Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for enzalutamide

Proprietary Product Name: Xtandi

Sponsor: Astellas Pharma Australia Pty Ltd

March 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ADT	Androgen Deprivation Therapy
AE	adverse event
ASA	Australian Specific Annex
AUC	area under the plasma concentration time curve
BMD	bone mineral density
Cmax	maximum drug serum concentration
CMI	Consumer Medicines Information
CRPC	castration-resistant prostate cancer
EMA	European Medicines Agency
FDA	Food and Drug Administration (US)
GLP	Good Laboratory Practice
GnRH	gonadotropin releasing hormone
HR	hazard ratio
HRQoL	Health Related Quality of Life
IQR	interquartile range
ITT	intention to treat
OS	overall survival
PFS	progression free survival
PI	Product Information
PRES	posterior reversible encephalopathy syndrome
PSA	prostate-specific antigen
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
rPFS	radiographic progression free survival

Abbreviation	Meaning
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SJS	Stevens-Johnson syndrome
TEAE	treatment emergent adverse event
TEN	toxic epidermal necrolysis

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	6 November 2015
Date of entry onto ARTG	13 November 2015
Active ingredient:	Enzalutamide
Product name:	Xtandi
Sponsor's name and address:	Astellas Pharma Australia Pty Ltd 4/6 Eden Park Drive Macquarie Park NSW 2113
Dose form:	Soft capsule
Strength:	40 mg
Container:	Blister pack
Approved therapeutic use:	For the treatment of patients with metastatic castration-resistant prostate cancer following failure of androgen deprivation therapy in whom chemotherapy is not yet indicated
Route of administration:	Oral
Dosage:	Recommended dose is 160 mg (four 40 mg capsules) as a single oral daily dose.
ARTG number:	210494

Product background

This AusPAR describes the application by Astellas Pharma Australia Pty Ltd to extend the indications for Xtandi (enzalutamide). The currently approved indication is:

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

The proposed additional indication is:

Xtandi is indicated for:

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

Regulatory status

The international regulatory status at the time of this submission is listed in Table 1.

Table 1: International regulatory status of Xtandi at time of submission.

Country/ region	Submission date	Type of application	Status and date	Proposed indication
EU	4 Apr 2014	Centralised, Type II variation	Positive CHMP opinion adopted 23 Oct 2014	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
US	17 Mar 2014	National	Approved 10 Sep 2014	The treatment of patients with metastatic castration-resistant prostate cancer
Japan	24 Mar 2014	National	Approved 21 Oct 2014	Castration-resistant prostate cancer
Switzerland	22 Jun 2014	National	Under review (fast-track)	Treatment in combination with luteinizing hormone-releasing hormone (LHRH) analogues of adult men with metastatic prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) in whom chemotherapy is not yet clinically indicated
South Korea	8 Aug 2014	National	Under review	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

Following submission, the product received marketing approval in the US, EU, Japan and South Korea, amongst a number of countries.

Product information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

Introduction

New nonclinical studies were submitted, but none directly related to support the new indication. The nonclinical submission consisted of additional toxicity data that were absent from the original submission for Xtandi (toxicity of the M2 metabolite and definitive embryofoetal development studies in two species), as well as additional information regarding possible pharmacokinetic drug interactions.

Pharmacology

Enzalutamide was ~3 times more potent at the human androgen receptor (AR) than at the rat AR. The difference in potency is not expected to significantly impact the use of rats as an animal model for toxicity.

Pharmacokinetics

Newly submitted pharmacokinetic studies examined tissue distribution of drug related material in rats following repeated dosing and attempted to further clarify the metabolic breakdown of enzalutamide.

Consistent with previous pharmacokinetic data, in a tissue distribution study, there was no evidence of accumulation of drug related material in rats.

In human subjects, enzalutamide is extensively metabolised to M1 (amide hydrolysis product) and M2 (N-desmethyl product). At the time of the original submission for enzalutamide, enzymes involved in the formation of M1 had not been identified. In incubations with hepatocytes, liver S9 fractions and blood from various species (rats, rabbits, dogs and humans), M1 was produced from enzalutamide in rat and rabbit hepatocytes, from M2 in rat, rabbit, dog and human hepatocytes and in rat and rabbit blood. The data are consistent with the original nonclinical evaluator's suggestion that multiple pathways may be involved in M1 formation. The data also suggest there may be species differences in the relative contribution of each pathway in M1 formation.

There was no significant metabolism of M2 (N-desmethyl enzalutamide) in *in vitro* incubations with CYP450 enzymes (CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4, or 3A5). The data are consistent with previously submitted data indicating that M2 was not significantly metabolised in incubations with human liver microsomes.

The new pharmacokinetic data do not raise any new safety concerns and do not affect the conclusions or interpretation of the original data. Minor amendment of the PI document is warranted.

Pharmacokinetic drug interactions

In vitro, the level of enzalutamide binding to human plasma protein was unaltered by the presence of various common medications (warfarin, ibuprofen, or salicylic acid). Likewise, enzalutamide did not alter the extent of protein binding of these compounds. This suggests that these drugs do not have potential for interaction with enzalutamide via displacement from protein binding sites.

Previous clinical data indicated that enzalutamide was likely to be an inducer of CYP2C9, 2C19 or UGT isoforms, but there were no supporting *in vitro* data to confirm this. Newly submitted data indicated that, in human hepatocytes, enzalutamide was an inducer of CYP2B6 (mRNA and enzyme activity), CYP3A4 (mRNA and enzyme activity), UGT1A1 (mRNA), UGT1A4 (mRNA) and P-glycoprotein (mRNA). M2 induced CYP2C8 (mRNA and enzyme activity) and CYP3A4 (mRNA and enzyme activity). No significant induction of CYP isoforms (CYP1A2, 2B6, 2C8, 2C9, 2C19, and CYP3A4/5), UGT isoforms (UGT1A1, 1A4, 1A6, 1A9, and 2B7) or P-glycoprotein was observed with M1. No significant induction of UGT isoforms or P-glycoprotein was observed with M2. The pattern of gene induction suggests that enzalutamide and/or M2, but not M1, act through the pregnane X and/or the constitutive androstane receptors.

The data indicate that enzalutamide administration may decrease the exposure of drugs that are metabolised by CYP2B6, CYP3A4, UGT1A1 or UGT1A4. While the *in vitro* data indicated possible induction of CYP2C8, clinically there was no effect of enzalutamide administration on exposures to pioglitazone, a CYP2C8 substrate. Enzalutamide administration may alter the exposure to drugs that are P-glycoprotein substrates. Minor amendment to the "Interactions with other medicines" section of the PI document is warranted.

A new study, using BCRP-expressing vesicles, suggested that M2 is not a substrate of the efflux transporter BCRP. Previous studies demonstrated that enzalutamide is also not a substrate of BCRP. As indicated previously, enzalutamide, M1 and M2 are inhibitors at BCRP. A newly submitted study re-confirmed this, though lower IC50 values were determined. Therefore, as stated in the original evaluation for Xtandi, given the high local concentrations of enzalutamide in the GI tract (where BCRP is expressed), inhibition of this transporter in the intestines should be considered as possible. No changes to the Product Information document are warranted.

Excretion of drug related material in human subjects is primarily via the urine (71% of the dose), with M1 forming a significant component of this excreted material. *In vitro*, M1 was a substrate for OAT3 (Km 16μM and Vmax 60.6 pmol/min/mg protein) but was not a substrate for OAT1. The significance of this transport to the excretion of drug-related material *in vivo* is uncertain, therefore, inhibitors/inducers of OAT3 may alter the disposition of M1. As M1 is not pharmacologically-active, this may not significantly alter the efficacy/safety profile of enzalutamide.

