ITT, intent-to-treat; NYR, not yet reached.

- Quality of Life: Time to Degradation of FACT-P

The FACT-P was only collected during the treatment period. As a result, the median follow-up times based on reverse Kaplan-Meier estimation corresponded to treatment exposure time and were 16.6 months in the enzalutamide group and 5.6 months in the placebo group.

Table 28: Time to Degradation of Functional Assessment of Cancer Therapy-Prostate (ITT Population)

FACT-P Total Score	Enzalutamide (N = 872)	Placebo (N = 845)	Enzalutamide vs Placebo
Degradation of FACT-P status			
Events	456 (52.3%)	409 (48.4%)	
Censored[a]	416 (47.7%)	436 (51.6%)	
Time to degradation of FACT-P (months)[a,b]			
Censored	416 (47.7%)	436 (51.6%)	
25th percentile	2.8	2.7	
Median (95% CI)	11.3 (11.1, 13.9)	5.6 (5.5, 5.6)	
75th percentile	NYR	16.6	
P-value (unstratified)			< 0.0001
Hazard ratio (95% CI)[c]			0.625 (0.542, 0.720)
Median follow-up time based on reverse Kaplan-Meier estimates - all patients (months)	16.6	5.6	

Source: [MDV3100-03 Table 14.2.4.1.2]
Degradation of FACT-P is defined as at least a 10-point decrease from baseline in the total score.
[a] Patients with no score degradation at the time of analysis data cutoff were censored at the date of the last assessment showing no degradation.
[b] Based on Kaplan-Meier estimates.
[c] Based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favoring enzalutamide.
ITT, intent-to-treat; NYR, not yet reached.

Statistically significant results ($p \leq 0.0001$) were also demonstrated in time to degradation of each of the 5 individual domains, defined as a decrease in at least 3 points from baseline in the domain. These domains assess physical well-being, social/family well-being, emotional well-being, functional well-being, and prostate cancer symptoms (hazard ratio range, 0.664-0.745).

- Quality of Life: Summary of the European Quality of Life 5-Domain Scale

As specified in the statistical analysis plan, no statistical tests were performed on the differences in quality of life as measured by the EQ-5D between treatment groups or over time. Summary data throughout the study are difficult to interpret given the decreasing number of patients completing the questionnaire over time, especially in the placebo group.

After week 25, the differences in the number of patients completing the assessment between groups is too large to provide meaningful comparisons. Overall through week 25, patients treated with enzalutamide had numerically higher quality of life scores across all domains as measured by the EQ-5D compared with patients treated with placebo

- Quality of Life: Pain Progression as Assessed by the Brief Pain Inventory

At baseline, the mean/median pain intensity score was 0.8/0.3 in the enzalutamide group and 0.7/0.0 in the placebo group. At month 6, the mean/median pain intensity score was 1.0/0.0 in the enzalutamide group and 1.2/0.5 in the placebo group. At month 6, 31.8% of the enzalutamide group had progression of pain compared with 37.2% of the placebo group. The difference in the rate of pain progression between treatment groups (enzalutamide minus placebo; 5.35%) was not statistically significant based on an unstratified Cochran-Mantel-Haenszel score test ($p = 0.082$). At month 6, the mean change from baseline for each component of the pain intensity score was numerically less in the enzalutamide group compared with the placebo group. However, less than half of the placebo group remained on study and completed a baseline and week 25 BPI assessment (42.4% compared with 80.0% of the enzalutamide group) and overall pain intensity scores were generally very low at each assessment (median scores of 0, mean < 2 for each question).

Similarly, pain interference scores evaluating the effect of pain across 7 different daily activities were low in both groups at baseline (median score of 0 at for each domain; mean score of < 1 for each domain); however, the change from baseline in mean pain interference scores at month 6 was numerically less in the enzalutamide group compared with the placebo group for each of the 7 domains. Mean pain interference scores, defined as the average of each of the 7 domains, were calculated at baseline and month 6. Patients treated with enzalutamide had a lower percentage change from baseline to month 6 in mean pain interference scores. No statistical comparisons were made between treatment groups in evaluating pain interference.

Ancillary analyses

Sub-group analyses

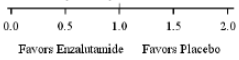
Subgroup analyses of overall survival and rPFS were performed to determine if the treatment effect was consistent among subgroups. The same methodology used for overall survival and rPFS respectively, was applied to each subgroup which was defined by the following variables:

- Baseline ECOG performance status (0 or 1)
- Age category (< 75 and ≥ 75 years)
- Geographic region (North America, Europe, and rest of world)
- Total Gleason score (≤ 7 and ≥ 8) at diagnosis
- Type of progression (PSA progression only vs. radiographic progression with or without PSA progression) at study entry
- Visceral disease (lung and/or liver) based on both target and nontarget lesions at screening (y/n)
- Baseline PSA value (≤ median vs. > median)
- Baseline LDH value (≤ median vs. > median)
- Baseline haemoglobin value (≤ median vs. > median)

“Baseline bisphosphonate or denosumab use (yes or no)” was added to the subgroup analysis for rPFS.

Table 29: MDV3100-03 Forest Plot for Duration of Overall Survival: Subgroup Analysis (ITT Population)

Subgroup	Number of Patients Enzalutamide / Placebo	Overall Survival Median (mo) Enzalutamide / Placebo	Hazard Ratio for Death	(95% CI)
All Patients	872 / 845	32.4 / 30.2		0.71 (0.60-0.84)
ECOG Performance Status at Baseline=0	584 / 585	32.4 / NYR		0.70 (0.56-0.87)
ECOG Performance Status at Baseline=1	288 / 260	27.9 / 26.9		0.69 (0.53-0.90)
Age < 75	555 / 553	31.5 / NYR		0.77 (0.62-0.96)
Age >=75	317 / 292	32.4 / 25.1		0.60 (0.47-0.79)
Geographic Region – North America	218 / 208	32.4 / NYR		0.83 (0.60-1.16)
Geographic Region - Europe	465 / 446	NYR / 28.0		0.68 (0.54-0.86)
Geographic Region - Rest of the World	189 / 191	NYR / 28.7		0.62 (0.42-0.92)
Total Gleason Score at Diagnosis <= 7	414 / 385	NYR / 30.0		0.66 (0.51-0.85)
Total Gleason Score at Diagnosis >= 8	424 / 423	31.5 / 30.2		0.77 (0.60-0.97)
Type of Progression at Study Entry– PSA Progression Only	375 / 369	NYR / NYR		0.60 (0.45-0.82)
Type of Progression at Study Entry – Radiographic Progression with or without PSA Progression	475 / 451	30.1 / 27.3		0.75 (0.61-0.92)
Visceral Disease (Lung and/or Liver) at Screening – Yes	98 / 106	27.8 / 22.8		0.82 (0.55-1.23)
Visceral Disease (Lung and/or Liver) at Screening - No	774 / 739	NYR / 30.2		0.69 (0.57-0.83)
Baseline PSA Value (ng/mL) <= Median (49.60)	420 / 440	NYR / NYR		0.78 (0.58-1.05)
Baseline PSA Value (ng/mL) > Median (49.60)	452 / 404	28.0 / 23.0		0.61 (0.49-0.75)
Baseline Lactate Dehydrogenase Value (U/L) <= Median (185)	443 / 423	NYR / NYR		0.57 (0.43-0.76)
Baseline Lactate Dehydrogenase Value (U/L) > Median (185)	428 / 421	30.1 / 26.0		0.80 (0.65-0.99)
Baseline Hemoglobin Value (g/L) <= Median (130)	455 / 416	28.4 / 24.5		0.69 (0.55-0.85)
Baseline Hemoglobin Value (g/L) > Median (130)	417 / 429	NYR / NYR		0.68 (0.52-0.91)

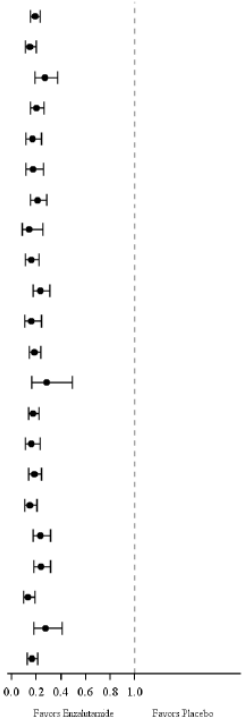


Source: MDV3100-03 Figure 14.2.1.5

Rest of world includes Australia, Japan, Singapore, and South Korea. Hazard ratio is based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favouring enzalutamide. ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; mo, months; NYR, not yet reached; PSA, prostate-specific antigen.

Table 30: MDV3100-03 Forest Plot for Duration of rPFS Based on Independent Central Review and Data Analysis Cut-off Date for the Interim Analysis - Subgroup Analysis (ITT Population)

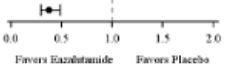
Subgroup	Number of Patients Enzalutamide / Placebo	rPFS Median (mo) Enzalutamide / Placebo	Hazard Ratio for rPFS (95% CI)
All Patients	832 / 801	NYR / 3.9	0.19 (0.15-0.23)
ECOG Performance Status at Baseline=0	557 / 549	NYR / 3.7	0.15 (0.11-0.20)
ECOG Performance Status at Baseline=1	275 / 252	14.1 / 4.0	0.27 (0.19-0.37)
Age < 75	529 / 517	NYR / 4.6	0.20 (0.15-0.26)
Age >=75	303 / 284	NYR / 3.7	0.17 (0.12-0.24)
Geographic Region – North America	214 / 204	NYR / 4.8	0.17 (0.12-0.25)
Geographic Region - Europe	456 / 435	13.8 / 3.8	0.21 (0.15-0.28)
Geographic Region - Rest of the World	162 / 162	NYR / 3.7	0.14 (0.08-0.25)
Total Gleason Score at Diagnosis <= 7	401 / 370	14.1 / 5.3	0.16 (0.11-0.22)
Total Gleason Score at Diagnosis >= 8	399 / 394	NYR / 3.7	0.23 (0.17-0.31)
Type of Progression at Study Entry– PSA Progression Only	348 / 341	NYR / 5.6	0.16 (0.11-0.24)
Type of Progression at Study Entry – Radiographic Progression with or without PSA Progression	464 / 435	14.1 / 3.7	0.18 (0.14-0.24)
Visceral Disease (Lung and/or Liver) at Screening – Yes	97 / 101	NYR / 3.6	0.28 (0.16-0.49)
Visceral Disease (Lung and/or Liver) at Screening - No	735 / 700	14.1 / 4.0	0.17 (0.14-0.22)
Baseline PSA Value (ng/mL) <= Median (51.10)	395 / 411	NYR / 5.5	0.16 (0.11-0.23)
Baseline PSA Value (ng/mL) > Median (51.10)	437 / 389	13.8 / 3.6	0.18 (0.14-0.24)
Baseline LDH Value (U/L) <= Median (185)	427 / 402	14.1 / 4.0	0.14 (0.10-0.20)
Baseline LDH Value (U/L) > Median (185)	404 / 398	NYR / 3.8	0.23 (0.17-0.31)
Baseline Hemoglobin Value (g/L) <= Median (130)	429 / 388	14.1 / 3.7	0.24 (0.18-0.31)
Baseline Hemoglobin Value (g/L) > Median (130)	403 / 413	NYR / 5.3	0.13 (0.09-0.19)
Baseline Bisphosphonate or Denosumab Use - Yes	215 / 222	13.8 / 5.6	0.27 (0.18-0.41)
Baseline Bisphosphonate or Denosumab Use - No	617 / 579	NYR / 3.7	0.16 (0.12-0.21)



The analysis data cutoff date is 06 May 2012. Patients randomized after the data cutoff date are not included in the analysis. Rest of world includes Australia, Japan, Singapore, and South Korea. Hazard ratio is based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favoring enzalutamide. ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; LDH, lactate dehydrogenase; mo, months; NYR, not yet reached; PSA, prostate-specific antigen.

Figure 9: **Forest Plot for Duration of Overall Survival – Subgroup Analysis of Selected Postbaseline Antineoplastic Therapies (ITT Population)**

Subgroup	Number of Patients Enzalutamide / Placebo	Overall Survival Median (mo) Enzalutamide / Placebo	Hazard Ratio for Death (95% CI)
All Patients	872 / 845	32.4 / 30.2	0.71 (0.60-0.84)
Treated With At least 1 of the 6 Selected Postbaseline Antineoplastic Therapies - Yes [1]	352 / 596	27.0 / 30.7	1.31 (1.06-1.63)
Treated With At least 1 of the 6 Selected Postbaseline Antineoplastic Therapies - No [1]	520 / 249	NYR / 23.0	0.29 (0.22-0.38)
Treated With Postbaseline Abiraterone - Yes	179 / 385	28.2 / NYR	1.23 (0.90-1.68)
Treated With Postbaseline Abiraterone - No	693 / 460	NYR / 26.1	0.47 (0.38-0.58)
Treated With Postbaseline Docetaxel - Yes	286 / 479	25.2 / 30.2	1.47 (1.17-1.85)
Treated With Postbaseline Docetaxel - No	586 / 366	NYR / NYR	0.38 (0.29-0.48)



The analysis data cutoff date is 2013-09-16.
Hazard ratio is based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favoring enzalutamide.
[1] The 6 selected postbaseline antineoplastic therapies are Abiraterone, Cabazitaxel, Docetaxel, Enzalutamide, Sipuleucel-t, and Radium-223.
NYR = Not Yet Reached

The following table summarise 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 31: Summary of Efficacy for trial MDV3100-03 (PREVAIL)

Title: PREVAIL: A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naïve Patients With Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy			
Study identifier	MDV3100-03		
Design	Phase 3, Randomized, Double-Blind, Placebo-Controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	28 Sep 2010-16 Sep 2013 (cutoff date) Study ongoing Not applicable Not applicable	
Hypothesis	Superiority		
Treatments groups	Enzalutamide		Enzalutamide (872 subjects)
	Placebo		Placebo (845 subjects)
Endpoints and definitions	Co-Primary endpoint	OS & rPFS	
	Secondary	Time to first skeletal-related event; Time to initiation of cytotoxic chemotherapy; Time to prostate-specific antigen (PSA) progression; PSA response ≥ 50%; Best overall soft tissue response	
	Exploratory	QoL; Emergence of pain relative to baseline at 6 months using the Brief Pain Inventory (BPI) Short Form; Time to first subsequent antineoplastic therapy (cytotoxic or hormonal); PSA response ≥ 90%; PK	
Database lock	Cutoff date (study ongoing) 16.09.2013		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Enzalutamide	Placebo
	Number of subject	872	845
	OS (median; months)	32.4	30.2
	95% CI	30.1, not yet reached	28.0, not yet reached
	OS (median; months) Update Jan 2014	NYR	31.0
	95% CI Update Jan 2014	30.7, not yet reached	28.9, not yet reached
	rPFS (median; months)	Not yet reached	3.9

	95% CI	13.8, not yet reached	3.7, 5.4
	Time to first skeletal-related event (median; months)	31.1	31.3
	95% CI	29.5, not yet reached	23.9, not yet reached
	Time to initiation of cytotoxic chemotherapy (median; months)	28	10.8
	95% CI	25.7, not yet reached	9.7, 12.2
	Time to PSA progression (median; months)	11.2	2.8
	95%CI	11.1, 13.7	2.8, 2.9
Effect estimate per comparison	Co-Primary endpoint; OS	Comparison groups	Enzalutamide vs placebo
		Hazard ratio	0.706
		95% CI	0.596, 0.837
		P-value	< 0.0001
		Hazard ratio (updated 01.2014)	0.730
		95% CI (updated 01.2014)	0.626, 0.852
	Co-Primary; rPFS	Comparison groups	Enzalutamide vs placebo
		Hazard ratio	0.186
		95% CI	0.149, 0.231
		P-value	< 0.0001
Notes	The type I error rate of 0.05 was allocated between the 2 coprimary efficacy endpoints: 0.049 (2-sided) for overall survival and 0.001 (2-sided) for rPFS. The analysis data cutoff date of 16 Sep 2013 was used for all analyses presented in this table, except 06 May 2012 was used for rPFS analyses		

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

The primary data characterising the efficacy of enzalutamide in chemotherapy-naïve men with metastatic prostate cancer that progressed on androgen deprivation therapy arises from the pivotal study in this population (MDV3100-03 in 1717 patients [872 enzalutamide, 845 placebo]). The efficacy of enzalutamide in this population was also assessed in a subset of patients in study S-3100-1-01 (65 chemotherapy-naïve patients of 140 patients enrolled with metastatic CRPC) and CRPC-MDA-1 (12 chemotherapy-naïve patients of 60 patients enrolled with metastatic CRPC).

The efficacy of enzalutamide in patients with metastatic CRPC who previously received docetaxel was primarily assessed in CRPC2 (1199 patients [800 enzalutamide, 399 placebo]), S-3100-1-01 (75 patients of 140 enrolled), CRPC-MDA-1 (44 patients of 60 enrolled), and 9785-CL-0111 (all 38 patients enrolled in the efficacy cohort).

The most well-established endpoints for evaluating the efficacy of enzalutamide in patients with metastatic CRPC are overall survival and rPFS as assessed in the controlled clinical studies, MDV3100-03 and CRPC2. Long-term follow-up for overall survival was not performed in any of the open-label studies, and radiographic data from these studies focused primarily on radiographic response rate. An additional clinically relevant endpoint only obtained within the controlled studies included time to first skeletal-related event. Evaluation of quality of life measures varied between the 2 controlled studies given the different study populations, although both utilised the FACT-P, EQ-5D, and BPI. Best overall soft tissue response was evaluated in MDV3100-03, CRPC2, S-3100-1-01, and 9785-CL-0111. Markers of bone turnover were included in S-3100-1-01 and 9785-CL-0111. Circulating tumour cell counts were included in CRPC2, S-3100-1-01, and 9785-CL-0111, but data were only available from S-3100-1-01 and 9785-CL-0111. PSA response rates were obtained across all studies.

Although initial evidence of efficacy assessed by PSA response rate has been demonstrated in patients with hormone-naïve prostate cancer in study [9785-CL-0321], this comparative section will focus on a discussion of the data from studies of patients with metastatic prostate cancer that progressed on androgen deprivation therapy.