Toxicology

Repeat dose toxicity

The sponsor has presented pilot studies in mice and rats to aid in the selection of doses for future carcinogenicity studies. Four week and 39 week repeat dose toxicity studies in mice and dogs, respectively, were also submitted. The latter two studies were performed to GLP

standards, included animals of both sexes, and involved daily oral dosing (consistent with the clinical dosing regimen).

Relative exposures to enzalutamide at the highest doses in the GLP compliant studies were similar to or marginally above clinical exposures; exposures to the pharmacologically active metabolite, M2, were all subclinical and exposures to total pharmacologically active material (that is, enzalutamide and M2) were similar to the clinical AUC at the highest dose in one mouse strain but were subclinical in the other mouse strain (CD-1) and dogs (see table following). Higher exposures were achieved in previously submitted rat (26-week) and dog (4 week) studies.

Table 2: Relative exposure in repeat dose toxicity studies after PO administration of enzalutamide.

Species	Study duration	Dose (mg/kg/day)	Enzalutamide		M2		Enzalutamide + M2	
			AUC0–24 h (µg·h/mL)	ER	AUC 0–24 h (µg·h/mL)	ER	AUC0–24 h (µg·h/mL)	ER
Mouse (CD-1)	4 weeks	10	130	0.4	8.1	0.03	138	0.2
		30	324	1.0	33	0.12	357	0.6
		60	442	1.4	66	0.24	508	0.8
Mouse (rasH2; non-transgenic littermates)	4 weeks	10	171	0.5	10.4	0.04	181	0.3
		30	436	1.4	36	0.13	472	0.8
		60	579	1.8	75	0.27	654	1.1
Dog (Beagle)	39 weeks	5	137	0.4	8.7	0.03	146	0.2
		15	261	0.8	17.7	0.06	279	0.5
		45	362	1.1	24.1	0.09	386	0.6
Human (patients)	steady state	[160 mg]	322	–	278	–	600	–

AUC values are the average for male and female data obtained from the final sampling point.

Major toxicities

In general, the toxicities observed in the newly submitted toxicity studies were similar to those observed previously. The male reproductive organs were the major targets for enzalutamide dosing-associated toxicity in both mice and dogs. This is consistent with the

pharmacological activity of enzalutamide and with reported findings for other anti-androgenic drugs in laboratory animals.[1]

Both mouse studies showed statistically significant, dose-dependent, decreases in weight for prostate, epididymis, and seminal vesicle. Prostate and epididymis showed no histological correlates of their weight changes, whilst seminal vesicles showed a minimal level of atrophy in some animals dosed at 30 or 60 mg/kg/day. There was a minimal level of Leydig cell hypertrophy in enzalutamide dosed animals in one of the mouse studies. Daily dosing of dogs for 9 months with enzalutamide produced statistically significant, dose-dependent, decreases in prostate weight and increases in testis weight. The weight changes were correlated with histological findings of atrophy in prostate, epididymis, and seminiferous tubules of testis. These changes were reversed following a 13 week recovery period, suggesting that they are not of toxicological concern. Serum testosterone levels were increased in dogs treated daily with 5 or 15 mg/kg/day PO enzalutamide, but not 45 mg/kg/day PO enzalutamide. These testosterone increases correlated with the severity of Leydig cell hypertrophy and/or hyperplasia in the testes. The findings for mice and dogs are expected consequences of long term blockage of the androgen receptor (atrophy) and an exaggerated compensatory response to increased secretion of luteinising hormone (Leydig cell hypertrophy/hyperplasia).

Male mice in one study and mice of both sexes in the other study showed dose dependent increases in plasma concentrations of alkaline phosphatase (ALP) and alanine aminotransferase (ALT) and decreases in total cholesterol concentration at the conclusion of dosing at enzalutamide exposure levels similar to clinical levels. Histological examination showed minimal to mild hepatocytic hypertrophy, but there was no evidence for liver toxicity that might correlate with the plasma changes. Dogs did not show changes in plasma concentrations of markers for liver toxicity, although males dosed at 45 mg/kg/day showed a significant increase in liver weight that was not correlated with histological change. These hepatic findings are likely adaptive in nature and not considered to be of toxicological concern.

Histological changes in the zona fasciculata of adrenal gland were noted in enzalutamide treated mice, but not in dogs. Mice of both sexes, and in all dose groups, showed minimal to moderate decrease of the cytoplasmic vacuoles and increased cytoplasmic eosinophilia. The basis of these changes was not explored, but may be related to an effect on cholesterol metabolism and/or the observed decrease in plasma cholesterol concentration. Notably, these changes were not associated with necrosis and degeneration and were therefore considered to be of little toxicological significance.

In mice, the stomach appeared to be a target organ for toxicity, with thickening of the mucosa, ulcers, focal mucosal hyperplasia and perforation observed in the forestomach and erosion observed in the glandular stomach. Most of these gastrointestinal lesions were observed at 60 mg/kg/day, though ulcers were also seen at 30 mg/kg/day. The underlying cause of these gastrointestinal changes is unknown. In one study, the study author claimed the lesions in the forestomach were secondary to the poor physical condition of the animals. This is plausible, as the changes were observed at reasonably high doses. However, they may also be attributable to the irritating nature of the enzalutamide and Labrasol (excipient) combination at high local concentrations within the stomach. Previous studies have suggested this combination may have an additive or synergistic irritating effect. Similar gastrointestinal lesions have not been observed in rats or dogs. If the gastrointestinal tract changes are secondary to poor animal condition or associated with local irritation, they are not considered to be relevant to human subjects.

[1] Okahara A, et al. (2000) Collaborative work to evaluate toxicity on male reproductive organs by repeated dose studies in rats 5). Effects of repeated doses of flutamide for 2 and 4 weeks. *Journal of Toxicological Sciences* 25 Spec No: 63-70; Frank D, et al. (2004) Chronic effects of flutamide in male beagle dogs. *Toxicologic Pathology* 32: 243-249.

Convulsions have been observed in mice and dogs. This is likely associated with the off-target activity of enzalutamide and M2 at the GABA gated chloride channel. As stated previously, convulsions are considered a risk in patients.

There were no changes in serum progesterone or oestradiol levels in female dogs treated for 9 months. However, exposures in dogs were subclinical and, therefore, little weight can be placed on the negative findings alone. As reported previously, both enzalutamide and M2 have inhibitory activity at the progesterone receptor, but, based on potency, this activity is not expected to be clinically relevant.

The new toxicity studies do not alter the toxicity profile of enzalutamide, with the exception of Leydig cell changes (hypertrophy/hyperplasia) observed in the testes of both mice and dogs. These changes are suggestive of proliferative effects in this tissue. Carcinogenicity studies in rats with related anti androgenic drugs, such as flutamide, showed an increased incidence of Leydig cell adenomas.[2] The Leydig cell changes observed with enzalutamide, indicates a risk of Leydig cell adenomas may also exist with this drug. The sponsor has indicated that carcinogenicity studies with enzalutamide are planned. These studies should be submitted for evaluation when they are available. These studies are not considered essential to the approval of the new indication.

Reproductive toxicity

Only a preliminary embryofoetal development study in mice was submitted in the original submission for Xtandi. The sponsor has now provided definitive embryofoetal development studies in mice and rabbits, as well as a pilot study in the latter species. Critical studies were performed to GLP standards.

Relative exposure values for enzalutamide, M2 and total pharmacologically active material were generally subclinical (Table 3). The highest tested doses are considered acceptable based on findings in pilot studies and an abortion observed at the highest dose in mice. Relative exposure to enzalutamide at the no observed adverse effect level (NOAEL) for maternal toxicity (10 mg/kg/day PO in both species) was low (~0.4).

Table 3: Relative exposure in pregnant animals in embryofetal development studies.

Species	Dose (mg/kg /day PO)	Enzalutamide		M2		Enzalutamide + M2	
		AUC0–24 h (µg·h/mL)	ER	AUC0–24 h (µg·h/mL)	ER	AUC0–24 h (µg·h/mL)	ER
Mouse (CD-1)	1	11.8	0.04	0.146	0.0005	11.9	0.02
	10	127	0.4	9.11	0.03	136.1	0.2
	30	354	1.1	82.5	0.3	436.5	0.7
Rabbit (NZW)	0.3	5.17	0.02	0.621	0.002	5.8	0.01
	3	32.8	0.1	3.62	0.01	36.4	0.06

[2] Clegg ED, et al. (1997) Leydig cell hyperplasia and adenoma formation: mechanisms and relevance to humans. *Reproductive Toxicology* 11: 107-121.

Species	Dose (mg/kg /day PO)	Enzalutamide		M2		Enzalutamide + M2	
		AUC0–24 h (µg·h/mL)	ER	AUC0–24 h (µg·h/mL)	ER	AUC0–24 h (µg·h/mL)	ER
	10	116	0.4	11.8	0.04	127.8	0.2
Human (patients)	[160 mg]	322	–	278	–	600	–

AUC values are from the final sampling point.

Oral enzalutamide dosing to pregnant mice at ≥10 mg/kg/day produced increases in early and late resorptions and increases in external abnormalities, including cleft palate (correlating with an absent palatine bone) and shortened anogenital distance (males only). These are similar findings to that observed in the pilot embryofoetal development study in mice. The results are not surprising given that anti androgens are known teratogens in both humans and laboratory animals.[3]

No adverse embryofoetal effects were observed in rabbits. The reason for the species differences in embryofoetal effects is unknown. Possible reasons include species differences in the extent of placental transfer of pharmacologically active material or species differences in the potency of enzalutamide. Nonetheless, based on embryofoetal lethality and toxicity observed in mice and the pharmacological action of enzalutamide, this drug should be considered to be teratogenic.

Pregnancy classification

No change to the pregnancy category is considered necessary. Category X is still considered appropriate for enzalutamide.[4]

Metabolites

Two repeat dose toxicity studies with M2 were submitted. These were pilot studies conducted in non-transgenic littermates of Jic:CB6F1-Tg rasH2@Jcl mice to aid in the selection of doses for a carcinogenicity study. The 4 week study was GLP compliant and findings in this study are discussed below. Exposures to M2 were similar to or marginally above the clinical exposure to M2 (Table 4). Significant exposures to M1 were also evident suggesting this metabolite is formed from M2 in this species.

Table 4: Relative exposure to M2 and M1 in repeat-dose toxicity studies with M2.

Species	Dose (mg/kg/day PO)	M2		M1	
		AUC_{0-24h} (µg·h/mL)	ER	AUC_{0-24h} (µg·h/mL)	ER
Mouse	50	180	0.6	77.2	0.4

[3] Gray LE, et al. (2001) Effects of environmental antiandrogens on reproductive development in experimental animals. *Human Reproduction Update* 7: 248-264.
[4] Category X: Drugs which have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

Species	Dose (mg/kg/day PO)	M2		M1	
		AUC_{0-24h} (µg·h/mL)	ER	AUC_{0-24h} (µg·h/mL)	ER
(Jic:CB6F1-Tg rasH2@Jcl; non-transgenic littermates)	100	357	1.3	226	1.2
	200	678	2.4	203	1.1
Human (patients)	[160 mg enzalutamide]	278	–	193	–

AUC values are the average for male and female data obtained from the final sampling point, with the exception of AUC values for the 200 mg/kg/day dose (no data available in week 4 due to premature termination of this dose group).

The maximum tested dose of M2 is considered acceptable, given that test item-related deaths were observed at all tested doses. Perimortem clinical signs included decreased spontaneous movement, bradypnea, hypothermia, irregular breathing, clonic convulsion, tremor and/or prone/lateral position. These clinical signs were also observed in toxicity studies with enzalutamide.

In general, the toxicity findings were similar to those observed in repeat-dose toxicity studies with enzalutamide, with changes in the male reproductive organs (decreased prostate and epididymal weights and Leydig cell hypertrophy in the testes; consistent with the pharmacological action of M2 [and enzalutamide]), liver (increased weight and enlargement correlating microscopically with centrilobular hypertrophy), adrenal gland (eosinophilic change in the zona fasciculata) and gastrointestinal tract (perforation, erosion and mucosal thickening of the forestomach).

More pronounced effects were observed on liver enzymes (elevations in ALT, aspartate aminotransferase [AST] and ALP levels at ≥50 mg/kg/day [exposure ratio based on the AUC for M2 = 0.6]) and myocardial mineralisation in males at ≥100 mg/kg/day (exposure ratio based on the AUC for M2 = 1.3). The magnitude of the increase in ALT levels in mice (up to 4 times) should be considered as potentially adverse even in the absence of histopathological changes of liver damage.[5]

The main human metabolites, M1 and M2, are considered to have low genotoxic potential based on *in vitro* mutagenicity studies in bacterial and mammalian cells.

The newly submitted toxicity data with M2 suggest a possible risk of hepatotoxicity and cardiotoxicity in patients receiving Xtandi. The risk is not considered to be greater with the new indication.

Impurities

No new issues have been raised by the sponsor.

Nonclinical summary and conclusions

- The submission consisted of additional toxicity data that were absent from the original submission for Xtandi (toxicity of the M2 metabolite and definitive embryofoetal

[5] European Medicines Agency, "Nonclinical Guideline on Drug-Induced Hepatotoxicity (EMEA/CHMP/SWP/150115/2006)", 24 January 2008.

development studies in two species), as well as additional information regarding possible pharmacokinetic drug interactions.

- New nonclinical studies were submitted, but none directly related to support the new indication.
- *In vitro* pharmacokinetic data indicated:
  - Drug interactions involving displacement from protein binding sites are not anticipated.
  - Enzalutamide administration may decrease the exposure of drugs that are metabolised by CYP2B6, CYP3A4, UGT1A1 or UGT1A4.
  - Exposures to drugs that are P-glycoprotein substrates may be altered with enzalutamide co-administration.
- *In vitro*, M1, the pharmacologically inactive carboxylic acid metabolite of enzalutamide, was a substrate for OAT3. The clinical relevance of this finding is uncertain.
- The sponsor has presented pilot toxicity studies in mice and rats to aid in the selection of doses for future carcinogenicity studies, and 4 and 39 week repeat dose toxicity studies in mice and dogs, respectively. In general, the toxicities observed in the newly submitted studies were similar to those observed previously. The new toxicity studies do not alter the toxicity profile of enzalutamide, with the exception of Leydig cell changes (hypertrophy/hyperplasia) observed in the testes of both mice and dogs. These changes are suggestive of proliferative effects in this tissue.
- Definitive embryofoetal development studies in mice and rabbits were submitted. No adverse embryofoetal effects were observed in rabbits. Embryofoetal lethality and toxicity were observed at subclinical exposures in mice. Enzalutamide was teratogenic in the latter species (consistent with previously submitted data.
- Two repeat dose toxicity studies with the pharmacologically active metabolite, M2, were submitted. In general, the toxicity findings were similar to those observed in repeat dose toxicity studies with enzalutamide, with changes in the male reproductive organs (decreased prostate and epididymal weights and Leydig cell hypertrophy in the testes; consistent with the pharmacological action of M2 [and enzalutamide]), liver (increased weight and enlargement correlating microscopically with centrilobular hypertrophy), adrenal gland (eosinophilic change in the zona fasciculata) and gastrointestinal tract (perforation, erosion and mucosal thickening of the forestomach). The newly submitted toxicity data with M2 suggest a possible risk of hepatotoxicity and cardiotoxicity in patients receiving Xtandi. The risk is not considered to be greater for the new indication.
- There are no nonclinical objections to the proposed extension of indication for enzalutamide.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