Demographic and baseline characteristics of patients with metastatic CRPC enrolled across the studies were generally well matched. The major differences between the studies were related to the target study population and to prior treatments for prostate cancer: MDV3100-03, the pivotal study for this application, enrolled only chemotherapy-naïve patients with metastatic CRPC; CRPC2 enrolled only patients with metastatic CRPC who previously received docetaxel. The other presented studies enrolled patients with metastatic CRPC without regard to prior chemotherapy. Other differences among the study populations were primarily related to eligibility for each study (eg, inclusion of only Japanese patients in 9785-CL-0111, exclusion of patients with ECOG performance status > 1 in MDV3100-03).

OS

Overall survival was assessed as a primary endpoint in both controlled studies, and was defined as the time from randomization to death due to any cause.

Enzalutamide treatment resulted in a statistically significant reduction in the risk of death compared with placebo treatment in both studies. In MDV3100-03, the unstratified hazard ratio was 0.706 (95% CI: 0.596, 0.837; $p < 0.0001$). In CRPC2, the stratified hazard ratio was 0.631 (95% CI: 0.529, 0.752; $p < 0.0001$).

In both studies, the survival benefit was observed early, with separation of the Kaplan Meier curves 3 to 4 months after randomization. The longer estimated median durations of survival in MDV3100-03 compared with CRPC2 reflect the earlier stage disease of the MDV3100-03 patient population. In MDV3100-03, the estimated medians are considered unstable because of the small number of patients at risk at the times the medians were estimated and shorter duration of follow up for overall survival relative to the estimated medians, both of which contribute to the large variability associated with the medians.

rPFS

Radiographic progression free survival was a coprimary endpoint in MDV3100-03 and a key secondary endpoint in CRPC2. In MDV3100-03, rPFS was defined as the time from randomization to first objective evidence of radiographic progression or death within 168 days of treatment discontinuation, whereas in CRPC2, rPFS was defined as the time from randomization to the earliest objective evidence of disease progression or death due to any cause. Both studies utilized PCWG2 and RECIST 1.1 criteria for determining progression, although in MDV3100-03, radiographic progression was evaluated by

independent blinded central reviewers and by investigators, whereas in CRPC2 radiographic progression was evaluated only by investigators. The 2 studies also utilized different censoring rules, although both studies demonstrated that results were robust to sensitivity analyses evaluating the impact of different censoring conventions

A final important difference in rPFS evaluations between the 2 studies was in the radiographic assessment schedule. In MDV3100-03, on study imaging occurred at weeks 9, 17, 25, and every 12 weeks thereafter whereas in CRPC2, on study imaging occurred at week 13 and every 12 weeks thereafter. This difference allowed for an earlier separation of Kaplan Meier curves in MDV3100-03 compared with CRPC2. In both studies, enzalutamide treated patients had a statistically significant decreased risk of radiographic progression or death. In MDV3100-03, the unstratified hazard ratio was 0.186 (95% CI: 0.149, 0.231; $p < 0.0001$). In CRPC2, the stratified hazard ratio was 0.404 (95% CI: 0.350, 0.466; $p < 0.0001$).

Supportive studies

Study 9785-CL-0111

Study 9785-CL-0111 was a phase 1/2, multicentre, open-label, uncontrolled, dose-escalation study in 47 Japanese patients with metastatic CRPC, including 43 previously treated with docetaxel and 4 chemotherapy-naïve patients. Nine patients were in the dose-escalation cohort and 38 patients were in the dose-expansion cohort used for efficacy analyses. After receiving single doses of enzalutamide 80, 160, or 240 mg, patients received 80 or 160 mg once daily during a multiple-dose period and subsequently commenced long-term dosing with enzalutamide 160 mg/day. Efficacy endpoints included radiographic objective response at day 85, PSA response, circulating tumor cells, and markers of bone turnover. Radiographic response was evaluated by an independent RECIST evaluation committee and by the investigator.

Of the 38 patients in the dose-expansion cohort included in efficacy analyses, the median age was 71.5 years (range, 50-85 years) and all were of Japanese descent. Twenty-five patients (65.8%) entered the study with an ECOG performance status of 0 and 13 (34.2%) had an ECOG performance status of 1. Twenty-nine patients (76.3%) had Gleason scores at diagnosis of 8 to 10 and median PSA at baseline was 65.8 ng/dL. A major difference in this small study population compared with the CRPC2 study population was that most patients received prior treatment with estramustine in addition to prior treatment with docetaxel and had a greater number of prior hormonal treatments.

The radiographic objective response rate (CR or PR) at day 85 was 5.3% as assessed by the independent RECIST evaluation committee and 7.9% as assessed by the investigator. When evaluating best overall radiographic response rates during long-term dosing, the values were 11.1% by the RECIST committee and 5.9% by the investigator. Radiographic disease control rate (CR, PR, or stable disease) at day 85 was 47.4% as assessed by the RECIST committee and 50% as assessed by the investigator. Best overall radiographic disease control rate during long-term dosing was 66.7% as assessed by the RECIST committee and 64.7% by the investigator. Eleven of 38 patients (28.9%) had a ≥ 50% decrease in PSA at the time of nadir; 4 of 38 patients (10.5%) had a ≥ 90% decrease in PSA at the time of nadir.

Of the 38 evaluable patients, 20 patients had favourable circulating tumour cell counts at baseline (< 5 per 7.5-mL blood), and a total of 26 patients had evaluable baseline and post-baseline circulating tumour cell data.

Of the 20 patients with favourable circulating tumour counts at baseline, enzalutamide treatment was associated with maintenance of favourable circulating tumour counts in 53.8% of patients. Of the 18 patients with unfavourable circulating tumour counts at baseline, 9 patients had post-baseline samples.

Of those, enzalutamide treatment was associated with conversion to favourable circulating tumour counts in 5 patients (56%) who had previously received chemotherapy.

Serum markers of bone turnover (bone-specific alkaline phosphatase and urinary N-telopeptide) were variable and mean concentrations did not change substantially over the course of the study.

This study showed the antitumor effects of enzalutamide (160 mg/day) by radiographic response, PSA response, and circulating tumor cells in Japanese patients with metastatic CRPC, the majority of whom previously received docetaxel. The magnitudes of the benefits observed in this study were not as large as those observed in CRPC2; however, this study population was small and uncontrolled and included patients treated with a higher number of previous therapies.

Study 9785-CL-0321

Study 9785-CL-0321 was a phase 2, multicentre, open-label, single-arm efficacy and safety study of enzalutamide 160 mg/day for 24 weeks in patients with prostate cancer who had non-castrate levels of testosterone at study entry. The primary objective was to evaluate PSA response rate ≥ 80% at week 25. Secondary and exploratory efficacy objectives included an evaluation of the effect of enzalutamide on circulating hormones (bone-specific alkaline phosphatase and N-telopeptide), quality of life using the EORTC QLQ-C30 and QLQ-PR25, and objective tumor response (in the subset of patients with metastatic disease). Patients who had clinical benefit at week 25 could continue to receive enzalutamide until objective or clinical disease progression, or occurrence of an unacceptable toxicity at the discretion of the investigator. Sixty-seven men were enrolled; all patients received at least 1 dose of enzalutamide. Of these, 66 of patients were white (98.5%) and 1 was black or African American (1.5%). The median age was 73 years (range, 48-86 years) and the mean duration of prostate cancer was 2.8 years. Tumour was confined to the prostate in 31 patients (46.3%) and Gleason score was 8 to 10 at initial diagnosis in 16 patients (23.9%).

Overall, 62 patients (92.5%) had a PSA response ≥ 80% at week 25. Of the 5 patients categorized as non-responders, 4 patients did not complete 25 weeks of treatment; and 1 patient with a 57.0% PSA decline at week 25 had a 90.7% PSA decline at week 9. Of the 63 patients who completed 25 weeks of treatment, 62 patients (98.4%) had a ≥ 80% decline in PSA. The mean maximum PSA decline was 98.3% through week 25. At week 49 (1 year of treatment), 54 of 67 patients (80.6%) had a PSA response ≥ 80%; the 13 patients considered non-responders were those who did not complete 49 weeks of treatment. All 54 patients (100%) who were on treatment for 1 year had a ≥ 80% decline in PSA from baseline. The mean maximum PSA decline was 99.0% through week 49. At week 25 and week 49, increases were observed in mean bone-specific alkaline phosphatase (14.8% and 12.4%) and N-telopeptide (66.6% and 62.3%). Based on responses to the QLQ-C30, global health status was maintained at week 25 and week 49. At week 25 and week 49, sexual activity and sexual function were decreased, based on limited responses to the QLQ-PR25. Of 26 evaluable patients at week 25, 11.5% had a CR and 19.2% had a PR; and at week 49, 19.2% had a CR and 11.5% had a PR.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The placebo-controlled design of study MDV3100-03 (PREVAIL) is considered acceptable given that there were no other approved treatments in the EU for the intended population at the time of study initiation.

The patients enrolled in this trial were deemed as not yet candidates to receive docetaxel therapy when the study was carried out. Only asymptomatic or mildly symptomatic patients with disease

progression (PSA-Soft tissue-Bone) were recruited. During the study, all patients continued on a LHRH analogue or had prior bilateral orchiectomy. It has therefore been reflected in section 4.2 of the SmPC that medical castration with an LHRH analogue should be continued during treatment of patients not surgically castrated. Patients were allowed to receive Sipuleucel-T during the study. Importantly, concomitant treatment with abiraterone was allowed once patients had either confirmed radiographic progression or a skeletal-related event. Bisphosphonates, palliative therapy including radiation therapy and opiate analgesics were also allowed.

The primary objectives of study MDV3100-03 were to determine the benefit of enzalutamide compared with placebo on overall survival and rPFS. Secondary and exploratory objectives were to determine the benefit of enzalutamide compared with placebo on clinically relevant markers of disease progression and quality of life. The objectives of the study are considered acceptable as well as the endpoints proposed in this setting. The frequency and methods for scheduled assessments of the progression disease (intervals; 4 weeks through week 49 and then every 12 weeks thereafter) is considered acceptable and the use of central radiology review is of value, despite the double blind design. The censoring rules proposed are overall acceptable.

The concurrent interim analysis of overall survival and final analysis of rPFS were consistent with prior regulatory advice.

Between September 2010 and September 2012, 1717 patients were randomized 1:1 to treatment with enzalutamide or placebo across 207 study centres in 22 countries. As of January 2014, placebo treated patients began crossing-over to enzalutamide treatment on an amended MDV3100-03 protocol which could have biased future updates of the data.

The treatment groups were overall well balanced with respect to clinically relevant baseline demographic and disease characteristics. Of note, the percentage of patients with visceral disease was 11.2% and 12.5% in enzalutamide and placebo arms respectively. 2.5% and 3.0% of patients in each arm did not have disease progression per protocol at study entry.

In relation to prior therapy of prostate cancer, about 28 % and 18 % of patients had received 3 and ≥ 4 unique prior hormonal therapy. The number of unique prior hormonal therapies does not represent the number of “lines” and were defined as distinct hormonal drug treatments for prostate cancer that were started prior to randomization.

More than 50% (53.1%) of patients recruited into the trial were in Europe (including Israel). The most common reason for discontinuation for both groups was “Discontinuation due to disease progression” (enzalutamide group: 40.7% vs Placebo group: 68.3%). Of them, both radiographic progression and clinical progression were higher for the placebo group (enzalutamide arm: 32.7% and 9.7% vs Placebo group: 54.6% and 17.8% respectively). Discontinuations due to skeletal-related events were quite similar between arms (5.0% vs 5.4%). 5.6% subjects in the enzalutamide group and 6.0% subjects in the placebo group discontinued treatment due to AEs, which could give an overall impression of the tolerability of the drug.

The protocol of the study was modified several times, especially the fourth amendment was critical. This one was carried out after knowing the results from the study conducted with abiraterone. This was somehow expectable and the changes introduced will likely not modify the conclusions of the study. The second amendment was introduced after 153 patients were randomised. Due to the low number of subjects, a high impact on the results is unlikely.

Efficacy data and additional analyses

Enzalutamide has shown positive results in all the variables studied. Both co-primary endpoints were met. Data on OS with data cut-off date September 2013 clearly indicated a higher life expectancy for patients treated with enzalutamide (HR 0.706, 95% CI: 0.596, 0.837) even though the estimate in terms of medians was not accurate and could not provide a clear reflection of the benefit for the patients due to the immature nature of the data.

The updated analysis (cut-off January 2014; after four additional months and 116 additional deaths; 58 in each group) confirmed the observations from the pre-specified interim analysis (HR 0.730 and HR 0.706 respectively). The updated median overall survival was not yet reached in the enzalutamide group and was 31 months in the placebo group. The data are still considered immature (38 %) although an HR of 0.7 suggests a large treatment benefit. As a consequence, the MAH should submit an OS update together with an update on investigator assessed rPFS no later than September 2015 (see Annex II condition).

This outcome in terms of OS was supported by the vast majority of the subgroups analysed.

Results from the other co-primary endpoint were also positive (rPFS). A total of 118 patients (14.2%) in the enzalutamide group and 321 patients (40.1%) in the placebo group experienced radiographic progression or death within 168 days after study drug discontinuation at the time of the data cut-off date of 6 May 2012 (HR 0.186; 95% CI: 0.149, 0.231). Estimated median duration of rPFS was not yet reached in the enzalutamide group (95% CI: 13.8, not yet reached) and 3.9 months in the placebo group (95% CI: 3.7, 5.4) (see section 5.1 of the SmPC). As expected for this patient population, the rPFS endpoint comprised mainly radiographic progression events (89% enzalutamide group vs 92% placebo group) rather than death events prior to radiographic progression. In general, soft tissue progression was observed before bone progression which may be due to the fact that soft tissue progression required no confirmatory scan as per the protocol but also that metastatic spread involving soft tissue is associated with a more aggressive nature of the disease. Consistent rPFS benefit was observed across all pre-specified patient subgroups (e.g., age, baseline ECOG performance, baseline PSA and LDH, Gleason score at diagnosis, and visceral disease at screening).

Median follow-up time based on reverse Kaplan-Meier estimation was 5.4 months for the enzalutamide group versus 3.6 months for the placebo group. The separation of the curves was clearly shown. Both the subgroup analyses and the sensitivity analyses carried out pointed out in the same direction.

Regarding the use of subsequent therapies there was a higher and earlier use in the placebo group (70.3%) compared with the enzalutamide group (40.3%). While according to the patient disposition a total of 932 patients were considered to have disease progression, a total of 1024 subjects received any post-baseline antineoplastic therapy. This apparent discrepancy is a result of patients in both treatment groups discontinuing treatment for reasons other than disease progression, such as withdrawal of consent, an adverse event or rising prostate-specific antigen (PSA), but then requiring subsequent antineoplastic therapies at some point between discontinuation and the data cut-off date.

Only a small proportion (0.8%) of patients randomized to enzalutamide received concomitant treatment with abiraterone, almost 20% received subsequent treatment with abiraterone, and the majority of patients (79.5%) received neither subsequent nor concomitant treatment with abiraterone. The hazard ratio was less favourable for enzalutamide-treated patients who received subsequent treatment with abiraterone (HR 1.23 [95% CI: (0.89, 1.68)]) and for enzalutamide-treated patients who received subsequent treatment with docetaxel (HR 1.47 [95% CI: (1.17, 1.85)]). Notwithstanding the inherent bias associated to these analyses, a possible cross-resistance among treatments cannot

be totally ruled out. Results of ongoing studies may provide further evidence on the sequential use of abiraterone-enzalutamide. “Patients with metastatic castration-resistant prostate cancer previously treated with abiraterone” has been included as missing information in the RMP and a study will collect data on the efficacy and safety of enzalutamide in these patients.

Regarding the secondary endpoints, time to initiation of cytotoxic chemotherapy, time to first skeletal-related event, best overall soft tissue response, time to PSA progression, and PSA response ≥ 50% were in favour of enzalutamide. The median time to initiation of cytotoxic chemotherapy was 28.0 months for patients receiving enzalutamide and 10.8 months for patients receiving placebo (HR=0.350, 95% CI: [0.303, 0.403], p<0.0001) (see section 5.1 of the SmPC).

Exploratory analyses were in line with the results observed from primary and secondary endpoints. Even though data of QoL should be cautiously interpreted, overall, they seemed to favour enzalutamide.

The apparent imbalance between the two arms with regard to deaths as primary reason for study drug discontinuation with more events in the enzalutamide arm (17 patients) compared to placebo (7 patients) may be due to the longer time on study for enzalutamide treated patients compared with placebo-treated patients, as the median time on enzalutamide treatment was 3.6-fold longer than the median time on placebo treatment.

Comparison between the two phase III pivotal studies (MDV3100-03 and CRPC2) is marked by the different prognosis of patients recruited in each study, making difficult to draw conclusions in terms of consistency. However, regardless of the setting studied in the different studies, it can be concluded that the efficacy of enzalutamide has been shown in the docetaxel naïve subjects as it was shown in patients previously treated with docetaxel.

In relation to the supportive studies provided, they can only be deemed exploratory in nature as they refer to a different population.

2.4.4. Conclusions on the clinical efficacy

The efficacy of enzalutamide has been reasonably shown in 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.

The CHMP considers the following measure necessary to address issues related to efficacy:

- In order to address the uncertainties regarding long-term efficacy, the MAH should submit updated results from the PREVAIL study and more specifically updated OS and investigator assessed rPFS data. The MAH should present the data based on the latest time point where investigator assessed rPFS data according to the study protocol is available and where data is not significantly affected by cross-over. The due date for the submission of these data is 30/09/2015.

2.5. Clinical safety

2.5.1. Introduction

The safety profile of enzalutamide in patients with metastatic CRPC is derived primarily from 9 clinical studies including 3702 patients. These studies include two randomized, placebo-controlled, phase 3 studies (MDV3100-03 and CRPC2), 4 open-label safety and tolerability studies (S-3100-1-01, CRPC-MDA-1, 9785-CL-0111, 9785-CL-0121), an open-label relative bioavailability study (9785-CL-0003), an open-label drug-drug interaction study (9785-CL-0007), and an expanded access protocol (9785-CL-0401). Together these studies include 2509 patients treated with enzalutamide plus

standard of care and 1243 patients treated with placebo plus standard of care (50 patients later crossed over to open-label enzalutamide treatment in CRPC2). Of the 2509 enzalutamide-treated patients in the integrated safety population, 967 patients (38.5%) did not receive prior docetaxel and are considered chemotherapy-naïve, and 1542 patients (61.5%) previously received docetaxel (or another cytotoxic chemotherapy). All patients received ongoing androgen deprivation therapy or had prior bilateral orchiectomy to maintain castrate levels of testosterone.