As per the currently approved PI for enzalutamide:

> *Enzalutamide is an androgen receptor signalling inhibitor that blocks the androgen receptor signalling pathway. Enzalutamide competitively inhibits binding of androgens to androgen receptors, and consequently inhibits the nuclear translocation of these receptors and inhibits the binding of androgen receptor to DNA. In vitro, enzalutamide treatment decreased proliferation and induced prostate cancer cell death. Decreased tumour growth was seen in a mouse prostate cancer xenograft model. In preclinical studies enzalutamide lacked androgen receptor agonist activity against several prostate cancer cell lines. The active metabolite, N-desmethyl enzalutamide, exhibited similar in vitro activity to enzalutamide in the inhibition of testosterone binding to the androgen receptor.*

The rationale for the proposed new indication is that in patients with castration-resistant prostate cancer (CRPC) who fail androgen deprivation therapy, disease progression may present as either a continuous rise in prostate-specific antigen (PSA), the progression of pre existing malignant disease, and/or the appearance of new metastases.

Contents of the clinical dossier

The submission contained the following clinical information:

- Three clinical pharmacology studies
- Two population pharmacokinetic analyses.
- One pivotal efficacy/safety study, two non pivotal studies of efficacy and safety
- Line listing of adverse events (AEs)

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The clinical studies reviewed in this evaluation were in compliance with published guidelines.[6]

Pharmacokinetics

Studies providing pharmacokinetic data

Table 5 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

[6] Therapeutic Goods Administration, "Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)", July 2000.

Table 5: Submitted pharmacokinetic studies.

Study ID	Study type	Phase, design	Study population	Assessment	Number of subjects
MDV3100-06	PK, safety, tolerability	Phase Ib, open-label	Patients with metastatic CRPC	Primary analysis	22
9785-CL-0321	Efficacy, safety, tolerability, PD, PK	Phase II, open-label, single arm	Patients with hormone-naïve prostate cancer	1-year analysis	67
9785-CL-0111	Efficacy, safety, tolerability, PK	Phase I-II open label, uncontrolled, dose-escalation	Japanese patients with metastatic CRPC, with or without prior docetaxel	Primary analysis	47

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

Evaluator's conclusions on pharmacokinetics

The results of Study MDV-3100-06 demonstrated that the pharmacokinetic profile of docetaxel was not significantly altered by the co-administration of enzalutamide. The sponsor has proposed to include the results of this study in the PI, reporting the observed change in AUClast and Cmax. Although a reduction in the AUClast of docetaxel of 12% was observed, the effect of this reduction on the efficacy of docetaxel has not been correlated with clinical outcomes. Safety during co-administration of docetaxel and enzalutamide is discussed below.

The results of Study 9875-CL-0111 in a very small number of Japanese patients demonstrates that there was no significant difference between the three patients who received the recommended dose of 160 mg when compared with the data in the currently approved PI, as assessed in non-Japanese subjects.

The participants in PREVAIL were permitted to be concomitantly administered enzalutamide and abiraterone. Abiraterone is metabolised by CYP3A4 and enzalutamide induces this enzyme. No pharmacokinetic analysis has been presented to justify the use of this experimental combination of therapies.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 6 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 6: Submitted pharmacodynamic studies.

Study ID	Study type	Phase, design	Study population	Assessment	Number of subjects
9785-CL-0321	Efficacy, safety, tolerability, PD, PK	Phase II, open-label, single arm	Patients with hormone-naïve prostate cancer	1-year analysis	67

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

Evaluator's conclusions on pharmacodynamics

Change in PSA concentration was observed as a marker of enzalutamide exposure and efficacy. There was no data presented to enable clinicians to use change in PSA concentration over time as a prognostic or diagnostic measure.

The sponsor is proposing to include a statement in the PI regarding the proportion of patients that achieved a reduction in PSA of 50%. This exploratory outcome has not been correlated with disease progression, and should therefore be removed from the PI.[7]

Dosage selection for the pivotal studies

N/A

Efficacy

Studies providing efficacy data

Table 7 shows efficacy studies.

Table 7: Submitted efficacy studies.

Study ID	Study type	Phase, design	Study population	Results	Number of subjects
MDV3100-03	Efficacy & safety	Phase III, randomised, double-blind,	Chemotherapy naïve patients with	Primary analysis	871 enzalutamide,

[7] This information was proposed based on PREVAIL (MDV-3100-03) data and not 9785-CL-0321 data. The sponsor agreed to remove this statement from the PI following second round evaluation.

Study ID	Study type	Phase, design	Study population	Results	Number of subjects
PREVAIL		placebo controlled, multicentre	metastatic CRPC		844 placebo
MDV3100-06	PK, safety, tolerability	Phase Ib, open-label	Patients with metastatic CRPC	Primary analysis	22
9785-CL-0321	Efficacy, safety, tolerability, PD, PK	Phase II, open-label, single arm	Patients with hormone-naïve prostate cancer	1-year analysis	67

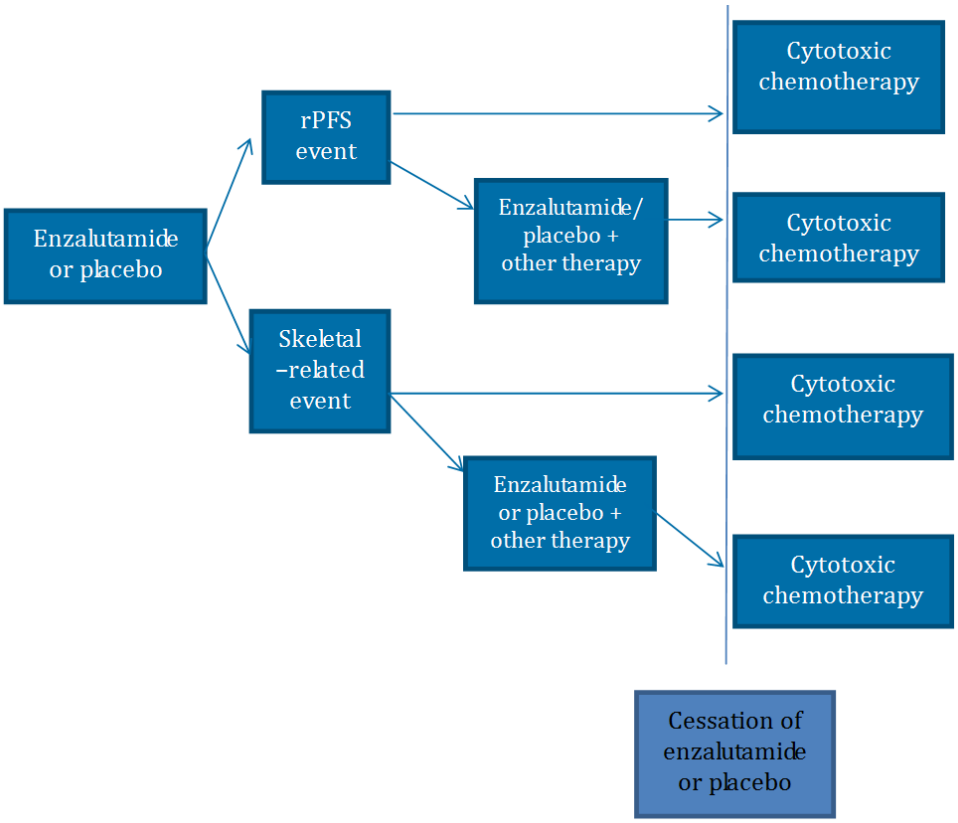
Evaluator's conclusions on efficacy

Given the approved indication of abiraterone, the best contemporary practice of the treatment of patients fulfilling the proposed indication is no longer placebo. A direct comparison of monotherapy enzalutamide and monotherapy abiraterone is the critical comparison to sufficiently inform prescribers and patients.