The MAH provided safety data in three main populations of patients with metastatic CRPC:

- The controlled study in chemotherapy-naïve patients with metastatic CRPC: MDV3100-03 (N = 871 enzalutamide, N = 844 placebo).
- The combined controlled studies in metastatic CRPC: patients with chemotherapy-naïve metastatic CRPC (MDV3100-03) and patients with metastatic CRPC previously treated with docetaxel (CRPC2) (N = 1671 enzalutamide, N = 1243 placebo).
- The integrated safety population of all enzalutamide-treated patients (N = 2509). This population includes enzalutamide-treated patients in the combined controlled population and enzalutamide-treated patients in the combined open-label population (N = 1001).

Patient exposure

A total of 871 patients in the enzalutamide group and 844 patients in the placebo group received at least 1 dose or partial dose of study drug in MDV3100-03. The median treatment duration for the enzalutamide group was 16.6 months compared with 4.6 months for the placebo group. Approximately 68% of patients treated with enzalutamide remained on study drug for at least 1 year compared with 18% of patients treated with placebo; approximately 16% of patients treated with enzalutamide remained on study drug for at least 2 years compared with approximately 3% of patients treated with placebo. Of note, some patients currently on study drug have not reached 2 years on study drug as enrolment ended approximately 1 year before the data cut-off date. The dose of enzalutamide was 160 mg once daily, although dose interruptions and reductions were permitted as needed.

The extent of exposure to enzalutamide and placebo in MDV3100-03 is summarized in the below table.

Table 32: Extent of Exposure in MDV3100-03

	Enzalutamide (N = 871)	**Placebo (N = 844)**
Time on study drug (months)		
Mean (SD)	15.8 (7.64)	7.0 (6.05)
Median	16.6	4.6
Min, max	0.2, 35.6	0.1, 31.7
Time on study drug category		
< 3 months	42 (4.8%)	221 (26.2%)
≥ 3 to < 6 months	79 (9.1%)	305 (36.1%)
≥ 6 to < 12 months	159 (18.3%)	166 (19.7%)
≥ 12 months	591 (67.9%)	152 (18.0%)
≥ 24 months	142 (16.3%)	22 (2.6%)

Source: Module 5.3.5.3, SCS [Table 4]

Adverse events

As expected for patients with advanced prostate cancer, most patients in the integrated safety population experienced at least 1 adverse event. Consistent with the inclusion of patients with more advanced disease in the combined controlled population and integrated safety population, the incidence of grade 3 and higher adverse events, serious adverse events, adverse events as the primary reason for treatment discontinuation, adverse events leading to dose interruption, and adverse events leading to dose reduction were generally higher in the enzalutamide group of the combined controlled population and/or the integrated safety population compared with the enzalutamide group of MDV3100-03. A similar pattern was observed in the placebo group of the combined controlled population compared with the placebo group of MDV3100-03.

Table 33: Incidence of Adverse Events in MDV3100-03, the Combined Controlled Population, and the Integrated Safety Population

	MDV3100-03		**Combined Controlled Population**		**Integrated Safety Population**
Patients With any Adverse Event	**Enzalutamide (N = 871)**	**Placebo (N = 844)**	**Enzalutamide (N = 1671)**	**Placebo (N = 1243)**	**Enzalutamide (N = 2509)**
Any	844 (96.9%)	787 (93.2%)	1631 (97.6%)	1177 (94.7%)	2390 (95.3%)
Grade ≥ 3	374 (42.9%)	313 (37.1%)	756 (45.2%)	527 (42.4%)	1150 (45.8%)
Serious	279 (32.0%)	226 (26.8%)	566 (33.9%)	381 (30.7%)	813 (32.4%)
As primary reason for treatment discontinuation	49 (5.6%)	51 (6.0%)	113 (6.8%)	92 (7.4%)	186 (7.4%)
Associated with treatment discontinuation	148 (17.0%)	216 (25.6%)	281 (16.8%)	290 (23.3%)	396 (15.8%)
Leading to dose interruption	98 (11.3%)	88 (10.4%)	205 (12.3%)	151 (12.1%)	314 (12.5%)
Leading to dose reduction	18 (2.1%)	8 (0.9%)	35 (2.1%)	19 (1.5%)	69 (2.8%)
Leading to death	37 (4.2%)	32 (3.8%)	63 (3.8%)	47 (3.8%)	116 (4.6%)

Source: Module 5.3.5.3, SCS [Table 24]

Table 34: Adverse events reported in at least 5% of patients in either treatment group by system organ class in MDV3100-03

System Organ Class Preferred Term	Enzalutamide (N = 871)	Placebo (N = 844)
Blood and Lymphatic System Disorders	87 (10.0%)	86 (10.2%)
Anaemia	66 (7.6%)	69 (8.2%)
Gastrointestinal Disorders	510 (58.6%)	438 (51.9%)
Nausea	201 (23.1%)	190 (22.5%)
Constipation	**193 (22.2%)**	**145 (17.2%)**
Diarrhoea	**142 (16.3%)**	**119 (14.1%)**
Vomiting	59 (6.8%)	70 (8.3%)
Abdominal pain	46 (5.3%)	33 (3.9%)
General Disorders and Administration Site Conditions	527 (60.5%)	400 (47.4%)
Fatigue	**310 (35.6%)**	**218 (25.8%)**
Asthenia	**113 (13.0%)**	**67 (7.9%)**
Oedema peripheral	**92 (10.6%)**	**69 (8.2%)**
Infections and Infestations	349 (40.1%)	228 (27.0%)
Urinary tract infection	58 (6.7%)	58 (6.9%)
Nasopharyngitis	**62 (7.1%)**	**42 (5.0%)**
Upper respiratory tract infection	**53 (6.1%)**	**30 (3.6%)**
Injury, Poisoning, and Procedural Complications	191 (21.9%)	117 (13.9%)
Fall	**101 (11.6%)**	**45 (5.3%)**
Investigations	202 (23.2%)	162 (19.2%)
Weight decreased	**100 (11.5%)**	**71 (8.4%)**
Metabolism and Nutrition Disorders	240 (27.6%)	193 (22.9%)
Decreased appetite	**158 (18.1%)**	**136 (16.1%)**
Musculoskeletal and Connective Tissue Disorders	555 (63.7%)	518 (61.4%)
Back pain	**235 (27.0%)**	**187 (22.2%)**
Arthralgia	**177 (20.3%)**	**135 (16.0%)**
Pain in extremity	102 (11.7%)	97 (11.5%)
Musculoskeletal pain	87 (10.0%)	73 (8.6%)
Bone pain	80 (9.2%)	116 (13.7%)
Musculoskeletal chest pain	59 (6.8%)	43 (5.1%)
Myalgia	52 (6.0%)	49 (5.8%)
Nervous System Disorders	403 (46.3%)	253 (30.0%)
Headache	**91 (10.4%)**	**59 (7.0%)**
Dizziness	**76 (8.7%)**	**53 (6.3%)**
Dysgeusia	**66 (7.6%)**	**31 (3.7%)**
Psychiatric Disorders	161 (18.5%)	99 (11.7%)
Insomnia	**70 (8.0%)**	**47 (5.6%)**
Renal and Urinary Disorders	248 (28.5%)	228 (27.0%)
Haematuria	**73 (8.4%)**	**49 (5.8%)**
Pollakiuria	50 (5.7%)	37 (4.4%)
Respiratory, Thoracic, and Mediastinal Disorders	241 (27.7%)	175 (20.7%)
Dyspnoea	69 (7.9%)	60 (7.1%)
Cough	72 (8.3%)	58 (6.9%)
Vascular Disorders	302 (34.7%)	141 (16.7%)
Hot flush	**157 (18.0%)**	**65 (7.7%)**
Hypertension	**117 (13.4%)**	**35 (4.1%)**

Source: Module 5.3.5.3, SCS [Table 27]
Adverse events with at least a 2% higher absolute incidence in the enzalutamide group compared with the placebo group are shown in bold font.

Table 35: Adverse Events Reported in at Least 5% of Enzalutamide-Treated Patients and With at Least a 2% Higher Incidence than Placebo-Treated Patients by Onset Day and Event Rate in MDV3100-03

	Adverse Events		Adverse Events Within 90 Days of Treatment Initiation		Total Number of Events (Event Rate per 100 Patient-Years)	
	Enzalutamide (N = 871)	Placebo (N = 844)	Enzalutamide (N = 871)	Placebo (N = 844)	Enzalutamide (N = 871)	Placebo (N = 844)
Fatigue	310 (35.6%)	218 (25.8%)	187 (21.5%)	162 (19.2%)	353 (29.9)	233 (43.0)
Back pain	235 (27.0%)	187 (22.2%)	72 (8.3%)	114 (13.5%)	279 (23.6)	230 (42.5)
Constipation	193 (22.2%)	145 (17.2%)	89 (10.2%)	94 (11.1%)	218 (18.5)	154 (28.4)
Arthralgia	177 (20.3%)	135 (16.0%)	63 (7.2%)	83 (9.8%)	220 (18.6)	160 (29.5)
Decreased appetite	158 (18.1%)	136 (16.1%)	61 (7.0%)	90 (10.7%)	175 (14.8)	146 (27.0)
Diarrhoea	142 (16.3%)	119 (14.1%)	74 (8.5%)	81 (9.6%)	180 (15.3)	153 (28.3)
Hot flush	157 (18.0%)	65 (7.7%)	119 (13.7%)	57 (6.8%)	160 (13.6)	66 (12.2)
Asthenia	113 (13.0%)	67 (7.9%)	69 (7.9%)	40 (4.7%)	149 (12.6)	72 (13.3)
Weight decreased	100 (11.5%)	71 (8.4%)	18 (2.1%)	41 (4.9%)	102 (8.6)	74 (13.7)
Oedema peripheral	92 (10.6%)	69 (8.2%)	38 (4.4%)	35 (4.1%)	105 (8.9)	73 (13.5)
Hypertension	117 (13.4%)	35 (4.1%)	57 (6.5%)	18 (2.1%)	127 (10.8)	36 (6.6)
Headache	91 (10.4%)	59 (7.0%)	50 (5.7%)	48 (5.7%)	117 (9.9)	67 (12.4)
Fall	101 (11.6%)	45 (5.3%)	20 (2.3%)	21 (2.5%)	128 (10.8)	48 (8.9)
Dizziness	76 (8.7%)	53 (6.3%)	32 (3.7%)	31 (3.7%)	83 (7.0)	57 (10.5)
Haematuria	73 (8.4%)	49 (5.8%)	34 (3.9%)	31 (3.7%)	105 (8.9)	60 (11.1)
Insomnia	70 (8.0%)	47 (5.6%)	42 (4.8%)	29 (3.4%)	74 (6.3)	47 (8.7)
Nasopharyngitis	62 (7.1%)	42 (5.0%)	22 (2.5%)	23 (2.7%)	71 (6.0)	45 (8.3)
Dysgeusia	66 (7.6%)	31 (3.7%)	25 (2.9%)	23 (2.7%)	68 (5.8)	31 (5.7)
Upper respiratory tract infection	53 (6.1%)	30 (3.6%)	12 (1.4%)	16 (1.9%)	65 (5.5)	38 (7.0)

Source: Module 5.3.5.3, SCS [Table 30, Table 32, Table 33]

Adverse events with at least a 0.5% higher incidence within the first 90 days OR a higher event rate per 100 patient-years in the enzalutamide group compared with the placebo group are shown in bold font.

Grade 3 or Higher Adverse Events in MDV3100-03

The incidence of grade 3 or higher adverse events (of any causality) in MDV3100-03 was higher in the enzalutamide group (42.9%) than in the placebo group (37.1%); however, the difference was primarily due to the longer exposure time in the enzalutamide group. The incidence of grade 3 or higher adverse events was lower in the enzalutamide group within the first 90, 180, and 365 days of treatment. The imbalance toward higher incidence in the enzalutamide group was observed after 1 year of treatment when 67.8% of patients in the enzalutamide group remained on study drug (compared with 18.0% of patients in the placebo group). Similarly, the time to first grade 3 or higher adverse event was longer in the enzalutamide group (22.3 months) than the placebo group (13.3 months), a delay of 9 months.

Table 36: Grade 3 or higher adverse events reported in at least 1% of either treatment group by system organ class in MDV3100-03

System Organ Class **Preferred Term**	**Enzalutamide (N = 871)**	**Placebo (N = 844)**
Patients with any grade ≥ 3 adverse event	374 (42.9%)	313 (37.1%)
Blood and Lymphatic System Disorders	37 (4.2%)	31 (3.7%)
Anaemia	29 (3.3%)	25 (3.0%)
Eye Disorders	14 (1.6%)	2 (0.2%)
Cataract	**11 (1.3%)**	**1 (0.1%)**
Gastrointestinal Disorders	37 (4.2%)	25 (3.0%)
Nausea	**9 (1.0%)**	**4 (0.5%)**
General Disorders and Administration Site Conditions	58 (6.7%)	49 (5.8%)
Fatigue	16 (1.8%)	16 (1.9%)
General physical health deterioration	**18 (2.1%)**	**10 (1.2%)**
Asthenia	11 (1.3%)	8 (0.9%)
Infections and Infestations	45 (5.2%)	37 (4.4%)
Urinary tract infection	13 (1.5%)	11 (1.3%)
Pneumonia	**11 (1.3%)**	**7 (0.8%)**
Injury, Poisoning, and Procedural Complications	29 (3.3%)	19 (2.3%)
Fall	**12 (1.4%)**	**6 (0.7%)**
Musculoskeletal and Connective Tissue Disorders	68 (7.8%)	78 (9.2%)
Back pain	22 (2.5%)	25 (3.0%)
Bone pain	12 (1.4%)	20 (2.4%)
Arthralgia	12 (1.4%)	9 (1.1%)
Pathological fracture	9 (1.0%)	7 (0.8%)
Neoplasms Benign, Malignant, and Unspecified (including cysts and polyps)	52 (6.0%)	38 (4.5%)
Metastatic pain	14 (1.6%)	16 (1.9%)
Nervous System Disorders	73 (8.4%)	53 (6.3%)
Spinal cord compression	**33 (3.8%)**	**24 (2.8%)**
Syncope	**14 (1.6%)**	**8 (0.9%)**
Renal and Urinary Disorders	49 (5.6%)	68 (8.1%)
Urinary retention	8 (0.9%)	14 (1.7%)
Hydronephrosis	5 (0.6%)	16 (1.9%)
Haematuria	9 (1.0%)	11 (1.3%)
Urinary tract obstruction	9 (1.0%)	9 (1.1%)
Vascular Disorders	69 (7.9%)	26 (3.1%)
Hypertension	**59 (6.8%)**	**19 (2.3%)**

Source: Module 5.3.5.3, SCS [Table 40]
Adverse events with at least a 0.5% higher incidence in the enzalutamide group compared with the placebo group are shown in bold font.

Table 37: Time-adjusted grade 3 or higher adverse events in MDV3100-03

Preferred Term	Adverse Events		Adverse Events Within 90 Days of Treatment Initiation		Total Number of Events (Event Rate per 100 Patient-Years)	
	Enzalutamide (N = 871)	Placebo (N = 844)	Enzalutamide (N = 871)	Placebo (N = 844)	Enzalutamide (N = 871)	Placebo (N = 844)
Cataract	**11 (1.3%)**	**1 (0.1%)**	**3 (0.3%)**	**1 (0.1%)**	**15 (1.3)**	**1 (0.2)**
Nausea	9 (1.0%)	4 (0.5%)	2 (0.2%)	3 (0.4%)	10 (0.8)	4 (0.7)
General physical health deterioration	18 (2.1%)	10 (1.2%)	4 (0.5%)	3 (0.4%)	18 (1.5)	10 (1.8)
Pneumonia	11 (1.3%)	7 (0.8%)	1 (0.1%)	2 (0.2%)	13 (1.1)	8 (1.5)
Fall	12 (1.4%)	6 (0.7%)	0 (0.0%)	2 (0.2%)	13 (1.1)	6 (1.1)
Spinal cord compression	33 (3.8%)	24 (2.8%)	4 (0.5%)	11 (1.3%)	34 (2.9)	24 (4.4)
Syncope	14 (1.6%)	8 (0.9%)	5 (0.6%)	4 (0.5%)	14 (1.2)	8 (1.5)
Hypertension	**59 (6.8%)**	**19 (2.3%)**	**32 (3.7%)**	**9 (1.1%)**	**64 (5.4)**	**20 (3.7)**

Source: Module 5.3.5.3, SCS [Table 40, Table 40.1, Table 45]
Time-adjusted adverse events more common in the enzalutamide group are shown in bold font.

The higher incidence of grade 3 events of cataract was evaluated further along with additional events of grade 3 cataract operation. When these terms were combined, the incidence of grade 3 cataract/cataract operation was 1.3% vs 0.2%. Of the 11 enzalutamide-treated patients with grade 3 cataract/cataract operation, the events were reported as early as study day 20 and as late as study day 600. Three patients (0.3%) had cataract events within the first 90 days of treatment, 1 patient had a cataract event between 90 and 180 days of treatment, 3 patients had cataract events between 180 and 365 days of treatment, and 4 patients had cataract events after 365 days of treatment. Two of the 11 enzalutamide-treated patients had a medical history of cataracts, although this condition may have been underreported as the CRF included only medical history considered clinically relevant for participation in the study. These 11 patients had no clear increase in risk factors (eg, higher incidence of corticosteroid use or diabetes mellitus), and the etiology of this observation remains unknown.

Study Drug-Related Adverse Events in MDV3100-03

Study drug related adverse events with an absolute increase of ≥ 1% in the enzalutamide group compared with the placebo group include diarrhoea, constipation, fatigue, asthenia, peripheral oedema, dysgeusia, headache, hot flush, and hypertension (shown in bold font). Vomiting was the only study drug related adverse event with at least a 1% higher absolute incidence in the placebo group compared with the enzalutamide group.

Hypertension was the only grade 3 or higher study drug related adverse event that had a higher absolute incidence of at least 0.5% in the enzalutamide group (2.8%) compared with the placebo group (0.7%). By contrast, ECG QT prolonged was the only study drug related grade 3 or higher adverse event that had a lower absolute incidence by at least 0.5% in the enzalutamide group (0.0%) compared with the placebo group (0.5%).