The general scheme of PREVAIL is represented in Figure 1 below. Following either first confirmed radiographic progression or a skeletal related event (whichever came first) **and** commencement of cytotoxic chemotherapy was the trigger to cease enzalutamide/placebo. However, patients in either treatment arm were permitted to be co-administered other active agents prior to the administration of cytotoxic chemotherapy, including abiraterone.[8] Thus, the reported time to commence cytotoxic chemotherapy is not solely representative of the difference between enzalutamide and placebo.

[8] Concomitant treatment with abiraterone was allowed once patients had either confirmed radiographic progression or a skeletal related event.

Figure 1: General scheme of PREVAIL until commencement of cytotoxic chemotherapy.



1. Enzalutamide or placebo
2. rPFS event
    a. Enzalutamide or placebo + other therapy
        i. Cytotoxic chemotherapy
    b. Cytotoxic chemotherapy
3. Skeletal related event
    a. Enzalutamide or placebo + other therapy
        i. Cytotoxic chemotherapy
    b. Cytotoxic chemotherapy
4. Cessation of enzalutamide or placebo

The impact of crossover has not been addressed by the sponsor. Once patients have commenced an agent other than that allocated by the randomisation procedure, this randomisation scheme is broken; a substantial (and discrepant) proportion of each study arm discontinued study treatment. The use of the intention to treat analysis may be an appropriate method in some circumstances, such as where only crossover from placebo to active treatment occurs, however there are limitations to this approach.[9] The intention to treat analysis in PREVAIL includes not only crossover from placebo to an alternative therapy, but also from enzalutamide to an alternative therapy and the nesting of patients who could be concomitantly administered abiraterone with study drug: an experimental regimen on its own. Thus, contamination of both treatment arms has occurred, with the

[9] Ishak K, et al. (2014) Methods for adjusting of bias due to cross-over in oncology trials. *Pharmacoeconomics* 32: 533-546.

multiple treatment options employed. It is impossible for the evaluator to tell whether the difference in co-primary outcomes is due to the study treatment, post randomisation therapy, or concomitant therapy or a combination of each.[10]

The co-primary endpoint of PREVAIL was "to determine the benefit of enzalutamide as compared to placebo as assessed by overall survival". Due to the inclusion of patients who discontinued the study therapy in both treatment arms, and commencement of non study agents, the sponsor has not demonstrated what the magnitude of median overall survival (OS) difference of 2.2 months between study arms which is due to enzalutamide/placebo separate from that of the effect of the agglomeration of additional therapies which patients received prior to, and following cessation of enzalutamide/placebo. The proportion of patients in each study arm receiving concomitant abiraterone has not been reported: it is plausible that discrepant exposure between treatment arms biases the OS outcome in favour of enzalutamide.

The co-primary end point of radiographic progression free survival (rPFS) was met, demonstrating a benefit from enzalutamide, as compared to placebo. The difference in time to rPFS was longer in the enzalutamide arm: median not reached for enzalutamide, median 3.9 months for placebo. However, the magnitude of benefit in delay of rPFS was not translated into a substantial difference in OS, with only a 2.2 month difference, in favour of enzalutamide (plus all other subsequent therapies). Furthermore, this outcome may also be confounded: patients may have had a skeletal related event and commenced cytotoxic chemotherapy and ceased study drug before a rPFS event.

The pivotal study efficacy outcomes have to be interpreted according to the median duration of follow-up (22.2 months for the enzalutamide arm and 22.4 months for placebo arm). Not only is OS potentially affected by concomitant disproportionate abiraterone administration, the sponsor states that "the median overall survival estimates are considered unstable because of the small number of patients at risk at the estimated medians (4 patients in the enzalutamide group and 24 patients in the placebo group) and the lower median time of follow-up for overall survival (22.2 months in the enzalutamide group and 22.4 months in the placebo group) relative to the estimated median survival".

The median time to initiation of chemotherapy in the placebo arm was 10.8 months (interquartile range [IQR] 9.7, 12.2) whereas that for the enzalutamide arm was 28.8 months (IQR 25.8, NYR). It is not clear from the reporting methods used in the dossier whether additional therapies, in particular concomitant abiraterone administration, influenced this outcome.

For the secondary efficacy outcomes of PREVAIL:

- The time to first skeletal related event was not different between the study arms for patients who fulfilled this composite outcome of diagnoses and does not represent a clinical benefit to patients. The median time to initiation of chemotherapy for the placebo arm was 10.8 months with a median time to first skeletal related event of 31.3 months. This data would imply that most skeletal related events in the placebo arm occurred after chemotherapy was commenced. The sponsor should confirm that this outcome has been reported for the placebo controlled period only. The proportion of each treatment arm which had a skeletal related event following cessation of enzalutamide or placebo has not been reported.
- The median time to commencement of additional cytotoxic chemotherapy was longer following enzalutamide as compared to placebo (28.0 months versus 10.8 months respectively) , but was only associated with a difference in 2.2 months median overall survival, in favour of enzalutamide.

[10] Hernán MA, Hernández-Díaz S. (2012) Beyond the intention to treat in comparative effectiveness research. *Clin Trials* 9: 48-55.

- Time to PSA progression has been presented using the incorrect denominator of patients, and requires re-calculation.
- The proportion of patients achieving a reduction in PSA concentration of >50% from baseline was presented and included in the proposed PI. However, the PCWG2 recommendations state that this outcome should not be reported.
- In patients with baseline soft- tissue disease, who comprised less than half of each treatment arm, the proportion of patients achieving a complete or partial soft tissue response was higher following enzalutamide treatment than with placebo. This finding is descriptive only; the trial was not powered to formally assess a difference in this outcome.
- Important missing information is the number of PFS events in each treatment arm following cessation of enzalutamide/placebo and commencement of cytotoxic chemotherapy.
- The proposed indication is for patients who are 'mildly symptomatic'. There is no suitable definition of this term provided for this term. Indeed, the word mildly may be considered superfluous, the descriptor is symptom status – 'mildly symptomatic' patients are nonetheless symptomatic.
- Study 9875-CL0321 has a substantial proportion of patients with an inadequate assessment of baseline disease status and therefore results from this study are non-informative.

Safety

Studies providing safety data

Table 8 shows safety studies.

Table 8: Submitted safety studies.