Table 38: Study drug-related adverse events reported in at least 2% of patients in either treatment group by system organ class in MDV3100-03

System Organ Class Preferred Term	Enzalutamide (N = 871)	Placebo (N = 844)
Any study drug-related event	566 (65.0%)	421 (49.9%)
Gastrointestinal Disorders	239 (27.4%)	206 (24.4%)
Nausea	116 (13.3%)	110 (13.0%)
Diarrhoea	**58 (6.7%)**	**46 (5.5%)**
Constipation	**58 (6.7%)**	**33 (3.9%)**
Vomiting	15 (1.7%)	29 (3.4%)
General Disorders and Administration Site Conditions	306 (35.1%)	192 (22.7%)
Fatigue	**220 (25.3%)**	**143 (16.9%)**
Asthenia	**67 (7.7%)**	**29 (3.4%)**
Oedema peripheral	**29 (3.3%)**	**16 (1.9%)**
Investigations	47 (5.4%)	40 (4.7%)
Weight decreased	20 (2.3%)	17 (2.0%)
Metabolism and Nutrition Disorders	71 (8.2%)	61 (7.2%)
Decreased appetite	62 (7.1%)	56 (6.6%)
Musculoskeletal and Connective Tissue Disorders	75 (8.6%)	71 (8.4%)
Arthralgia	25 (2.9%)	18 (2.1%)
Myalgia	13 (1.5%)	17 (2.0%)
Nervous System Disorders	157 (18.0%)	76 (9.0%)
Dysgeusia	**47 (5.4%)**	**20 (2.4%)**
Headache	**33 (3.8%)**	**17 (2.0%)**
Dizziness	24 (2.8%)	17 (2.0%)
Lethargy	14 (1.6%)	17 (2.0%)
Psychiatric Disorders	32 (3.7%)	17 (2.0%)
Insomnia	17 (2.0%)	11 (1.3%)
Skin and Subcutaneous Tissue Disorders	63 (7.2%)	37 (4.4%)
Hyperhidrosis	18 (2.1%)	12 (1.4%)
Vascular Disorders	167 (19.2%)	68 (8.1%)
Hot flush	**117 (13.4%)**	**48 (5.7%)**
Hypertension	**41 (4.7%)**	**11 (1.3%)**

Source: Module 5.3.5.3, SCS [Table 52]
Adverse events with at least a 1% higher absolute incidence in the enzalutamide group compared with the placebo group are shown in bold font.

Table 39: Common adverse events by exposure time in MDV3100-03

Preferred Term	Onset During First 90 Days of Enzalutamide	Onset During First 180 Days of Enzalutamide	Onset During First 365 Days of Enzalutamide	Total
Fatigue	187 (21.5%)	227 (26.1%)	273 (31.3%)	310 (35.6%)
Hot flush	119 (13.7%)	134 (15.4%)	146 (16.8%)	157 (18.0%)
Asthenia	69 (7.9%)	83 (9.5%)	102 (11.7%)	113 (13.0%)
Hypertension	57 (6.5%)	79 (9.1%)	100 (11.5%)	117 (13.4%)
Fall	20 (2.3%)	37 (4.2%)	75 (8.6%)	101 (11.6%)
Insomnia	42 (4.8%)	50 (5.7%)	59 (6.8%)	70 (8.0%)
Dysgeusia	25 (2.9%)	44 (5.1%)	59 (6.8%)	66 (7.6%)

Source: Module 5.3.5.3, SCS [Table 27, Table 33]

Adverse events with at least a 1% higher absolute incidence in the enzalutamide group compared with the placebo group within the first 90 days of treatment were asthenia, fatigue, restless legs syndrome, insomnia, flushing, hot flush, and hypertension. Adverse events that were more common within the first 90 days in the placebo group by at least 1% were generally associated with disease progression and included anaemia, abdominal pain, diarrhoea, dry mouth, nausea, vomiting, pyrexia, urinary tract infection, weight decreased, decreased appetite, arthralgia, back pain, bone pain, groin pain, myalgia, pain in extremity, spinal cord compression, dysuria, hydronephrosis, urinary retention, pelvic pain, and cough.

An exposure response analysis for adverse events was performed in both MDV3100-03 and CRPC2. Mean/median C_{min} concentrations of enzalutamide, M2, and the sum of enzalutamide and M2 were similar between the two studies as were exposure quartiles of each analyte. Results of these exposure response analyses showed no clear or consistent relationships between plasma concentrations of enzalutamide, M2, and the sum of enzalutamide and M2, and any specific adverse event or group of events. Therefore, there is no plasma concentration threshold in patients receiving enzalutamide 160 mg orally once daily that is associated with a greater risk of experiencing specific adverse events.

Adverse events of special interest

Seizure

Seizure was identified as a dose-limiting toxicity in the initial dose-escalation study S-3100-1-01 at enzalutamide doses ≥ 360 mg daily. In CRPC2, seizure was reported in < 1% of patients receiving enzalutamide at a dose of 160 mg daily compared with no patients in the placebo group. The overall incidence of seizure in patients with metastatic CRPC who previously received docetaxel within the larger integrated safety population was comparable with the incidence observed in CRPC2 (approximately 0.7%).

An increased incidence of seizure was not observed in chemotherapy-naïve patients with metastatic CRPC treated with enzalutamide in MDV3100-03 despite the longer duration of exposure and less stringent entry criteria in this study (e.g., no exclusion for concomitant medications that lower the seizure threshold). In MDV3100-03, none of the 871 enzalutamide-treated patients had a seizure (or event within the narrow standardized MedDRA query [SMQ] of 'convulsion') before the data cutoff date of 16 Sep 2013 (median safety reporting period of 17.1 months). By comparison, 1 of the 844 placebo-treated patients (0.1%) had a seizure before the data cut-off date (median safety reporting period of 5.4 months). After the data cutoff date, 1 enzalutamide-treated patient (0.1%) had a seizure.

One additional seizure was previously reported in a chemotherapy-naïve patient participating in the open-label study 9785-CL-0007, leading to an estimated seizure incidence in chemotherapy-naïve patients of 0.1% (1 of 967 patients) through the data cut-off date of MDV3100-03 or 0.2% (2 of 967 patients) including the patient in MDV3100-03 with an event of seizure after the data cut-off date. For many events of seizure in the integrated safety population, confounding factors were present that could have independently increased the risk of seizure, such as the presence of brain metastases or a history of seizure.

Based on the method described by the MAH for calculation of the event-rate per 100 patient-years (PY), the event rate for Convulsions SMQ events was as follows:

MDV3100-03: Enzalutamide: 1/1180.07x100 = 0.08474 events per 100 PY (= 0.85 per 1000 PY)

Placebo: 1/541.57x100 = 0.18464 events per 100 PY (= 1.85 per 1000 PY)

Combined Controlled Population (CCP):

Enzalutamide: 6/1856.85x100 = 0.32312 events per 100 PY (= 3.2 per 1000 PY)

Placebo: 1/713.14x100 = 0.14022 events per 100 PY (= 1.4 per 1000 PY)

Cardiac disorders

The overall incidence of adverse events within the Cardiac Disorders system organ class in MDV3100-03 was higher in the enzalutamide group compared with the placebo group (10.1% vs 7.8%). The incidence of grade 3 or higher cardiac adverse events was higher in the enzalutamide group compared with the placebo group of MDV3100-03 (2.8% vs 2.1%).

The imbalance in events in MDV3100-03 was evaluated further and determined to be a result of longer duration of exposure in the enzalutamide group. The incidence of major adverse cardiovascular events was comparable between groups within the first 90 days of treatment (0.9% vs 0.8%) and 180 days of treatment (1.0% vs 1.3%) and 365 days of treatment (1.7% vs 1.8%). Additionally, when adjusted for length of exposure, the event rates per 100 patient-years were lower in the enzalutamide groups of MDV3100-03, CRPC2, and the combined controlled population compared with the placebo groups (2.0 vs 3.0 events per 100 patient-years in MDV3100-03, 2.2 vs 5.2 events per 100 patient-years in CRPC2, and 2.1 vs 3.5 events per 100 patient-years in the combined controlled population). Review of individual adverse events in these SMQs did not reveal a clear relationship with prior adverse events of hypertension or increased blood pressure in either study.

Review of adverse events within the 'torsades de pointes / QT prolongation' narrow SMQ did not reveal a safety signal. The incidence of adverse events of ventricular tachycardia and prolonged QT were comparable between treatment groups. Only 1 enzalutamide treated patient (< 0.1%) in the combined controlled population had an event (QT prolongation) leading to dose interruption compared with 5 placebo treated patients (0.4%).

Table 40: Summary of major cardiovascular adverse events

System Organ Class Preferred Term	MDV3100-03		Combined Controlled Population	
	Enzalutamide (N = 871)	Placebo (N = 844)	Enzalutamide (N = 1671)	Placebo (N = 1243)
Patients with any major adverse cardiovascular event, n (%)	23 (2.6%)	16 (1.9%)	38 (2.3%)	24 (1.9%)
Cardiac Disorders	7 (0.8%)	4 (0.5%)	10 (0.6%)	7 (0.6%)
Acute myocardial infarction	3 (0.3%)	0 (0.0%)	6 (0.4%)	1 (< 0.1%)
Myocardial infarction	3 (0.3%)	2 (0.2%)	3 (0.2%)	4 (0.3%)
Acute coronary syndrome	1 (0.1%)	1 (0.1%)	1 (< 0.1%)	1 (< 0.1%)
Angina unstable	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (< 0.1%)
Eye Disorders	1 (0.1%)	1 (0.1%)	1 (< 0.1%)	1 (< 0.1%)
Retinal artery occlusion	1 (0.1%)	0 (0.0%)	1 (< 0.1%)	0 (0.0%)
Amaurosis fugax	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (< 0.1%)
Injury, Poisoning, and Procedural Complications	2 (0.2%)	2 (0.2%)	4 (0.2%)	3 (0.2%)
Subdural haematoma	0 (0.0%)	2 (0.2%)	2 (0.1%)	3 (0.2%)
Extradural haematoma	1 (0.1%)	0 (0.0%)	1 (< 0.1%)	0 (0.0%)
Subdural haemorrhage	1 (0.1%)	0 (0.0%)	1 (< 0.1%)	0 (0.0%)
Investigations	1 (0.1%)	0 (0.0%)	1 (< 0.1%)	0 (0.0%)
Troponin increased	1 (0.1%)	0 (0.0%)	1 (< 0.1%)	0 (0.0%)
Nervous System Disorders	12 (1.4%)	9 (1.1%)	22 (1.3%)	14 (1.1%)
Transient ischaemic attack	4 (0.5%)	4 (0.5%)	7 (0.4%)	5 (0.4%)
Cerebrovascular accident	4 (0.5%)	1 (0.1%)	7 (0.4%)	2 (0.2%)
Cerebral infarction	1 (0.1%)	1 (0.1%)	1 (< 0.1%)	1 (< 0.1%)
Carotid artery stenosis	1 (0.1%)	1 (0.1%)	1 (< 0.1%)	1 (< 0.1%)
Cerebral haemorrhage	0 (0.0%)	1 (0.1%)	1 (< 0.1%)	2 (0.2%)
Lacunar infarction	0 (0.0%)	0 (0.0%)	1 (< 0.1%)	0 (0.0%)
Embolic stroke	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (< 0.1%)
Cerebral small vessel ischaemic disease	1 (0.1%)	0 (0.0%)	1 (< 0.1%)	0 (0.0%)
Haemorrhage intracranial	0 (0.0%)	0 (0.0%)	1 (< 0.1%)	0 (0.0%)
Haemorrhagic stroke	0 (0.0%)	0 (0.0%)	1 (< 0.1%)	0 (0.0%)
Ischaemic stroke	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (< 0.1%)
Meningorrhagia	1 (0.1%)	0 (0.0%)	1 (< 0.1%)	0 (0.0%)
Subarachnoid haemorrhage	1 (0.1%)	0 (0.0%)	1 (< 0.1%)	0 (0.0%)
Thalamus haemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Reversible ischaemic neurological deficit	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (< 0.1%)
Any event within first 90 days of treatment	8 (0.9%)	7 (0.8%)	na	na
Any event within first 180 days of treatment	9 (1.0%)	11 (1.3%)	na	na
Any event within first 365 days of treatment	15 (1.7%)	15 (1.8%)	na	na
Any event leading to death	3 (0.3%)	1 (0.1%)	8 (0.5%)	3 (0.2%)
Adverse event rates per 100 patient-years for major adverse cardiac events, n (event rate)	24 (2.0)	16 (3.0)	39 (2.1)	25 (3.5)

Source: Module 5.3.5.3, SCS [Table 144, Table 145, Table 151], [MDV3100-03 Table 14.3.2.13.2]
na, not applicable.

Hypertension

Hypertension (and related terms in the 'hypertension' narrow SMQ) was initially identified as an adverse drug reaction in CRPC2 (7.0% vs 3.3%), and was also observed with higher incidence in the enzalutamide group of MDV3100-03 (13.9% enzalutamide vs 4.7% placebo). The incidence of hypertension events in both treatment groups in MDV3100-03 was higher than in both treatment

groups in CRPC2. The incidence of hypertension events in the combined open-label studies was 4.7%, leading to an overall incidence of 8.8% in the integrated safety population.

The overall higher incidence of hypertension in both treatment groups of MDV3100-03 compared with CRPC2 may be partly due to the longer patient exposures in that study (100% longer exposure in the enzalutamide group and 50% longer exposure in the placebo group) as well as heightened awareness by patients and investigators. In addition, patients in MDV3100-03 had higher blood pressure at study entry (median baseline systolic 137 mm Hg; median baseline diastolic 79 mm Hg) compared with patients in CRPC2 (median baseline systolic 130 mm Hg; median baseline diastolic 75 mm Hg).

Hypertension was the most common grade 3 or higher event in the enzalutamide group of MDV3100-03 (6.8%), and was higher than the placebo group (2.3%). The high incidence of grade 3 events may be related in part to the relatively conservative grading scale for hypertension by CTCAE (≥ 160 mm Hg systolic blood pressure or ≥ 100 mm Hg diastolic), which was adhered to closely by investigators. In addition, hypertension was the most common comorbid condition in this patient population at study entry (reported in more than 60% of patients in MDV3100-03), with approximately 17% of patients entering the study with grade 3 hypertension at baseline (by screening or baseline blood pressure values). In CRPC2, approximately 50% of patients entered the study with a documented history of hypertension, and 11% of patients entered the study with grade 3 hypertension at baseline (by screening or baseline blood pressure values).

Hypertension events were more common in patients with a history of hypertension; approximately 70% of enzalutamide-treated patients with events of hypertension in MDV3100-03 and the combined controlled population had a documented medical history of hypertension, without important differences between treatment groups. The incidence of hypertension events was not affected by age at study entry. In both MDV3100-03 and CRPC2, the maximum mean change from baseline in systolic and diastolic blood pressure occurred in the first few months of enzalutamide treatment and did not worsen with time. Accordingly, approximately half of all events of hypertension in both studies were reported within the first 90 days of enzalutamide treatment. No clear relationship was apparent between the increased incidence of hypertension events and subsequent cardiovascular sequelae or renal impairment in MDV3100-03 or CRPC2.

The mechanism of hypertension associated with enzalutamide treatment is unknown. Hypertension was also reported in 22% of chemotherapy-naïve patients with metastatic CRPC taking abiraterone in combination with prednisone [Ryan et al, 2013], but the mechanism of action of hypertension in these patients is likely related to increased mineralocorticoid production and fluid retention along with the additive effects of corticosteroids. Enzalutamide treatment is not associated with hypokalemia, fluid overload, or other features of mineralocorticoid excess. In general, the hypertension observed with enzalutamide treatment was successfully treated with standard of care measures and rarely required treatment discontinuation or dose modification.

Fatigue

Fatigue is a common symptom in patients with advanced cancer as well as in patients receiving androgen deprivation therapy. Fatigue was a dose-dependent adverse event observed in the phase 1 dose-escalation study S-3100-1-01, and fatigue (with related terms of asthenia, lethargy, and malaise) was reported in a higher percentage of enzalutamide-treated patients than placebo-treated patients in CRPC2 (52.3% vs 46.6%). The incidence of fatigue-related events was also higher in the enzalutamide group of MDV3100-03 with a greater difference between treatment groups (48.3% vs 35.0%). The higher incidence of fatigue-related events was restricted to grade 1 and grade 2 events as the incidence of grade 3 events was identical in MDV3100-03 treatment groups (3.0% each group) and CRPC2 (9.0% each group). In both studies, enzalutamide-treated patients were less likely than placebo-treated patients to discontinue treatment because of fatigue, but were more likely to

modify dosing because of fatigue. In general, enzalutamide-treated patients with fatigue who reduced the dose to 80 mg or 120 mg daily had resolution of fatigue or improvement to a lower grade. A modest trend was observed with a higher incidence of fatigue and asthenia events with older patients (≥ 75 years at study entry), although this finding may be confounded by other comorbid conditions in older patients.

When adjusted for length of exposure, event rates per 100 patient-years for fatigue-related events were lower in the enzalutamide groups than placebo groups of MDV3100-03 (44.6 vs 60.9 events per 100 patient-years) and CRPC2 (78.0 vs 127.5 events per 100 patient-years). However, the cumulative incidence of fatigue-related events was consistently higher in the enzalutamide groups compared with the placebo groups of MDV3100-03 and the combined controlled population. In summary, grade 1 and 2 fatigue appears to be more prominent as an adverse drug reaction in the earlier-stage patient population of MDV3100-03. The aetiology of fatigue is difficult to discern as it may also be related to disease progression, progressive weakness associated with androgen deprivation therapy, and concomitant pain medications that are commonly used as the disease advances.

Hot Flush

Hot flush is a common side effect of androgen deprivation therapy reported in up to 50% to 80% of men with castrate levels of testosterone [Grossman & Zajac, 2011]. The exact mechanism of action is not known, although it is believed that a reduction of sex hormone levels causes thermoregulatory instability in the hypothalamus. Hot flush combined with flushing was among the adverse events with the largest absolute difference between treatment groups in MDV3100-03 (20.0% vs 7.9%). Nearly all events were grade 1 or grade 2; only 1 enzalutamide-treated patient had a grade 3 event. Hot flush was also observed at a substantially increased incidence in enzalutamide-treated patients compared with placebo-treated patients in the combined controlled population (20.4% vs 8.7%), but the event did not lead to treatment discontinuation in any patient in either study. When adjusted for length of exposure, the event rates per 100 patient-years for hot flush and flushing were higher in the enzalutamide group. The aetiology of the increased incidence of hot flush with enzalutamide treatment may result from a more complete inhibition of androgen signalling pathways.

Falls/Non-pathological Fractures

An increased incidence of falls was noted in patients treated with enzalutamide compared with placebo in MDV3100-03 (11.6% vs 5.3%), with both groups having a higher incidence of falls compared with the earlier CRPC2 study (4.5% vs 1.3%), likely due to the longer exposure time. In addition, as fall was observed as an adverse drug reaction in CRPC2, there was heightened vigilance in querying for and reporting fall events in MDV3100-03. Most falls were grade 1 or grade 2 in the combined controlled population, and most falls in the enzalutamide group were reported after at least 6 months of treatment. The incidence of falls increased with increasing patient age at study entry in the enzalutamide groups, although the same pattern was also observed for falls in the placebo groups of the controlled studies. The aetiology of the increased risk of falls is unknown, but may be multifactorial with possible contributing factors such as weakness associated with androgen deprivation, other concurrent adverse events, and concomitant medication use. The events of fall were not associated with an increased incidence of loss of consciousness or subdural hematoma. Where additional descriptive information was available from verbatim terms, falls were most often categorized as mechanical/accidental falls.

The increased incidence of falls in enzalutamide-treated patients appears to be associated with an increased incidence and tendency toward non-pathological fractures in both MDV3100-03 (7.8% vs 3.0%) and CRPC2 (4.1% vs 0.8%). Similar to events of fall, the majority of non-pathological fractures were reported after 6 months of treatment, which may explain the higher incidence in MDV3100-03 compared with CRPC2. When evaluating the correlation between falls and non-

pathological fractures, it was determined that approximately 50% of patients with a non-pathological fracture experienced a fall within the preceding 14 days in MDV3100-03. Both falls and non-pathological fractures were rarely associated with discontinuation of treatment or dose modification in either treatment group of either study. When adjusted for length of exposure, the event rate per 100 patient-years of falls and non-pathological fractures were higher in the enzalutamide groups of MDV3100-03, CRPC2, and the combined controlled population. The higher risk of fracture associated with fall in the enzalutamide groups may be related to longer exposure.

Mental Impairment

The incidence of cognitive and memory impairment-related adverse events under the Medical Dictionary for Regulatory Activities (MedDRA) high-level group term of mental impairment disorders was higher in the enzalutamide group of MDV3100-03 than CRPC2 (5.7% vs 1.5%), and the incidence was similar to that observed in CRPC2 (4.3% vs 1.8%) despite the longer exposure time in MDV3100-03. In the combined controlled population, nearly all events were grade 1 or 2 in severity (5.0% vs 1.6%); only 2 patients in each treatment group experienced grade 3 events (≤ 0.2%). No enzalutamide-treated patient in the combined controlled population experienced a serious adverse event involving mental impairment compared with 2 placebo-treated patients in MDV3100-03. Events involving mental impairment rarely led to discontinuation or modification of dosing, with no differences between treatment groups. When adjusted for length of exposure, event rates per 100 patient-years for mental impairment were higher in the enzalutamide groups than the placebo groups of MDV3100-03, CRPC2, and the combined controlled population. There was no evidence of an increase in road traffic accidents or other serious injuries resulting from mental impairment events in either treatment group of the combined controlled population. The etiology of these cognitive changes is unknown, although memory impairment and cognitive changes have also been observed with other drugs that inhibit the androgen signaling pathway [Nelson et al, 2008].

Neutropenia

The overall incidence of neutropenia or related adverse event terms was infrequent but slightly higher in the enzalutamide group of MDV3100-03 (1.5% enzalutamide vs 0.6% placebo). Based on central laboratory values, the incidence of grade 3 or 4 neutropenia was similar between treatment groups (0.9% vs 0.7%). An increased incidence of neutropenia was previously observed in the earlier CRPC2 study when assessed by grade 3 or 4 central laboratory values (1.1% vs 0%), but not by adverse event terms (1.4% vs 1.3%). In both studies, mean neutrophil counts were below baseline at postbaseline time points in the enzalutamide groups, but the maximum decrease was smaller and occurred later in MDV3100-03 (maximum mean decrease of approximately 560 cells/µL at week 97) compared with CRPC2 (maximum mean decrease of approximately 680 cells/µL at week 5) during the relevant study periods. Only 1 enzalutamide-treated patient experienced a serious adverse event of neutropenia in the combined controlled population (< 0.1%). In general, events of neutropenia were transient, did not require treatment discontinuation or dose modification, and were not related to an increased risk of infection in either treatment group. Enzalutamide was not associated with changes in red blood cells, platelets, or other white blood cells. The mechanism for neutropenia associated with enzalutamide treatment is not known.

Headache

Headache is a common adverse event in clinical studies, in patients with advanced cancer, and in patients receiving androgen deprivation therapies and was assessed as an adverse drug reaction for enzalutamide. The incidence of headache was 2-fold higher in enzalutamide-treated patients compared with placebo-treated patients in CRPC2 (12.1% vs 5.5%); however, the difference in incidence of headaches was smaller in MDV3100-03 (10.4% vs 7.0%), and the incidence was lower in the combined open-label population (7.7%). In the combined controlled population, most events were

grade 1 or 2; ≤ 0.5% of patients experienced grade 3 events of headache, with no clear difference between treatment groups. Headache events were generally reported early, with over half of all events reported within the first 90 days of treatment. When adjusted for length of exposure, the event rate for headache was lower in the enzalutamide group compared with the placebo group of MDV3100-03 (9.9 vs 12.4 events per 100 patient-years) but higher in the enzalutamide group of CRPC2 (16.6 vs 14.1 events per 100 patient-years). The etiology for the increased incidence in the more advanced patients of CRPC2 compared with MDV3100-03 is not known; potential reasons may include increased use of concomitant medications associated with headache such as opiates or manifestations of disease progression (e.g., skull metastases) that are more common in patients with later-stage disease.

Anxiety

Anxiety was assessed as an adverse drug reaction in the original marketing application as a result of a higher incidence in the enzalutamide group of CRPC2 (6.4% vs 4.0%) as well as a pattern of dose dependence in open-label studies. In MDV3100-03, the overall incidence of anxiety and the difference in incidence between treatment groups was lower (3.8% vs 2.6%), despite the longer exposure duration. Although an increased incidence of anxiety in the enzalutamide group was observed within the first 90 and 180 days of CRPC2 (4.5% vs 3.3% within the first 90 days and 5.4% vs 3.3% within the first 180 days), a lower incidence of anxiety was observed within the first 90 and 180 days of MDV3100-03 (0.8% vs 1.4% within the first 90 days, 1.8% vs 2.1% in the within the first 180 days). In MDV3100-03, no enzalutamide-treated patient had a grade 3 or higher event or an event leading to treatment discontinuation or dose modification. When adjusted for length of exposure, the event rate was lower in the enzalutamide group in MDV3100-03 (2.9 vs 4.1 events per 100 patient-years) and in CRPC2 (8.0 vs 9.4 events per 100 patient-years). The etiology of the increased incidence of anxiety associated with enzalutamide treatment is unknown.

Hallucination

Hallucination was identified as an adverse drug reaction in CRPC2 after a finding of increased incidence in the enzalutamide group (1.6% vs 0.3%), and were primarily events of visual hallucination. In CRPC2, nearly all patients were receiving concomitant opiate medications at the time of the hallucination event. The incidence of hallucination events was 0.9% in the combined open-label studies, which are also largely composed of patients who previously received docetaxel. An increased incidence of hallucination was not observed in MDV3100-03. One patient in each treatment group (0.1%) experienced an event of hallucination, and similar to CRPC2, both patients were receiving concomitant opiate medications at the time of the event. A total of 23 patients (0.9%) in the integrated safety population experienced events of hallucination, of whom only 1 enzalutamide-treated patient in CRPC2 experienced a grade 3 event. The aetiology of hallucination in patients with advanced CRPC is not known, but use of opiate-containing medications appears to be a confounding factor.

Dry Skin/Pruritus

Events of dry skin and pruritus were considered adverse drug reactions in CRPC2 as a result of higher incidences in the enzalutamide group (3.5% vs 1.3% for dry skin, 3.8% vs 1.3% for pruritus) along with higher event rates when adjusted for length of exposure. In addition, both of these events have been described with other antiandrogen treatments [bicalutamide prescribing information; nilutamide prescribing information]. In MDV3100-03, the overall incidences of these events were lower than in CRPC2 for both groups, and although the incidences were higher in the enzalutamide group than the placebo group, the differences between groups were smaller (< 1%) and not considered clinically relevant. Additionally, in MDV3100-03, the event rate per 100 patient-years for each of these events was lower in the enzalutamide group when adjusted for length of exposure.

Gynecomastia

An increased incidence of gynecomastia was observed in the enzalutamide group of MDV3100-03 (3.3% enzalutamide vs 1.3% placebo), although when adjusted for length of exposure, the event rate was only marginally higher in the enzalutamide group (2.5 vs 2.0 events per 100 patient-years). An increased incidence of gynecomastia was also observed in CRPC2 (2.5% vs 1.0%), although the absolute difference between groups was smaller. Approximately half of gynecomastia events in enzalutamide-treated patients occurred in the first 90 days of treatment in both the combined controlled population and the integrated safety population. All events of gynecomastia in the combined controlled population were grade 1 or 2 in severity, except 1 enzalutamide-treated patient in CRPC2 had grade 3 gynecomastia. Gynecomastia did not lead to treatment discontinuation or dose modification in any patient in the integrated safety population. In the phase 2 study of enzalutamide monotherapy in hormone-naïve patients with prostate cancer, the incidence of gynecomastia was nearly 50%. The etiology of gynecomastia associated with enzalutamide treatment is likely related to its primary pharmacology of androgen receptor inhibition and has also been reported with other antiandrogens [bicalutamide prescribing information]. Given the consistent increase in incidence in enzalutamide-treated patients across studies as well as the pharmacologic basis, gynecomastia is considered an adverse drug reaction.

Restless Legs Syndrome

Restless legs syndrome was reported in a higher proportion of enzalutamide-treated patients in MDV3100-03 (2.1% vs 0.4%) and CRPC2 (1.5% vs 0.3%). In the integrated safety population, the incidence was 1.8%. Nearly all events in the integrated safety population were grade 1 or grade 2; only 1 enzalutamide-treated patient experienced a grade 3 event in MDV3100-03. Approximately 91% of the events of restless legs syndrome across studies were reported within the first 90 days of treatment. When adjusted for length of exposure, the event rate per 100 patient-years was higher in the enzalutamide groups of MDV3100-03, CRPC2, and the combined controlled population. Restless legs syndrome was reported as a medical history event in 1.3% of MDV3100-03 patients and 1.1% of CRPC2 patients, although this may be an underestimate as the overall prevalence in North America and Europe has been estimated at 5% to 10%. The etiology of restless legs syndrome associated with enzalutamide is unknown. Other medications such as centrally acting antihistamines, serotonergic antidepressants, and dopamine-blocking antiemetics have been linked to initiation or worsening of restless legs syndrome, but it has not been consistently reported with antiandrogens. Although the incidence is low across studies, given the consistency of findings and the occurrence within the first 90 days of treatment, restless legs syndrome is considered an adverse drug reaction.

Neoplasms Benign, Malignant, and Unspecified

A higher incidence of events of second malignancy, including non-melanoma skin cancer, was observed in the MDV3100-03 enzalutamide group compared with the placebo group (3.9% vs 1.1%; 3.1 vs 0.7% excluding nonmelanoma skin cancer). A smaller imbalance was observed in CRPC2 (1.0% vs 0.5% for all second malignancies). When adjusted for length of exposure in MDV3100-03, the event rate remained higher in the enzalutamide group compared with the placebo group (3.3 vs 1.8 events per 100 patient-years for any second malignancy, and 2.0 vs 0.7 events per 100 patient-years for any grade 3 or higher second malignancy). In CRPC2, the event rates were comparable or lower in the enzalutamide group relative to placebo (1.2 vs 1.2 events per 100 patient-years for any second malignancy, and 0.6 vs 1.2 events per 100 patient-years for any grade 3 or higher second malignancy). There was no overall pattern by anatomic location or cell type for the other events of second malignancy observed in enzalutamide-treated patients

Excluding the events of non-melanoma skin cancer, 40 enzalutamide-treated patients (1.6%) in the integrated safety population and 8 placebo-treated patients in the combined controlled population

(0.6%) experienced 50 adverse events of second malignancy. In order to provide context for the limited size of the integrated studies database, the observed incidence of second malignancy (excluding non-melanoma skins cancer) in the enzalutamide integrated safety population was compared with the expected overall incidence of malignancy, and the incidence of each type of malignancy, using cancer statistics data from the Surveillance, Epidemiology, and End Results (SEER) Program database (www.seer.cancer.gov). The overall incidence of second malignancy in the 40 enzalutamide-treated patients in the integrated safety population is within the expected incidence for all cancer sites combined per SEER-18 (64 events expected in a population ≥ 65 years). Further, there was no overall pattern of higher than expected incidence by anatomic location or cell type, with some malignancies occurring at higher than expected frequency in the SEER data (e.g., tonsil, gastric) and others at lower than expected frequency (e.g., lung).

A review of postmarketing adverse events of Xtandi (enzalutamide) capsules (data collected through 31 Oct 2013) did not identify a safety signal in the Neoplasms Benign, Malignant, and Unspecified system organ class. In the postmarketing data, events considered unrelated to prostate cancer include 6 patients with hematologic malignancy (2 patients with acute myeloid leukaemia and 1 patient each with chronic myeloid leukaemia, unspecified hematologic malignancy, leukaemia, and lymphoma), and 1 patient each with bladder cancer, colon cancer, small cell lung cancer metastatic, testis cancer, and cholangiocarcinoma. Events considered likely to be associated with underlying prostate cancer included malignant neoplasm (unspecified, 4 patients), bone cancer (3 patients), and lymphangiosis carcinomatosa (1 patient). A causal relationship with enzalutamide could not be established due to the limited clinical information available through spontaneous reporting.

Although no carcinogenicity studies have been performed with enzalutamide (per ICH S9), nonclinical studies have not revealed evidence of cytotoxicity, genotoxicity, or mutagenicity..

Based on the overall incidence rate of second malignancy consistent with the SEER-18 data, second malignancies observed across different organ systems and cell types, median onset latency of second malignancies of 199 days (a relatively short latency) in enzalutamide-treated patients in the integrated safety population, and evidence of pre-existing malignancy in some patients at study entry, a causal relationship between enzalutamide treatment and second malignancy is unlikely.

Serious adverse event / deaths / other significant events

Deaths

Overall, deaths from prostate cancer disease progression, deaths from other causes (unrelated to prostate cancer disease progression) and deaths from unknown (or unspecified) causes were all lower in the enzalutamide group than the placebo group. Two patients (1 in the enzalutamide group and 1 in the placebo group) died within 30 days of initiation of study drug. The enzalutamide-treated patient died of unknown causes at home, the placebo-treated patient died of an acute subdural hematoma associated with a fall.

Deaths within 30 days of discontinuation of study drug were higher in the enzalutamide group compared with the placebo group (4.0% vs 3.4%), with the small overall difference resulting from deaths due to other causes (unrelated to prostate cancer) and unknown (or unspecified) causes. The proportion of patients with deaths due to prostate cancer was similar between treatment groups. Most deaths within 30 days of discontinuation of study drug are within the treatment-emergent period and are also reported as adverse events leading to death, although 5 deaths (2 in the enzalutamide group and 3 in the placebo group) were after the reporting period (e.g., patients who discontinued study drug and immediately initiated cytotoxic chemotherapy prior to death).

Table 41: Summary of deaths in MDV3100-03

Death Summary	Enzalutamide (N = 871)	Placebo (N = 844)
Total number of deaths	240 (27.6%)	298 (35.3%)
Deaths due to disease progression	182 (20.9%)	226 (26.8%)
Deaths due to other causes	35 (4.0%)	41 (4.9%)
Deaths from unknown causes	23 (2.6%)	31 (3.7%)
Deaths within 30 days of initiation of study drug	1 (0.1%)	1 (0.1%)
Deaths due to disease progression	0 (0%)	0 (0%)
Deaths due to other causes	0 (0%)	1 (0.1%)
Deaths due to unknown causes	1 (0.1%)	0 (0%)
Deaths within 30 days of discontinuation of study drug	35 (4.0%)	29 (3.4%)
Deaths due to disease progression	14 (1.6%)	14 (1.7%)
Deaths due to other causes	17 (2.0%)	14 (1.7%)
Deaths from unknown causes	4 (0.5%)	1 (0.1%)

Source: Module 5.3.5.3, SCS [Table 74]

Adverse events leading to death occurred in 37 patients (4.2%) in the enzalutamide group and 32 patients (3.8%) in the placebo group. Adverse events reported in more than 1 enzalutamide-treated patient and at a higher incidence than in placebo-treated patients include cardiac arrest, cardiac failure, general physical heath deterioration, death, and cerebrovascular accident (shown in bold font).