Study ID	Study type	Phase, design	Study population	Results	Number of subjects
9785-CL-0007	DDI	Phase I, nonrandomised, open label, single sequence crossover. Effect of repeat doses of enzalutamide on single dose PK of pioglitazone, warfarin, omeprazole, and midazolam	Patients with CRPC	Primary analysis	14
MDV3100-03 (PREVAIL)	Efficacy and safety	Phase III, randomised, double blind, placebo controlled,	Chemotherapy naïve patients with metastatic CRPC	Primary analysis	1717

Study ID	Study type	Phase, design	Study population	Results	Number of subjects
		multicentre			
S-3100-1-01	Safety, tolerability, MTD, PK, efficacy	Phase I, open label, uncontrolled, dose escalation and dose expansion cohorts	Patients with metastatic CRPC	Primary analysis	140
MDV3100-06	PK, safety, tolerability	Phase Ib, open label	Patients with metastatic CRPC	Primary analysis	22
9785-CL-0321	Efficacy, safety, tolerability, PD, PK	Phase II, open label, single arm	Patients with hormone-naïve prostate cancer	1-year analysis	67

Patient exposure

In PREVAIL, treatment duration for the interim analysis was calculated up to the data analysis cut off date for patients receiving ongoing therapy. Patients were required to return any unused medicines; it was assumed that non returned medicine was taken. The exposure of patients in PREVAIL is shown in Table 9.

Table 9: Exposure to enzalutamide and placebo, PREVAIL.

	Enzalutamide (N = 871)	Placebo (N = 844)
Treatment duration (months)[a]		
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
Treatment duration 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 to < 24 months	449 (51.5%)	130 (15.4%)
≥ 24 months	142 (16.3%)	22 (2.6%)
Total number of capsules taken[b]		
Mean (SD)	2019.2 (1018.29)	868.2 (777.51)
Median	2040.0	546.0
Min, max	37.0, 4836.0	4.0, 4464.0

Dose modifications were permitted in the study, with 11.8% and 10.0% of the enzalutamide and placebo arms having at least one dose modification, respectively.

> *Comment: As noted in the efficacy evaluation above, patients enrolled in this study could receive concomitant study treatment, including abiraterone (plus steroid),*

prior to cessation of study drug.[11] The safety analysis does not state that the safety outcomes were reported only for the enzalutamide/placebo monotherapy period for each patient, which is consistent with the proposed indication. The evaluator has to assume, therefore, that the safety data also includes periods of concomitant administration, which is unrepresentative of the difference between enzalutamide and placebo. The sponsor should clarify the reporting method.

The evaluator cannot therefore satisfactorily ascertain the relative difference in safety between enzalutamide exposure and placebo exposure, as required by the relevant legislation, owing to the unclear reporting methods in the dossier. The evaluation of all of the safety analyses below are predicated upon this concept.

Furthermore, the incidence of adverse events will be influenced by the highly discrepant duration of study drug exposure between the treatment arms. The total exposure period was 1180 patient-years for enzalutamide and 541 patient-years for placebo (see footnote of Table 10). These total exposure durations will also include concomitant abiraterone use. The incidence of adverse events in each study arm should also be reported standardised for the duration of exposure during the placebo controlled period only.

Reasons for dose modification are shown in Table 10.

Table 10: Dose modifications, PREVAIL safety population.

	Enzalutamide (N = 871)	Placebo (N = 844)
Number of dose modifications[a]		
0 (ie, no dose modification)	768 (88.2%)	760 (90.0%)
1	74 (8.5%)	67 (7.9%)
2	15 (1.7%)	15 (1.8%)
3	6 (0.7%)	0 (0.0%)
≥ 4	8 (0.9%)	2 (0.2%)
Number of dose interruptions		
0 (ie, no dose interruption)	772 (88.6%)	761 (90.2%)
1	82 (9.4%)	72 (8.5%)
2	9 (1.0%)	10 (1.2%)
3	5 (0.6%)	0 (0.0%)
≥ 4	3 (0.3%)	1 (0.1%)
Reason for dose interruption[b]		
Adverse events	93 (10.7%)	75 (8.9%)
Other	9 (1.0%)	13 (1.5%)
Number of dose reductions		
0 (ie, no dose reduction)	852 (97.8%)	836 (99.1%)
1	12 (1.4%)	7 (0.8%)
2	3 (0.3%)	1 (0.1%)
3	3 (0.3%)	0 (0.0%)
≥ 4	1 (0.1%)	0 (0.0%)
Reason for dose reduction[b]		
Adverse events	18 (2.1%)	8 (0.9%)
Other	3 (0.3%)	1 (0.1%)

a Includes dose interruptions and dose reductions.
b Patients can be summarised for both reasons but counted only once for each reason.

[11] Concomitant treatment with abiraterone was allowed once patients had either confirmed radiographic progression or a skeletal related event.

The median duration of the reporting period for TEAEs was 17.1 months and 5.4 months for the enzalutamide and placebo groups respectively. The total exposure period was 1180 patient-years for enzalutamide and 541 patient-years for placebo.

AEs were assessed according to MedDRA version 16.1 and laboratory parameters were graded according to CTCAE version 4.0.

Safety issues with the potential for major regulatory impact

Second malignancies (including post marketing experience)

Events of non-melanoma, second malignancy were observed to occur more commonly in the enzalutamide arm (3.1%) as compared to placebo (0.7%). The incidence of grade 3 or higher non-melanoma, second malignancy was 2.4% and 0.5% in the enzalutamide and placebo arms respectively. When adjusted for exposure to study treatment, the difference in incidence remained present: 1.9 versus 0.7 events per 100 patient-years with enzalutamide and placebo, respectively.

As presented in the dossier, among the reported specific diagnoses of grade 3, or higher, second malignancies, there was no preponderant disease type occurring in the enzalutamide arm (Table 11).

Table 11: Summary of grade 3 or higher second malignancies.

	Enzalutamide (N = 871)	Placebo (N = 844)
Patients with any second malignancy, n (%)	21 (2.4%)	4 (0.5%)
Gastric cancer	2 (0.2%)	1 (0.1%)
Transitional cell carcinoma	3 (0.3%)	0 (0.0%)
Adenocarcinoma of colon	2 (0.2%)	0 (0.0%)
Lung adenocarcinoma	1 (0.1%)	1 (0.1%)
Rectal cancer	2 (0.2%)	0 (0.0%)
Adenocarcinoma gastric	1 (0.1%)	0 (0.0%)
Anal cancer	0 (0.0%)	1 (0.1%)
Basal cell carcinoma	1 (0.1%)	0 (0.0%)
Bladder cancer	1 (0.1%)	0 (0.0%)
Bladder transitional cell carcinoma	1 (0.1%)	0 (0.0%)
Colon cancer	1 (0.1%)	0 (0.0%)
Colorectal cancer	1 (0.1%)	0 (0.0%)
Hepatocellular carcinoma	1 (0.1%)	0 (0.0%)
Intestinal adenocarcinoma	1 (0.1%)	0 (0.0%)
Lung neoplasm malignant	1 (0.1%)	0 (0.0%)
Malignant melanoma	1 (0.1%)	0 (0.0%)
Neuroendocrine carcinoma of the skin	0 (0.0%)	1 (0.1%)
Osteosarcoma	1 (0.1%)	0 (0.0%)
Renal cell carcinoma	1 (0.1%)	0 (0.0%)
Small cell lung cancer limited stage	1 (0.1%)	0 (0.0%)
Tonsil cancer	1 (0.1%)	0 (0.0%)
Event rate per 100 patient-years for second malignancies, n (event rate)	23 (1.9)	4 (0.7)

In the unrandomised trial 9785-CL-0321, there was one reported case (1.5% of all patients) of treatment emergent transitional cell carcinoma of the bladder. This was diagnosed at day 66 on-study, after approximately nine weeks of enzalutamide exposure. This patient died in the immediate post operative period, with the event of bladder cancer being ascribed 'not related' to study drug or disease progression.

No second malignancies were reported within trial 9785-CL-0111, but the median duration of exposure in the expansion cohort was only 121 days.