Table 42: Adverse events leading to death in MDV3100-03

System Organ Class Preferred Term	Enzalutamide (N = 871)	Placebo (N = 844)
Any adverse event leading to death	37 (4.2%)	32 (3.8%)
Blood and Lymphatic System Disorders	1 (0.1%)	0 (0.0%)
Disseminated intravascular coagulation	1 (0.1%)	0 (0.0%)
Cardiac Disorders	7 (0.8%)	3 (0.4%)
Cardiac arrest	**2 (0.2%)**	**1 (0.1%)**
Arteriosclerosis coronary artery	1 (0.1%)	1 (0.1%)
Cardiac failure	**2 (0.2%)**	**0 (0.0%)**
Acute myocardial infarction	1 (0.1%)	0 (0.0%)
Cardiac failure congestive	0 (0.0%)	1 (0.1%)
Cardiopulmonary failure	1 (0.1%)	0 (0.0%)
Gastrointestinal Disorders	0 (0.0%)	1 (0.1%)
Intestinal obstruction	0 (0.0%)	1 (0.1%)
General Disorders and Administration Site Conditions	17 (2.0%)	13 (1.5%)
General physical health deterioration	**9 (1.0%)**	**4 (0.5%)**
Disease progression	3 (0.3%)	6 (0.7%)
Death	**4 (0.5%)**	**1 (0.1%)**
Drowning	1 (0.1%)	0 (0.0%)
Performance status decreased	0 (0.0%)	1 (0.1%)
Sudden death	0 (0.0%)	1 (0.1%)

System Organ Class **Preferred Term**	**Enzalutamide (N = 871)**	**Placebo (N = 844)**
Hepatobiliary Disorders	1 (0.1%)	0 (0.0%)
Hepatic failure	1 (0.1%)	0 (0.0%)
Infections and Infestations	1 (0.1%)	1 (0.1%)
Pneumonia	1 (0.1%)	0 (0.0%)
Septic shock	0 (0.0%)	1 (0.1%)
Injury, Poisoning, and Procedural Complications	0 (0.0%)	2 (0.2%)
Road traffic accident	0 (0.0%)	1 (0.1%)
Subdural haematoma	0 (0.0%)	1 (0.1%)
Metabolism and Nutrition Disorders	0 (0.0%)	1 (0.1%)
Cachexia	0 (0.0%)	1 (0.1%)
Neoplasms Benign, Malignant, and Unspecified (including cysts and polyps)	2 (0.2%)	4 (0.5%)
Prostate cancer metastatic	0 (0.0%)	2 (0.2%)
Lung adenocarcinoma	0 (0.0%)	1 (0.1%)
Prostate cancer	1 (0.1%)	0 (0.0%)
Rectal cancer	1 (0.1%)	0 (0.0%)
Tumour embolism	0 (0.0%)	1 (0.1%)
Nervous System Disorders	2 (0.2%)	3 (0.4%)
Cerebrovascular accident	**2 (0.2%)**	**0 (0.0%)**
Brain injury	0 (0.0%)	1 (0.1%)
Coma hepatic	0 (0.0%)	1 (0.1%)
Metabolic encephalopathy	0 (0.0%)	1 (0.1%)
Renal and Urinary Disorders	2 (0.2%)	3 (0.4%)
Renal failure acute	0 (0.0%)	2 (0.2%)
Hydronephrosis	0 (0.0%)	1 (0.1%)
Obstructive uropathy	1 (0.1%)	0 (0.0%)
Postrenal failure	0 (0.0%)	1 (0.1%)
Urinary bladder haemorrhage	1 (0.1%)	0 (0.0%)
Respiratory, Thoracic, and Mediastinal Disorders	2 (0.2%)	3 (0.4%)
Aspiration	1 (0.1%)	0 (0.0%)
Chronic obstructive pulmonary disease	0 (0.0%)	1 (0.1%)
Pleural effusion	0 (0.0%)	1 (0.1%)
Pulmonary embolism	1 (0.1%)	0 (0.0%)
Pulmonary haemorrhage	0 (0.0%)	1 (0.1%)
Vascular Disorders	2 (0.2%)	0 (0.0%)
Aortic aneurysm rupture	1 (0.1%)	0 (0.0%)
Circulatory collapse	1 (0.1%)	0 (0.0%)

Adverse events reported in more than 1 enzalutamide-treated patient and at a higher incidence than in placebo-treated patients are shown in bold font.

Of the 37 deaths reported during the treatment-emergent period in the enzalutamide group, investigators assessed on the end of study CRF that 17 patients had death due to disease progression, 16 patients had death due to causes other than disease progression, and 4 had death due to unknown (or unspecified) causes. Of the 32 deaths reported during the treatment-emergent period in the placebo group, investigators assessed that 18 patients had causes of death assessed as due to disease progression, 13 as due to causes other than disease progression, and 1 due to unknown causes. A slightly higher incidence of treatment-emergent deaths was due to causes unrelated to prostate cancer in the enzalutamide group (18 patients, 2.1%) compared with the placebo group (13 patients, 1.5%)

Of these, a total of 9 enzalutamide-treated patients (1.0%) and 5 placebo-treated patients (0.6%) died of cardiovascular-related causes during the treatment-emergent period; most of these patients had multiple cardiac risk factors. Of note, only 1 patient in each treatment group had an adverse event of hypertension prior to a cardiovascular-related death.

A review of sudden or unexpected deaths due to unknown causes reported with different preferred terms under different system organ classes did not reveal any safety finding associated with enzalutamide treatment. Review of the narratives for all patients with adverse events leading to death revealed 16 patients with sudden and/or unexpected deaths: 10 patients (1.1%) in the enzalutamide group and 6 patients (0.7%) in the placebo group. Nearly all of these patients had significant cardiac risk factors at baseline, and patients in both treatment groups had occasional episodes of increased blood pressure and/or prolonged QTcF interval with no clear difference between treatment groups. When adjusted for exposure duration, the event rates of sudden or unexpected death were lower in the enzalutamide group compared with the placebo group (0.8 vs 1.1 events per 100 patient-years).

Deaths from accidents or acute injuries during the treatment-emergent period included 1 patient in the enzalutamide group (accidental drowning) and 2 patients in the placebo group (road traffic accident and subdural hematoma). One patient in each treatment group died of a second malignancy during the treatment-emergent period (1 enzalutamide-treated patient died of rectal cancer diagnosed on study day 8 and 1 placebo-treated patient died of lung adenocarcinoma diagnosed on study day 58). One patient in each treatment group died of infectious causes during the treatment-emergent period.

Serious AEs

Patients treated with enzalutamide in MDV3100-03 had a higher overall incidence of serious adverse events than patients treated with placebo (32.0% vs 26.8%); however, the difference between groups is primarily due to the longer duration of exposure in the enzalutamide group. When serious adverse events are compared by treatment group within the first 90 days, 180 days, and 365 days of treatment, the incidences of these events was lower in the enzalutamide group. The imbalance toward a higher incidence in the enzalutamide group is observed only after 1 year of treatment, when 67.8% of patients in the enzalutamide group and 18.0% of patients in the placebo group remained on study drug treatment. Similarly, the median time to the first serious adverse event is longer in the enzalutamide group than the placebo group (not yet reached vs 23.3 months).

Table 43: Summary of serious adverse events by increasing exposure time in MDV3100-03

	Enzalutamide (N = 871)	Placebo (N = 844)
Patients with any serious adverse event, n (%)	279 (32.0%)	226 (26.8%)
Within first 90 days	57 (6.5%)	116 (13.7%)
Within first 180 days	111 (12.7%)	167 (19.8%)
Within first 365 days	193 (22.2%)	203 (24.1%)
Time to first serious adverse event (months)		
Median (95% CI)	NYR (28.3, NYR)	23.3 (16.1, NYR)

Source: Module 5.3.5.3, SCS [Table 61.3, Table 65]
NYR, not yet reached.

A review of major system organ classes (i.e., those with more than 5 patients with adverse events in either treatment group) revealed that nearly all have a lower proportion of patients with serious adverse events within the first 90 days and 180 days of treatment. Vascular Disorders was the only system organ class with a higher proportion of enzalutamide-treated patients within the first 180 days of treatment (0.5% each group within 90 days; 1.0% enzalutamide vs 0.7% placebo within 180 days).

No serious adverse event terms were reported with at least a 1% higher absolute incidence in the enzalutamide group compared with the placebo group. Hydronephrosis was the only serious adverse event with at least a 1% higher incidence in the placebo group compared with the enzalutamide group (1.3% placebo vs 0% enzalutamide). Serious adverse events with at least a 0.5% higher absolute incidence in the enzalutamide group compared with the placebo group included anemia, coronary artery disease, fatigue, femoral neck fracture, pathological fracture, syncope, cauda equina syndrome, and hypertension. Serious adverse events reported in the placebo group with at least a 0.5% higher absolute incidence compared with the enzalutamide group included disease progression, hematuria, hydronephrosis, and obstructive uropathy.

Table 44: Serious adverse events reported in at least 0.5% of patients in either treatment group by system organ class in MDV3100-03

	Enzalutamide (N = 871)	**Placebo (N = 844)**
Blood and Lymphatic System Disorders	17 (2.0%)	9 (1.1%)
Anaemia	**14 (1.6%)**	**8 (0.9%)**
Cardiac Disorders	27 (3.1%)	18 (2.1%)
Atrial fibrillation	6 (0.7%)	6 (0.7%)
Coronary artery disease	**4 (0.5%)**	**0 (0.0%)**
Gastrointestinal Disorders	27 (3.1%)	16 (1.9%)
Constipation	4 (0.5%)	5 (0.6%)
General Disorders and Administration Site Conditions	32 (3.7%)	27 (3.2%)
General physical health deterioration	14 (1.6%)	10 (1.2%)
Disease progression	3 (0.3%)	7 (0.8%)
Death	4 (0.5%)	1 (0.1%)
Fatigue	**4 (0.5%)**	**0 (0.0%)**
Infections and Infestations	38 (4.4%)	28 (3.3%)
Pneumonia	10 (1.1%)	6 (0.7%)
Urinary tract infection	6 (0.7%)	5 (0.6%)
Urosepsis	5 (0.6%)	3 (0.4%)
Sepsis	1 (0.1%)	4 (0.5%)
Injury, Poisoning, and Procedural Complications	31 (3.6%)	18 (2.1%)
Fall	7 (0.8%)	3 (0.4%)
Femoral neck fracture	**5 (0.6%)**	**0 (0.0%)**
Musculoskeletal and Connective Tissue Disorders	28 (3.2%)	32 (3.8%)
Pathological fracture	**10 (1.1%)**	**5 (0.6%)**
Back pain	4 (0.5%)	5 (0.6%)
Bone pain	3 (0.3%)	5 (0.6%)
Neoplasms Benign, Malignant, and Unspecified (including cysts and polyps)	56 (6.4%)	37 (4.4%)
Metastatic pain	17 (2.0%)	17 (2.0%)
Nervous System Disorders	57 (6.5%)	43 (5.1%)
Spinal cord compression	28 (3.2%)	24 (2.8%)
Syncope	**6 (0.7%)**	**0 (0.0%)**
Cauda equina syndrome	**4 (0.5%)**	**0 (0.0%)**
Cerebrovascular accident	4 (0.5%)	1 (0.1%)
Psychiatric Disorders	2 (0.2%)	7 (0.8%)
Confusional state	1 (0.1%)	4 (0.5%)
Renal and Urinary Disorders	39 (4.5%)	60 (7.1%)
Urinary retention	10 (1.1%)	13 (1.5%)
Haematuria	5 (0.6%)	12 (1.4%)
Urinary tract obstruction	7 (0.8%)	8 (0.9%)
Hydronephrosis	0 (0.0%)	11 (1.3%)
Renal failure acute	5 (0.6%)	5 (0.6%)

Ureteric obstruction	4 (0.5%)	4 (0.5%)
Obstructive uropathy	2 (0.2%)	6 (0.7%)
Respiratory, Thoracic, and Mediastinal Disorders	21 (2.4%)	18 (2.1%)
Pulmonary embolism	5 (0.6%)	7 (0.8%)
Vascular Disorders	16 (1.8%)	7 (0.8%)
Deep vein thrombosis	4 (0.5%)	2 (0.2%)
Hypertension	**4 (0.5%)**	**0 (0.0%)**

Source: Module 5.3.5.3, SCS [Table 61]
Serious adverse events with at least a 0.5% higher absolute incidence in the enzalutamide group compared with the placebo group are shown in bold font.

The proportion of patients with serious adverse events of anemia was higher in the enzalutamide group overall, but lower within the first 90 days (0.1% enzalutamide vs 0.6% placebo) and 180 days (0.6% vs 0.7%) of treatment. The same finding is true for the incidence of pathological fractures within the first 90 days (0.2% enzalutamide vs 0.4% placebo) and 180 days (0.2% vs 0.5%) of treatment. Cauda equina syndrome was not reported in the placebo group, but most events in the enzalutamide group occurred after at least 180 days of treatment.

Overall, study drug-related serious adverse events were reported infrequently with no significant difference between treatment groups (2.9% of enzalutamide-treated patients vs 2.6% of placebo-treated patients). Acute renal failure (0.3% enzalutamide vs 0.1% placebo) and pulmonary embolism (0% vs 0.4%) were the only serious adverse events assessed as related to study drug reported in more than 2 patients (0.2%) in either treatment group.

Other significant events

There are no indications of enzalutamide causing nephrotoxicity, hepatotoxicity, substantial gastrointestinal toxicities, or an increased risk of venous thromboembolism. While keeping the increased risk of hypertension in mind, no association with major adverse cardiovascular events or QTc-prolongation was observed.

Table 45: Summary of events with lack of association in time-adjusted analysis

		MDV3100-03		**Combined Controlled Population**	
		Enzalutamide (N = 871)	**Placebo (N = 844)**	**Enzalutamide (N = 1671)**	**Placebo (N = 1243)**
Cardiac	Patients with any event in Cardiac Disorders system organ class, n (%)	88 (10.1%)	66 (7.8%)	141 (8.4%)	97 (7.8%)
	Adverse event rates per 100 patient-years for Cardiac Disorders system organ class, n (event rate)	121 (10.3)	80 (14.8)	197 (10.6)	118 (16.6)
	Patients with any major adverse cardiovascular event, n (%) a	23 (2.6%)	16 (1.9%)	38 (2.3%)	24 (1.9%)
	Adverse event rates per 100 patient-years for major adverse cardiac events, n (event rate)	24 (2.0)	16 (3.0)	39 (2.1)	25 (3.5)
QT	Patients with any event in torsades de pointes / QT prolongation SMQ, n (%)	11 (1.3%)	11 (1.3%)	14 (0.8%)	12 (1.0%)

	Adverse event rates per 100 patient-years in torsades de pointes SMQ, n (event rate)	12 (1.0)	11 (2.0)	15 (0.8)	12 (1.7)
Gastro-intestinal	Patients with any event in GI Disorders SOC, n (%)	510 (58.6%)	438 (51.9%)	1055 (63.1%)	718 (57.8%)
	Adverse event rates per 100 patient-years for common GI events, n (event rate)	699 (59.2)	605 (111.7)	1664 (89.8)	1129 (158.6)
Fatigue	Patients with any fatigue-related event	421 (48.3%)	295 (35.0%)	839 (50.2%)	481 (38.7%)
	Adverse event rates per 100 patient-years for fatigue-related events, n (event rate)	526 (44.6)	330 (60.9)	1051 (56.7)	547 (76.9)
Hepatic	Patients with any event in Hepatobiliary Disorders system organ class	7 (0.8%)	3 (0.4%)	16 (1.0%)	6 (0.5%)
	Adverse event rates per 100 patient-years in 'drug related hepatic disorders' SMQ, n (event rate)	38 (3.2)	29 (5.4)	69 (3.7)	45 (6.3)
Infection	Patients with any event in Infections and Infestations system organ class	349 (40.1%)	228 (27.0%)	643 (38.5%)	346 (27.8%)
	Adverse event rates per 100 patient-years for events of infection, n (event rate)	557 (47.2)	337 (62.2)	1039 (56.1)	500 (70.3)
	Grade ≥ 3 adverse event rates per 100 patient-years for events of infection, n (event rate)	54 (4.6)	45 (8.3)	123 (6.6)	68 (9.6)
Loss of consciousness	Patients with any event of loss of consciousness	16 (1.8%)	10 (1.2%)	24 (1.4%)	14 (1.1%)
	Adverse event rates per 100 patient-years for events of loss of consciousness, n (event rate)	16 (1.4)	10 (1.8)	26 (1.4)	14 (2.0)
Insomnia	Patients with any event of insomnia, n (%)	70 (8.0%)	47 (5.6%)	140 (8.4%)	71 (5.7%)
	Adverse event rates per 100 patient-years for events of insomnia, n (event rate)	74 (6.3)	47 (8.7)	147 (7.9)	71 (10.0)
Anxiety	Patients with any event of anxiety, n (%)	33 (3.8%)	22 (2.6%)	85 (5.1%)	38 (3.1%)
	Adverse event rates per 100 patient-years for events of anxiety, n (event rate)	34 (2.9)	22 (4.1)	88 (4.7)	38 (5.3)
Renal	Patients with any event in acute renal failure SMQ, n (%)a	32 (3.7%)	38 (4.5%)	51 (3.1%)	55 (4.4%)
	Adverse event rates per 100 patient-years in acute renal failure SMQ, n (event rate)	38 (3.2)	43 (7.9)	60 (3.2)	62 (8.7)

	Patients with any grade 3 or 4 central laboratory values, high: Creatinine (μmol/L), n (%)	2 (0.2%)	3 (0.4%)	2 (0.1%)	4 (0.3%)
	Patients with any change in 2 toxicity grades in central laboratory values, high: Creatinine (μmol/L), n (%)	6 (0.7%)	8 (1.0%)	8 (0.5%)	16 (1.3%)
VTE	Patients with any event in venous thromboembolic SMQ, n (%)[a]	15 (1.7%)	17 (2.0%)	34 (2.0%)	27 (2.2%)
	Adverse event rates per 100 patient-years in venous thromboembolic SMQ, n (event rate)	18 (1.5)	20 (3.7)	37 (2.0)	31 (4.4)

GI, gastrointestinal; SMQ, standardized MedDRA query, SOC, system organ class, VTE, venous thromboembolism
a Three SMQs involving myocardial infarction and stroke events were combined to assess a group of major adverse cardiovascular events (MACE)
a: Defined by the broad SMQ 'acute renal failure
a Defined by the narrow SMQ 'embolic and thrombotic events, venous.'

Laboratory findings

An association of enzalutamide treatment with decreased leukocyte and neutrophil counts was identified in both controlled studies. A review of clinical laboratory-related adverse events in the Investigations system organ class did not reveal any imbalances to suggest a safety signal apart from the imbalances in neutropenia/leukopenia.

Treatment with enzalutamide was not associated with any clinically significant changes in liver function tests, nor in renal function tests (blood urea nitrogen, creatinine, and potassium). No clinically relevant mean changes relative to baseline values or to the placebo group were noted for hemoglobin levels, platelets, sodium, chloride, magnesium, phosphate, calcium, or creatinine kinase levels over time. Although a greater proportion of patients had central laboratory CTCAE grade 1 hyperglycemia in the enzalutamide groups of MDV3100-03 and the combined controlled population compared with the placebo groups (73.0% vs 59.5% in MDV3100-03; 74.2% vs 62.1% in the combined controlled population), there was no difference between treatment groups in the proportion of patients with a toxicity change of 2 or more in elevated glucose (4.6% vs 4.3% in MDV3100-03; 3.7% vs 4.0% in the combined controlled population), or the proportion of patients with grade 3 or 4 hyperglycemia (4.0% vs 3.0% in MDV3100-03; 3.1% vs 2.8% in the combined controlled population). Furthermore, the proportion of patients with events in the narrow SMQ of 'hyperglycemia' was lower in the enzalutamide groups compared with the placebo groups (2.9% vs 3.6% in MDV3100-03; 2.0% vs 3.2% in the combined controlled population. Consistent with antitumor activity, enzalutamide treatment was associated with decreases in LDH and alkaline phosphatase levels over time compared to baseline and compared with placebo treatment.

Safety in special populations

Of the 1671 patients in the phase 3 trials who received enzalutamide, 1261 patients (75%) were 65 years and over and 516 patients (31%) were 75 years and over.

A trend toward increasing incidence of adverse events with increasing age was observed in both the enzalutamide and placebo groups. An increased incidence of fatigue and asthenia was observed with increasing age in the enzalutamide group of the combined controlled population and integrated safety population that was not apparent in the placebo group of the combined controlled population. The

increasing incidence of falls and peripheral edema with increasing age were observed in the enzalutamide and placebo groups, although the rates were generally lower in the placebo group. A reverse trend was observed for some common adverse events such as hot flush, musculoskeletal pain, insomnia and headache, where younger patients experienced increased incidence over older patients in both enzalutamide and placebo groups. The incidence of other adverse events was not significantly affected by age. In general, an increased incidence of non-pathological fracture was observed with increasing age in both treatment groups, consistent with the increased incidence of fall. No clear effect of age was observed on the incidence of hypertension, mental impairment, or seizure adverse events.

Safety related to drug-drug interactions and other interactions

Differences were observed with regard to use of concomitant medication in the enzalutamide and placebo arms, respectively, in study MDV3100-03. The largest difference between treatment groups with respect to ATC level 2 drug categories was seen with antibacterials for systemic use (35.9% in the enzalutamide group and 28.9% in the placebo group), anti-inflammatory and anti-rheumatic products (50.5% and 44.9%), agents acting on renin-angiotensin system (50.4% and 45.0%), and anti-anaemic preparations (13.0% and 7.8%), and analgesics (64.3% enzalutamide and 59.8% placebo).

Table 46: Classes of ATC Level 2 Concomitant Medications Used by ≥ 20% of Patients in Either Treatment Group by Decreasing Frequency, Study MDV3100-03

ATC Level 2 Category	Enzalutamide (N = 871)	Placebo (N = 844)	Total (N = 1715)
Patients taking any concomitant medication	871 (100%)	842 (99.8%)	1713 (99.9%)
Endocrine therapy[a]	831 (95.4%)	807 (95.6%)	1638 (95.5%)
Analgesics	560 (64.3%)	505 (59.8%)	1065 (62.1%)
Agents acting on the renin-angiotensin system	439 (50.4%)	380 (45.0%)	819 (47.8%)
Antiinflammatory and antirheumatic products	440 (50.5%)	379 (44.9%)	819 (47.8%)
Antithrombotic agents	418 (48.0%)	376 (44.5%)	794 (46.3%)
Lipid modifying agents	382 (43.9%)	369 (43.7%)	751 (43.8%)
Mineral supplements	366 (42.0%)	338 (40.0%)	704 (41.0%)
Drugs for acid related disorders	363 (41.7%)	320 (37.9%)	683 (39.8%)
Drugs for treatment of bone diseases	303 (34.8%)	296 (35.1%)	599 (34.9%)
Antibacterials for systemic use	313 (35.9%)	244 (28.9%)	557 (32.5%)
Vitamins	299 (34.3%)	257 (30.5%)	556 (32.4%)
Corticosteroids for systemic use	231 (26.5%)	255 (30.2%)	486 (28.3%)
Beta-blocking agents	225 (25.8%)	204 (24.2%)	429 (25.0%)
Laxatives	232 (26.6%)	193 (22.9%)	425 (24.8%)
Calcium channel blockers	225 (25.8%)	176 (20.9%)	401 (23.4%)
Psycholeptics	204 (23.4%)	196 (23.2%)	400 (23.3%)
Diuretics	218 (25.0%)	177 (21.0%)	395 (23.0%)
Urologicals	210 (24.1%)	185 (21.9%)	395 (23.0%)

Therapeutic class is based on WHO Drug Dictionary B2 Enhanced (September 2011). Patients are counted once at each level of summarization (overall, drug class, and generic name).
a: Patients were required to maintain androgen deprivation therapy.
ATC, anatomical therapeutic chemical.

Discontinuation due to adverse events

Discontinuations

The proportion of patients with adverse events that were the primary reason for discontinuation of study drug in MDV3100-03 was comparable between treatment groups (5.6% enzalutamide vs 6.0% placebo). A review of these adverse events by system organ class revealed that General Disorders and Administration Site Conditions was the only system organ class with a difference of at least 1% between treatment groups and demonstrated a lower incidence in the enzalutamide group (0.2% enzalutamide vs 1.3% placebo). This imbalance was primarily due to events of fatigue as the primary reason for discontinuation of study drug, reported in 2 patients (0.2%) in the enzalutamide group and 8 patients (0.9%) in the placebo group. One additional placebo-treated patient discontinued treatment primarily due to an event of asthenia, and 2 additional placebo-treated patients discontinued treatment primarily due to lethargy. Adverse events that were the primary reason for discontinuation of study drug reported in more than 1 patient in either treatment group and were more common in the enzalutamide group included cerebrovascular accident, syncope, and acute renal failure.

Table 47: Adverse events as the primary reason for discontinuation of study drug reported in more than 1 patient in either treatment group by system organ class in MDV3100-03

System Organ Class Preferred Term	Enzalutamide (N = 871)	Placebo (N = 844)
Patients with any adverse event as primary reason for treatment discontinuation	49 (5.6%)	51 (6.0%)
Gastrointestinal Disorders	4 (0.5%)	11 (1.3%)
Nausea	3 (0.3%)	3 (0.4%)
Dysphagia	0 (0.0%)	3 (0.4%)
Vomiting	0 (0.0%)	2 (0.2%)
General Disorders and Administration Site Conditions	2 (0.2%)	11 (1.3%)
Fatigue	2 (0.2%)	8 (0.9%)
Injury, Poisoning, and Procedural Complications	2 (0.2%)	3 (0.4%)
Subdural haematoma	0 (0.0%)	2 (0.2%)
Investigations	2 (0.2%)	2 (0.2%)
Hepatic enzyme increased	0 (0.0%)	2 (0.2%)
Nervous System Disorders	11 (1.3%)	6 (0.7%)
Cerebrovascular accident	**2 (0.2%)**	**1 (0.1%)**
Lethargy	0 (0.0%)	2 (0.2%)
Syncope	**2 (0.2%)**	**0 (0.0%)**
Renal and Urinary Disorders	3 (0.3%)	5 (0.6%)
Renal failure acute	**2 (0.2%)**	**1 (0.1%)**

Source: Module 5.3.5.3, SCS [Table 55]
Adverse events that were the primary reason for discontinuation of study drug in more than 1 patient in either treatment group and were more common in the enzalutamide group compared with the placebo group are shown in bold font.

Of the patients with adverse events that were the primary reason for treatment discontinuation, less than half in each treatment group were assessed as study drug-related, and the incidence was lower in the enzalutamide group compared with the placebo group (2.1% vs 2.8%). The study drug-related adverse events that were the primary reason for treatment discontinuation in more than 1 patient in either treatment group included acute renal failure (0.2% enzalutamide vs 0% placebo), nausea (0.2% vs 0.4%), fatigue (0.2% vs 0.8%), and hepatic enzymes increased (0% vs 0.2%)

The proportion of patients with adverse events associated with discontinuation of study drug in MDV3100-03 was lower in the enzalutamide group than the placebo group (17.0% enzalutamide vs 25.6% placebo). Back pain was the only adverse event associated with discontinuation of study drug that was more common in the enzalutamide group by at least 0.5% (2.2% vs 1.7%). Adverse

events associated with discontinuation of study drug that were more common in the placebo group by at least 0.5% included dysphagia (0% enzalutamide vs 0.5% placebo), fatigue (0.7% vs 1.8%), decreased appetite (0% vs 0.6%), bone pain (0.9% vs 3.2%), musculoskeletal pain (0.1% vs 0.6%), spinal cord compression (1.1% vs 1.9%), lethargy (0% vs 0.6%), hematuria (0% vs 0.5%), and hydronephrosis (0% vs 0.5%).

Dose Interruption

The proportion of patients with adverse events leading to dose interruption in MDV3100-03 was modestly higher in the enzalutamide group compared with the placebo group (11.3% enzalutamide vs 10.4% placebo). Within each system organ class, the absolute difference in incidence between treatment groups was less than 1%. The only adverse events with an incidence at least 0.5% higher in the enzalutamide group were asthenia (0.7% enzalutamide vs 0.1% placebo), vomiting (0.6% vs 0.1%), and renal failure (0.5% vs 0%). The increase in asthenia events was offset by a lower incidence of events of fatigue (0.5% enzalutamide vs 0.8% placebo) and a comparable incidence of events of malaise (0.1% vs 0.1%). The increase in acute renal failure events was offset by a lower incidence of obstructive uropathy (0.1% enzalutamide vs 0.4% placebo) and acute prerenal failure (0% vs 0.1%). Adverse events leading to dose interruption with an incidence at least 0.5% higher in the placebo group compared with the enzalutamide group were ECG QT prolonged (0% enzalutamide vs 0.6% placebo), decreased appetite (0.3% vs 0.8%), and dehydration (0% vs 0.6%). The incidences of the remainder of events were comparable between treatment groups.

Study drug-related adverse leading to dose interruption were less common in the enzalutamide group compared with the placebo group (3.1% vs 4.4%). No study drug-related events leading to dose interruption were reported with at least 0.5% increased incidence in the enzalutamide group compared with the placebo group. Study drug-related adverse events leading to dose interruption reported with at least 0.5% increased incidence in the placebo group compared with the enzalutamide group included ECG QT prolonged (0% enzalutamide vs 0.6% placebo) and decreased appetite (0.1% vs 0.8%)

Dose Reduction

Adverse events leading to dose reduction in MDV3100-03 were infrequent in both treatment groups, although the proportion of patients with adverse events leading to temporary dose reduction was higher in the enzalutamide group compared with the placebo group (2.1% vs 0.9%). No system organ class was represented by more than 1% of patients in either treatment group and no adverse event was reported with at least a 0.5% difference in incidence between treatment groups. Fatigue was the only adverse event reported in at least 0.5% of patients in a treatment group (0.5% enzalutamide vs 0.1% placebo). An additional enzalutamide-treated patient experienced an event of asthenia leading to dose reduction. In each enzalutamide-treated patient, the dose reduction (to 80 mg or 120 mg daily) led to resolution of the fatigue event or improvement to a lower grade.

Post marketing experience

Enzalutamide was commercially available as Xtandi in the US in September 2012. In Europe, enzalutamide was initially made available in France through a temporary authorization for use (ATU) in April 2013. Between June 2013 and October 2013, enzalutamide was marketed in Austria, Canada, Denmark, Finland Germany, Great Britain, Netherlands, Norway, Portugal, Spain, and Sweden.

Based on estimates obtained from Source Healthcare Analytics, the average treatment duration with enzalutamide in the US was 4.3 months through September 2013. Reliable estimates were not available for other markets, so patient treatment years (PTY) is provided as the unit of patient exposure.

The enzalutamide post marketing exposure estimates are based on internal sales data for all countries. These internal sales data represent product shipment from manufacturer to distributor (i.e., wholesaler, specialty pharmacy, etc). The initial sales of the product represent distributor stocking of the product. This may result in an overestimate of patient exposure following initial marketing.

A cumulative review and evaluation of post marketing serious adverse events for Xtandi (enzalutamide) was performed for all cases reported through 31 October 2013. Xtandi was first approved in the US on 31 August 2012.

A search of the global safety database was conducted on 08 November 2013 to retrieve all post marketing cases with at least 1 serious adverse event reported during the review period. The case report types include spontaneous cases, cases received from regulatory authorities, compassionate use cases, and investigator initiated trials cases. The post marketing serious and non-serious cases were also reviewed for events of interest.

A total of 1803 cases with at least 1 serious adverse event were reported during this review period, including 1278 spontaneous cases, 521 compassionate use cases, 3 cases received from a regulatory authority (European Union), and 1 investigator initiated trial case. These cases contained a total of 3093 serious adverse events, of which the most commonly reported events were from the system organ class of General Disorders and Administration Site Conditions (718 events), Neoplasms Benign, Malignant, and Unspecified (incl. cysts and polyps) (641 events), and Nervous System Disorders (253 events).

A review of all post marketing serious adverse events and events of interest reported through 31 October 2013 revealed no new safety information.

One Periodic Safety Update Report (PSUR) for the review period of 21 June 2013 to 20 December 2013 was submitted with a due date of 28 February 2014. The cumulative review detected no new safety signals or warranted any label changes during the reference period.

2.5.2. Discussion on clinical safety

The safety database of enzalutamide encompasses 2509 patients treated with enzalutamide plus standard of care. Of them, 967 patients (38.5%) did not receive prior docetaxel and therefore are considered the target population for this application of new indication. Within the main study (MDV3100-03, PREVAIL) the median treatment duration for the enzalutamide group was 16.6 months compared with 4.6 months for the placebo group, which intuitively foresee a higher incidence of AEs.

Overall, the treatment with enzalutamide was well tolerated, since the dose reductions, interruptions and discontinuations were similar or slightly higher for enzalutamide.

Regarding common AEs, the incidence of AEs in the MDV3100-03 study was high in both groups. More than 90% of patients had some AEs. Fatigue, back pain, constipation, arthralgia, decreased appetite, diarrhoea, hot flush, asthenia, weight decreased, peripheral oedema, hypertension, headache, fall, dizziness, haematuria, insomnia, nasopharyngitis, dysgeusia, and upper respiratory tract infection were the most reported AEs for enzalutamide when compared to placebo (AEs reported in at least 5% of patients in either treatment group with at least a 2% absolute increased incidence in the enzalutamide vs placebo).

When the AEs reported were adjusted for length of exposure, hot flush, hypertension, fall, and dysgeusia, were higher for patients treated with enzalutamide. Hypertension, fall, hot flush, dysgeusia, and upper respiratory tract infection were approximately twice more frequently reported in the enzalutamide arm. According to the investigators, diarrhoea, constipation, fatigue, asthenia, peripheral oedema, dysgeusia, headache, hot flush, and hypertension were probably related to the study drug.

The term gynaecomastia was not presented in the summary table provided by the MAH with 5% frequency cut-off. However, according to the source data the frequencies were 3.3% vs. 1.3% in the enzalutamide arm vs. placebo arm in study MDV3100-3, it has therefore been included in the section 4.8 of the SmPC under frequency “common”.

Grade 3 or higher AEs more frequently reported in the enzalutamide arm versus placebo were cataract (1.3% vs 0.1%) nausea (1.0% vs 0.5%) general physical health deterioration (2.1% vs 1.2%) pneumonia (1.3% vs 0.8%) fall (1.4% vs 0.7%) spinal cord compression (3.8% vs 2.8%) syncope (1.6% vs 0.9%) and hypertension (6.8% vs 2.3%). However, only hypertension and cataract remained higher in the enzalutamide arm after adjusting for the longer safety reporting period.

Fatigue, hot flush, hypertension, fall, mental impairment, neutropenia, hallucinations, seizure, fatal infections, hepatotoxicity, renal toxicity and cardiac disorders were considered AEs of special interest in the pre-docetaxel setting. Of them, hallucinations, seizure, fatal infections, hepatotoxicity and renal toxicity were not considered associated with the treatment of enzalutamide. Fatigue, hot flush, hypertension, fall, mental impairment, neutropenia and cardiac disorders had a higher rate of incidence in the patients treated with enzalutamide. Hypertension was clearly associated to enzalutamide, being the most reported AEs grade 3-4 (6.8%). The incidence of falls was numerically higher for the enzalutamide group (11.6% vs 5.3%). However, it was evenly balanced within the 180 days of treatment. This AE could be associated to non-pathological fractures (7.8% enzalutamide vs 3.0% placebo) or even seizures. Cardiac disorders, despite the higher incidence in AEs (10.1% enzalutamide vs 7.8% placebo) and grade 3-4 (2.8% vs 2.1%) were lower in the enzalutamide group when adjusted for length of exposure.

With regard to the important identified risk of hallucination, no difference between arms was observed in MDV3100-3. An event of hallucination was reported for 1 patient in each treatment group (0.1%). In CRPC2 the incidence was higher in the enzalutamide group compared with the placebo group (1.6% vs. 0.3%). The event rate /100 PY in the enzalutamide arm was higher in CRPC2 (2.2) and the pooled uncontrolled studies (1.6) was higher than that in MDV3100-3 (<0.1), despite a longer reporting time in the last one. The reason for this difference between studies is not known. The MAH argues that most patients with hallucinations were receiving concomitant opiate pain medications. On the basis of the data from MDV3100-3, the PRAC and CHMP consider that hallucinations can be removed from the list of the safety concerns in the RMP.

Of note, there was an increased occurrence of cataract in the enzalutamide arm compared with placebo in MDV3100-3. It is possible that increasing age and other risk factors increase the risk of cataract over time, thereby contributing to a higher time-adjusted rate in the enzalutamide-treated arm due to the 3 times longer observation time in this arm. It is also agreed that the time-to-onset is low (< 1 year) for most cases, suggesting other causative factors, and for the longer time spans only data from the enzalutamide arm is available. It was therefore not included in the SmPC.

Cognitive/memory impairment was proposed to be upgraded from important potential risk to important identified risk in the RMP by the MAH which is endorsed. In MDV3100-3, the rate of the MedDRA HLGT term of mental impairment disorders was 4.5 vs. 2.8 events/ 100 patient-years in the enzalutamide vs. placebo arm. However, due to the low frequencies, the size of the respective problems from a clinical perspective appears relatively small.

In the phase 3 clinical studies, 7 patients (0.4%) experienced a seizure out of 1671 patients treated with a daily dose of 160 mg enzalutamide, whereas one patient (<0.1%) receiving placebo experienced a 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. In both phase 3 studies, patients with prior seizure or risk factors for seizure were excluded.