In the post marketing safety report of April 2014, there was one case of colon adenoma and one of colon cancer, five assigned "neoplasm" or "neoplasm malignant", and one case of "bladder cancer".

> *Comment: The previous submission leading to the current registration of enzalutamide did not contain any preclinical carcinogenicity studies and did not specifically report the incidence of second malignancies in patients recruited into AFFIRM.*
>
> *The randomisation method used in PREVAIL yielded two comparable treatment arms in regard to their demographic variables and disease characteristics. Of note however, is the lack of reporting of prior or current tobacco usage, but given the exchangeability of the groups in other respects, this factor is unlikely to be unbalanced on its own. Evidence from a randomised controlled trial with a placebo comparator yields the best evidence of a difference in incidence between patients with pre-chemotherapy CRPC. Cross study comparisons between AFFIRM and PREVAIL for this outcome are not valid since there are substantial differences in baseline disease state, exposure to additional therapies, duration of exposure and population composition resulting in a difference in incidence. Reports of second malignancies from non randomised studies do not inform the relative incidence between patients receiving enzalutamide and placebo.*
>
> *The method of reporting the second malignancies in the PREVAIL study report leads the reader to believe that there is no overall cancer types more commonly associated with enzalutamide exposure. However, using the information from Table 12 and the associated patient narratives, it can be seen that a number of the reported malignancies are of the same histological type and may be amalgamated:*
>
> - *Of the four patients with 'gastric cancer' all had adenocarcinoma of the stomach.*
> - *Of the six patients with 'colorectal cancer', five had a histological diagnosis of adenocarcinoma. The remaining subject had a clinical diagnosis of 'rectal carcinoma' but no histological diagnosis was made.*
> - *Of the four patients with lung cancer, the patient in the placebo arm had a histological diagnosis of adenocarcinoma whereas among the three patients in the enzalutamide arm two had a diagnosis of adenocarcinoma and one of small cell lung cancer of the lung.*
> - *Of the five patients with cancer of the kidney or urinary tract, all had a histological diagnosis of transitional cell carcinoma.*

Table 12: Reported malignancies.

		Enzalutamide (N=871)	Placebo (N=844)
Gastric carcinoma	Number of patients, n (% of total)	3 (0.34%)	1 (0.12%)
	95% CI for incidence	0.1, 1.0	0.02, 0.6
	Age, years. Median (IQR)	73 (69, 80)	77

		Enzalutamide (N=871)	Placebo (N=844)
	Time on study at diagnosis, days. Median (IQR)	341 (212, 523)	120
Colorectal carcinoma	Number of patients	6 (0.69%)	0 (0%)
		0.32, 1.5	0, 0.4
	Age, years. Median (IQR)	67 (64,72)	-
	Time on study at diagnosis, days. Median (IQR)	202 (130, 251)	-
Lung	Number of patients	3 (0.34%)	1 (0.12%)
		0.1, 1.0	0.02, 0.6
	Age, years. Median (IQR)	69 (66, 74)	77
	Time on study at diagnosis, days. Median (IQR)	361 (338, 469)	58
Transitional cell cancer of the kidney or urinary tract	Number of patients	5 (0.57%)	0 (0%)
		0.2, 1.3	0, 0.4
	Age, years. Median (IQR)	68 (62, 79)	-
	Time on study at diagnosis, days. Median (IQR)	426 (148, 443)	
Among the patients with second malignancies, two died during the study: one patient in the enzalutamide arm died of rectal carcinoma, having been diagnosed eight days after randomisation and another in the placebo arm died of lung adenocarcinoma 58 days after randomisation. These two deaths cannot be considered attributable to the study treatment, but it is of concern that these two patients were recruited and randomised in to the study since they fulfil an exclusion criterion.			

Thus, given the randomisation method and if the two early on-study deaths are excluded, there appears a plausibly greater risk of gastric and colorectal adenocarcinoma and transitional cell carcinoma of the urinary tract, shown above, associated with enzalutamide exposure. These findings should be specifically included in the PI.

In the Summary of Clinical Safety, the sponsor has provided a comparison of the expected incidence of categorised types of malignancy and compared the expected incidence as observed form the SEER database. This analysis includes all patients that received enzalutamide in the clinical development program, and not those in PREVAIL separately. This information does not allow a potential prescriber to inform the patient with pre-chemotherapy CRPC of their potential risk of second malignancy. The SEER database is only representative of patients in the USA, whereas PREVAIL patients are from numerous

other countries which may have a different background risk of malignancy. This notwithstanding, the observed incidence of bladder and colorectal and gastric second malignancies are higher than that expected from the age adjusted SEER incidence.

Furthermore, there may be patients that withdrew from the Phase III study enzalutamide arm that are still at risk, but beyond the follow-up period determined by the sponsor, who may yield additional information on the risk of second malignancy.

In the submitted post marketing safety report, there are additional events of 'colon adenoma', 'colon cancer' and 'bladder cancer' occurring each in one patient. In addition six patients were reported to have 'neoplasm' or 'neoplasm malignant' or 'lymphangiosis carcinomatosa', but there is no description of the tumour type for these patients.

The findings have potential implications for the use of enzalutamide in patients either in the setting of pre-chemotherapy CRPC outside PREVAIL in the wider community, or in the adjuvant setting where exposure may be longer than that in PREVAIL, in a population with a different risk profile.

Liver toxicity

Overall, there was no preponderance of adverse hepatobiliary event in either treatment arm, with a similar AE rate adjusted for exposure duration (Table 13). Grade 3 or higher hepatobiliary disorder events occurred in a similar proportion of each treatment arm.

Table 13: Summary of events of hepatic impairment, safety population.

	Enzalutamide (N = 871)	Placebo (N = 844)
Patients with any event in Hepatobiliary Disorders SOC, n (%)	10 (1.1%)	8 (0.9%)
Jaundice	3 (0.3%)	0 (0.0%)
Cholelithiasis	3 (0.3%)	1 (0.1%)
Any grade ≥ 3 event in Hepatobiliary Disorders	3 (0.3%)	3 (0.4%)
Any event in Hepatobiliary Disorders as primary reason for treatment discontinuation	1 (0.1%)	1 (0.1%)
Any event in Hepatobiliary Disorders leading to dose interruption	0 (0.0%)	2 (0.2%)
Any event in Hepatobiliary Disorders leading to dose reduction	0 (0.0%)	0 (0.0%)
Any serious adverse event in Hepatobiliary Disorders	3 (0.3%)	3 (0.4%)
Adverse event rates per 100 patient-years in Hepatobiliary Disorders, n (event rate)	12 (1.0)	8 (1.5)
Patients with any event in hepatic impairment SMQ, n (%)[a]	25 (2.9%)	21 (2.5%)
Investigations	16 (1.8%)	17 (2.0%)
Aspartate aminotransferase increased	8 (0.9%)	7 (0.8%)
Alanine aminotransferase increased	8 (0.9%)	5 (0.6%)
Liver function test abnormal	4 (0.5%)	2 (0.2%)
Hepatic enzyme increased	1 (0.1%)	4 (0.5%)
International normalised ratio increased	1 (0.1%)	3 (0.4%)
Gamma-glutamyltransferase increased	2 (0.2%)	0 (0.0%)
Hepatobiliary Disorders	7 (0.8%)	3 (0.4%)
Jaundice	3 (0.3%)	0 (0.0%)
Any grade ≥ 3 event in hepatic impairment SMQ	9 (1.0%)	5 (0.6%)
Any event in hepatic impairment SMQ as primary reason for treatment discontinuation	2 (0.2%)	2 (0.2%)
Any event in hepatic impairment SMQ leading to dose interruption	2 (0.2%)	2 (0.2%)
Any event in hepatic impairment SMQ leading to dose reduction	0 (0.0%)	0 (0.0%)
Any 1 serious adverse event in hepatic impairment SMQ	4 (0.5%)	4 (0.5%)
Adverse event rates per 100 patient-years in hepatic impairment SMQ, n (event rate)	38 (3.2)	29 (5.4)

Safety of co-administration of enzalutamide and docetaxel

Study MDV 3100-06 assessed the safety of co-administration of docetaxel and enzalutamide (160 mg/day) in 22 patients with CRPC eligible to receive docetaxel (75 mg/m^2) as their first systemic chemotherapy regimen. Patients not tolerating the combination of docetaxel and enzalutamide were permitted to continue enzalutamide alone.