As discussed in the assessment of the initial MAA, enzalutamide 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. In the registration study CRPC2, a higher frequency of seizure was observed than placebo (0.8 vs. 0%, 6 vs. 0 patients). In the present pivotal study MDV3100-03, the incidence was lower and was the same in both treatment arms, (0.1 vs. 0.1%, 1 vs. 1 patient). The three-fold longer observation time in the enzalutamide arm compared to the placebo arm in study CRPC2, as well as in study MDV3100-03, should be kept in mind. In that perspective, the difference in seizure events between treatment groups in the Combined Controlled Population (CCP; 0.4 vs. 0.1 %) might not be of concern.

Considering the event-rate per 100 patient-years (PY) calculated for convulsions SMQ events, it is noted that an increased event rate persists compared with placebo in the combined phase-3 population (but not in MDV3100-03 alone), although the small numbers make the estimates uncertain (e.g. if only one more patient in the placebo group had a seizure, the event rate would be 2.8/1000= PY, similar to the rate in the active arm.) Taken together, the size of the clinical problem of seizures appears small, including the added information from MDV3100-03.

With regard to the eligibility criteria of MDV3100-03 versus CRPC2, the relevant difference in exclusion criteria concerned concomitant medications that lower the seizure threshold. However, the actual use of concomitant medications lowering the seizure threshold (that were not allowed in study CRPC2) was comparable in both studies as well as between study arms within each study. As a consequence, the difference in seizure between the two studies cannot be explained by the difference in the frequency of use of these drugs.

In conclusion, no explanation for the lower incidence of convulsions/seizure in the present MDV3100-03 compared with previous studies have been presented by the MAH. In the absence of other explanations, it is conceivable that this phenomenon could be due to a better identification of study participants at risk for seizure at screening. Overall, given the pre-clinical background, the presence of a potential mechanism and a dose-response relationship, and the overrepresentation in clinical other studies, seizure is still considered an important identified risk.

Falls are confirmed as a common ADR in MDV3100-03.The incidence of falls was numerically higher for the enzalutamide group (11.6% vs 5.3%). However, it was evenly balanced within the 180 days of treatment. The review of the clinical documentation associated to falls did not show any relationship between these events and seizures. Despite the higher AEs of falls in the enzalutamide group (11.6% vs 5.3%) there does not seem to be a clear association with seizures.

Although the incidence is low across studies, given the consistency of findings and the occurrence within the first 90 days of treatment, restless legs syndrome is considered an adverse drug reaction and included in section 4.8 of the SmPC.

Adverse events resulting in death occurred in 37 patients (4.2%) in the enzalutamide group and 32 patients (3.8%) in the placebo group. Cardiac disorders was reported as AE leading to death in 7 patients (0.8%) in the enzalutamide group vs 3 patients (0.4%) in the placebo group. 10 patients (1.1%) in the enzalutamide group and 6 patients (0.7%) in the placebo group experienced sudden or unexpected deaths, mostly due to cardiac or presumed cardiac causes during the study. According to the MAH, nearly all patients with a sudden death event had clinically significant cardiac risk factors at baseline. Within the profile of serious AEs in a higher frequency for enzalutamide group, coronary

artery disease was one of them (0.5% vs 0%). Once the cardiovascular adverse events have been adjusted for exposure duration, the risk is considered less of concern.

The fact that study MDV3100-03 allowed patients at higher cardiovascular risk as determined by less stringent blood pressure entry criteria, patients with a history of arrhythmias requiring treatment, and patients with a history of moderate (New York Heart Association [NYHA] class II) heart failure could have influenced these findings.

A higher incidence of events of secondary malignancy, including non-melanoma skin cancer, was observed in the MDV3100-03 enzalutamide group compared with the placebo group (3.9% vs 1.1%; 3.1 vs 0.7% excluding non-melanoma skin cancer. The time-adjusted event rate for secondary malignancy was also increased in the enzalutamide arm of MDV3100-3 compared to the placebo arm (3.3 vs. 1.8 events/ 100 PY) The difference in frequency of second malignancy between study arms in MDV3100-3 which persists in time-adjusted analysis is not explained. The numbers are small however, and chance findings cannot be ruled out. No difference in the rate of secondary malignancies across study arms was seen in time-adjusted analyses of Study CRPC2 (1.2 vs. 1.2 events/ 100 PY). Frequencies and cancer types in the enzalutamide arm in MDV3100-3 are overall within expected population-based frequencies. Given the relatively short time to onset, it is not likely that the observed cases represent a cancer-*inducing* effect of enzalutamide. Furthermore, as an anti-androgen, there is no obvious mechanism for a theoretical cancer-*promoting* effect of enzalutamide, as androgens normally promote growth. In addition, it could be hypothesised that the risk of secondary malignancies is not constant over time and that the higher rates of secondary malignancy, also in time-adjusted analyses, might partly be caused by other risk factors (age, radiotherapy) acting on the prolonged observation time in the enzalutamide arm. Secondary malignancies will continue to be closely monitored in PSURs and specifically addressed in the already planned updates from MDV3100-3 to the CHMP.

A total of 241 enzalutamide-treated patients (27.6%) and 299 placebo-treated patients (35.4%) died as of the data cut-off date. The vast majority were due to disease progression (21.0% of enzalutamide-treated patients and 26.9% of placebo-treated patients). On the contrary, a higher percentage of patients in the enzalutamide arm died within 30 days after discontinuation of study drug in comparison to placebo (4.0% vs 3.4%).

Regarding the serious AEs, a higher percentage of patients in the enzalutamide group had serious AEs than in placebo group (32.0% vs 26.8%). Nevertheless, it seems that this higher percentage is due to events occurring after 1 year of treatment. Serious AEs reported in a higher frequency in the enzalutamide group included anaemia (1.6% enzalutamide vs 0.9% placebo), coronary artery disease (0.5% vs 0%), fatigue (0.5% vs 0%), femoral neck fracture (0.6% vs 0%), pathological fracture (1.1% vs 0.6%), cauda equina syndrome (0.5% vs 0%), syncope (0.7% vs 0%), and hypertension (0.5% vs 0%).

No overall differences in safety or effectiveness were observed between older patients and younger patients.

Higher frequencies were observed in the enzalutamide arm compared to the placebo arm in study MDV3100-03 with regard to concomitant medication with anti-bacterials for systemic use (7.0% difference), anti-inflammatory and anti-rheumatic products (5.6% difference), anti-anaemic preparations (5.2% difference), and analgesics (4.5% difference). The differences might be attributable to the considerably longer observation time in the enzalutamide arm.

2.5.3. Conclusions on clinical safety

Overall, the safety profile of enzalutamide previously shown in the post-docetaxel setting seems to be quite similar to the one observed in the pre-docetaxel setting. Few additional adverse drug reactions have been included (restless legs syndrome, gynaecomastia and asthenia/fatigue) and some ADRs frequencies have changed likely due to the longer exposure in this setting (neutropenia, visual hallucinations, cognitive disorder, amnesia, hypertension, disturbance in attention).

2.5.4. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

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 48: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Seizure Hypertension Fall Neutrophil count decreased Non-pathological fracture Cognitive/memory impairment Interactions with strong inhibitors or inducers of CYP2C8 Interactions with medicinal products that are substrates of CYP3A4, CYP2C9 or CYP2C19
Important potential risks	None
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 Patients with metastatic castration-resistant prostate cancer previously treated with abiraterone.

Pharmacovigilance plans

Table 2.2: Ongoing and planned studies in the PhV development plan

Study /Activity Type, Title and Category (1-3)*	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports (planned or actual)**
Postauthorisation safety study Category: **3**	The safety of enzalutamide in patients excluded from the pivotal study due to certain baseline factors considered predisposing for seizure.	Seizure	Ongoing	Final protocol submission: July 2013 Study completion date: June 2018 Final report submission: March 2019
Clinical study Category: **3**	Assess, in subjects with normal hepatic function and patients with preexisting severe hepatic impairment, the effect of severe hepatic impairment on the pharmacokinetics of enzalutamide and N-desmethyl enzalutamide	Patients with severe hepatic impairment	Planned	Final protocol submission: March 2013 Study completion date: May 2014 Final report submission: November 2014
Clinical study Category: **3**	Assess, in subjects with normal hepatic function and patients with pre- existing moderate hepatic impairment, the effect of moderate hepatic impairment on the pharmacokinetics of enzalutamide and N desmethyl enzalutamide	Patients with moderate hepatic impairment	Planned	Draft protocol submission: February 2014 Final report submission: December 2015
Postauthorisation study Category: **3**	Collect data on the efficacy and safety of enzalutamide in patients with metastatic CRPC previously treated with abiraterone	Patients with metastatic CRPC previously treated with abiraterone	Ongoing	Final protocol submission: November 2013 Report of interim Analysis: June 2015 Final report submission: December 2016

CRPC: castration-resistant prostate cancer; TBD: to be determined
*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 49: Proposal from MAH for risk minimisation measures (copy from V.3 of RMP)

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Seizure	SmPC Sections 4.4, 4.8	None
Hypertension Hallucination Falls Cognitive/Memory Impairment Neutrophil Count Decreased Non-pathological Fracture	SmPC Section 4.8	None
Interactions with Strong Inhibitors or Inducers of CYP2C8 Interactions with Medicinal Products that are Substrates of CYP3A4, CYP2C9 or CYP2C19	SmPC Sections 4.2, 4.4, 4.5	None
Patients with Severe Renal Impairment	SmPC Sections 4.2, 4.4, 5.2	None
Patients with Moderate or Severe Hepatic Impairment	SmPC Sections 4.2, 4.4, 5.2	None
Reproduction/Fertility	SmPC Section 4.6	None
Patients of Non-white Race	SmPC Section 5.1, 5.2	None
Patients with ECOG PS ≥ 2	SmPC Section 5.1	None
Patients with Severe Cardiovascular Disease	SmPC Section 5.1	None
Brain Metastases or baseline Factors Predisposing for Seizure	SmPC Sections 4.4, 4.8, 5.1	None
Patients with Metastatic CRPC Previously Treated with Abiraterone	SmPC Section 5.1	None

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Xtandi 40 mg soft capsules. The MAH has submitted a bridging report justifying that no major changes have been made to the leaflet as a consequence of the new indication. There were no significant differences in the content of the daughter leaflet (i.e. 2014) compared to the parent one (i.e. 2012). In addition the key messages as well as the writing style and layout are the same. The justification is considered acceptable and thus a separate User Test is not considered required.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The administration of enzalutamide in the pre-chemotherapy setting resulted in a clinically meaningful and statistically significant benefit on both overall survival and rPFS (co-primary endpoints) as demonstrated by a 29% decrease in the risk of death for patients receiving enzalutamide compared with patients receiving placebo (HR 0.706 [95% CI: 0.596, 0.837]) and a 81% decrease in the risk of radiographic progression or death for patients receiving enzalutamide compared with patients receiving placebo (HR 0.186 [95% CI: 0.149, 0.231]).

The updated analysis (cut-off January 2014; after four additional months and 116 additional deaths; 58 in each group) confirmed the observations from the pre-specified interim analysis (HR 0.730 and HR 0.706 respectively).

To ascertain that the benefit by enzalutamide on OS was not influenced by post-baseline therapies, an analysis on subsequent treatments were conducted. In the placebo arm 76 % subjects received any post-baseline anti-neoplastic treatment compared to 44 % in the enzalutamide arm. Thus, it may be concluded that the OS benefit observed is attributable to enzalutamide.

Secondary endpoints also showed positive results for enzalutamide: Time to first skeletal-related event (HR 0.718 [95% CI: 0.610, 0.844]); Time to initiation of cytotoxic chemotherapy (HR 0.349 [95% CI: 0.303, 0.403]); Time to PSA progression (HR 0.169 [95% CI: 0.147, 0.195]); PSA response rate $\geqslant$ 50% (between-group difference of 74.5% [95% CI: 71.45-77.57%]; Best overall soft tissue response (between-group difference of 53.9% [95% CI: 48.53-59.17%]).

Results from the co-primary endpoints were robust, showing positive outcomes in all the sensitivity analyses and in the vast majority of subgroups.

Uncertainty in the knowledge about the beneficial effects

The study was stopped after an interim analysis on OS, allowing placebo treated patients to receive enzalutamide treatment. This fact will impact on more mature OS data. In fact, some of the estimates commonly used when it comes to describing the effect (i.e. median) have not been reached yet. In addition, the medians of the OS for both groups of treatment seem quite similar, which very likely is due to the immature data. An update of investigator assessed rPFS together with an OS update will be submitted (see Annex II).

The hazard ratio was less favourable for enzalutamide-treated patients who received sequential treatment with abiraterone (HR 1.23 [95% CI: (0.89, 1.68)]) and for enzalutamide-treated patients who received sequential treatment with docetaxel (HR 1.47 [95% CI: (1.17, 1.85)]). Notwithstanding the inherent bias associated to these analyses, a possible cross-resistance among treatments cannot

be totally ruled out. Results of ongoing studies may provide further evidence on the sequential use of abiraterone-enzalutamide. Patients with metastatic castration-resistant prostate cancer previously treated with abiraterone has been included as missing information in the RMP and a study will collect data on the efficacy and safety of enzalutamide in these patients.

Risks

Unfavourable effects

Overall, the treatment with enzalutamide is well tolerated, since the dose reductions, interruptions and discontinuations were similar or slightly higher for enzalutamide arm versus the placebo arm.

Despite the large difference in observation time, the crude frequencies of many AEs were often similar across arms or only slightly higher in the enzalutamide group of the pivotal study MDV3100-03.

The incidence of AEs in the MDV3100-03 study was high in both groups. More than 90% of patients had some AEs. The most common adverse events associated with enzalutamide treatment in MDV3100-03 were fatigue (35.6%) and asthenia (13.0%), hot flush (18.0%), hypertension (13.9%), fall (11.6%), non-pathological fractures (7.8%), and mental impairment (5.7%). The previously identified important risk of seizure was observed in only 1 patient (0.1%) in each study arm of MDV3100-3. When the AEs reported were adjusted for length of exposure, hot flush, hypertension, fall, and dysgeusia, were higher for patients treated with enzalutamide than in the placebo group.

Grade 3 or higher AEs occurring more frequently in the enzalutamide arm compared with placebo were cataract (1.3% vs 0.1%) nausea (1.0% vs 0.5%) general physical health deterioration (2.1% vs 1.2%) pneumonia (1.3% vs 0.8%) fall (1.4% vs 0.7%) spinal cord compression (3.8% vs 2.8%) syncope (1.6% vs 0.9%) and hypertension (6.8% vs 2.3%). However, only hypertension and cataract remained higher in the enzalutamide arm after adjusting for the longer safety reporting period.

The AEs reported as primary reason for discontinuation appeared mostly related to the underlying disease or comorbidities related to the age group. The frequency of patients discontinuing due to AE was similar across arms in study MDV3100-3 (5.6% vs. 6.0% in enzalutamide and placebo arms, respectively), as well as in the combined controlled population.

Uncertainty in the knowledge about the unfavourable effects

Enzalutamide has been associated with a potential for seizure in preclinical studies, a relationship with dose has been indicated in clinical studies, and a higher incidence compared with placebo was observed in the registration study CRPC2. However, the incidence of seizure was lower in MDV3100-03 and no increase over placebo was observed. No explanation for the lower incidence of convulsions/seizure in the present MDV3100-3 compared with previous studies have been presented by the MAH. In the absence of other explanations, it is conceivable that this phenomenon could be due to a better identification of study participants at risk for seizure at screening. Seizure is adequately addressed in the RMP.The time-adjusted event rate for second malignancy was increased in the enzalutamide arm of MDV3100-3 compared to the placebo arm (3.3 vs. 1.8 events/ 100 PY). Given the relatively short time to onset, it is not likely that the observed cases represent a cancer-inducing effect of enzalutamide. Furthermore, there is no obvious mechanism for a theoretical cancer-promoting effect of enzalutamide. Based on these considerations, secondary malignancy will be closely monitored in PSURs and will be specifically addressed in the already planned updates from MDV3100-3 to the CHMP.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The treatment with enzalutamide has shown an increase in the life expectancy of mCRPC patients not yet candidates for docetaxel. This positive and robust finding is accompanied by a meaningful delay in the radiological progression of the disease. Along with these important findings, other clinical endpoints such as time to chemotherapy, time to skeletal event and PSA response, are supporting the main outcomes.

Tolerability is of main importance in advanced cancer disease, and enzalutamide appears well-tolerated, with limited additional toxicity compared with placebo, on top of the underlying castration therapy that is required in all CRPC patients. In addition, although this is mainly due to the efficacy of enzalutamide affecting disease related adverse events, the time to first grade 3 or more AE, as well as the time to first serious adverse event is considerably longer in enzalutamide-treated patients compared with placebo, which is considered of high value to patients.

Benefit-risk balance

The benefit of enzalutamide over placebo treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated, as shown in the pivotal study MDV3100-03 is overall convincing and considered clinically meaningful.

Enzalutamide on top of castration therapy in chemotherapy-naïve metastatic castration-resistant prostate cancer is considered well-tolerated. The benefit-risk balance is considered positive.

Discussion on the Benefit-Risk Balance

Considering the benefits shown by enzalutamide in the population recruited in the pivotal trial and taking into account the positive results previously observed in the post-docetaxel setting, the use of enzalutamide in the proposed indication is supported by CHMP. The clinical value of the endpoints reached is clear. The efficacy results along with the observed safety profile and good tolerability support the use of enzalutamide in the proposed population.

The CHMP considers the following measure necessary to address issues related to long-term efficacy:

The MAH should submit updated results from the PREVAIL study and more specifically updated OS and investigator assessed rPFS data. The MAH should present the data based on the latest time point where investigator assessed rPFS data according to the study protocol is available and where data is not significantly affected by cross-over.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation(s) to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication for the treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. As a consequence, section 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and the package leaflet have been updated accordingly. Annex II has also been updated to include an obligation to conduct a post-authorisation measure. The MAH also propose to update the contact details of local representatives in the package leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

This CHMP recommendation is subject to the following new condition:

Conditions and requirements of the marketing authorisation

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to address the uncertainties regarding long-term efficacy, the MAH should submit updated results from the PREVAIL study and more specifically updated OS and investigator assessed rPFS data. The MAH should present the data based on the latest time point where investigator assessed rPFS data according to the study protocol is available and where data is not significantly affected by cross-over.	30 September 2015

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Additional data exclusivity / market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.