The median duration of enzalutamide therapy was 12 months (range 0.2, 17.2 months). The median duration of docetaxel therapy was 3.8 months (range 0.7, 14.9 months), representing a median number of 5.5 21-day cycles.

The majority of patients required no enzalutamide dose reductions or interruptions. Of the 19% of patients requiring enzalutamide dose interruptions, all were due to AEs. One patient (4.5%) required a dose reduction of docetaxel, which was due to an AE.

TEAEs occurred in all 22 patients during co-administration, whereas in the post docetaxel enzalutamide only phase, 17/21 (81%) had a TEAE. The reported incidence of TEAE due to docetaxel is shown in Table 14.

Table 14: TEAEs in MDV 3100-06 safety population.

	Combination Therapy[a] (N = 22)	Postdocetaxel Enzalutamide[b] (N = 21)
Any treatment-emergent adverse event	22 (100.0%)	17 (81.0%)
Related to enzalutamide	19 (86.4%)	7 (33.3%)
Related to docetaxel	22 (100.0%)	8 (38.1%)
Related to docetaxel and enzalutamide	19 (86.4%)	2 (9.5%)
Grade ≥ 3	21 (95.5%)	6 (28.6%)
Any treatment-emergent serious adverse event	8 (36.4%)	5 (23.8%)
Any treatment-emergent adverse event leading to:		
Enzalutamide dose reduction	0 (0.0%)	0 (0.0%)
Enzalutamide dose interruption (temporary)	3 (13.6%)	2 (9.5%)
Enzalutamide discontinuation (permanent)	2 (9.1%)	0 (0.0%)

The listing of TEAEs occurring in >5% of patients is reported for the combination and monotherapy study periods in Table 15.

Table 15: TEAEs reported in ≥5% of patients during either therapy window (Safety Population).

	Combination Therapy[a] (N = 22)	Postdocetaxel Enzalutamide[b] (N = 21)
Blood and lymphatic system disorders	20 (90.9%)	2 (9.5%)
Anaemia	4 (18.2%)	1 (4.8%)
Febrile neutropenia	4 (18.2%)	0 (0.0%)
Neutropenia	19 (86.4%)	1 (4.8%)
Cardiac disorders	2 (9.1%)	2 (9.5%)
Acute coronary syndrome	2 (9.1%)	0 (0.0%)
Atrial fibrillation	0 (0.0%)	2 (9.5%)
Eye disorders	7 (31.8%)	2 (9.5%)
Lacrimation increased	5 (22.7%)	1 (4.8%)
Vision blurred	2 (9.1%)	1 (4.8%)
Gastrointestinal disorders	19 (86.4%)	7 (33.3%)
Abdominal pain	3 (13.6%)	1 (4.8%)
Constipation	7 (31.8%)	5 (23.8%)
Diarrhoea	7 (31.8%)	0 (0.0%)
Dyspepsia	4 (18.2%)	0 (0.0%)
Nausea	8 (36.4%)	0 (0.0%)
Stomatitis	3 (13.6%)	0 (0.0%)
General disorders and administration site conditions	22 (100%)	8 (38.1%)
Asthenia	3 (13.6%)	2 (9.5%)
Chest pain	2 (9.1%)	1 (4.8%)
Fatigue	17 (77.3%)	4 (19.0%)
Oedema	2 (9.1%)	1 (4.8%)
Oedema peripheral	2 (9.1%)	0 (0.0%)
Pain	4 (18.2%)	0 (0.0%)
Pyrexia	2 (9.1%)	2 (9.5%)
Infections and infestations	4 (18.2%)	5 (23.8%)
Urinary tract infection	2 (9.1%)	0 (0.0%)
Investigations	9 (40.9%)	4 (19.0%)
Blood phosphorus decreased	2 (9.1%)	0 (0.0%)
White blood cell count decreased	4 (18.2%)	1 (4.8%)
Metabolism and nutrition disorders	10 (45.5%)	5 (23.8%)

Table 15 (continued): TEAEs reported in ≥5% of patients during either therapy window (Safety Population).

	Combination Therapy[a] (N = 22)	Postdocetaxel Enzalutamide[b] (N = 21)
Decreased appetite	6 (27.3%)	4 (19.0%)
Dehydration	3 (13.6%)	1 (4.8%)
Musculoskeletal and connective tissue disorders	15 (68.2%)	11 (52.4%)
Arthralgia	6 (27.3%)	3 (14.3%)
Back pain	6 (27.3%)	3 (14.3%)
Bone pain	2 (9.1%)	1 (4.8%)
Flank pain	3 (13.6%)	1 (4.8%)
Musculoskeletal chest pain	3 (13.6%)	2 (9.5%)
Musculoskeletal discomfort	2 (9.1%)	0 (0.0%)
Musculoskeletal pain	3 (13.6%)	4 (19.0%)
Pain in extremity	3 (13.6%)	0 (0.0%)
Nervous system disorders	19 (86.4%)	6 (28.6%)
Dizziness	4 (18.2%)	0 (0.0%)
Dysgeusia	5 (22.7%)	1 (4.8%)
Headache	3 (13.6%)	0 (0.0%)
Neuropathy peripheral	9 (40.9%)	1 (4.8%)
Peripheral motor neuropathy	3 (13.6%)	1 (4.8%)
Peripheral sensory neuropathy	7 (31.8%)	3 (14.3%)
Psychiatric disorders	3 (13.6%)	1 (4.8%)
Insomnia	3 (13.6%)	0 (0.0%)
Renal and urinary disorders	7 (31.8%)	5 (23.8%)
Haemorrhage urinary tract	2 (9.1%)	2 (9.5%)
Pollakiuria	3 (13.6%)	1 (4.8%)
Urethral pain	0 (0.0%)	2 (9.5%)
Respiratory, thoracic and mediastinal disorders	10 (45.5%)	2 (9.5%)
Dyspnoea	6 (27.3%)	1 (4.8%)
Dyspnoea exertional	4 (18.2%)	0 (0.0%)
Skin and subcutaneous tissue disorders	12 (54.5%)	2 (9.5%)
Alopecia	6 (27.3%)	0 (0.0%)
Nail disorder	3 (13.6%)	1 (4.8%)
Rash	3 (13.6%)	2 (9.5%)
Vascular disorders	5 (22.7%)	2 (9.5%)
Intermittent claudication	2 (9.1%)	0 (0.0%)

Grade 3 or higher TEAEs were reported in 21/22 (95.5%) of patients receiving combination therapy as opposed to 6/21 (28.6%) receiving enzalutamide alone. Among the reported severe TEAEs, neutropenia occurred in 19/22 (86.4%) with combination compared to 1/21 (4.8%) with monotherapy, and febrile neutropenia was reported in 4/22 (18.2%) and 0/21 for each phase respectively. Leukopenia was reported in 4 patients (18.2%) and a reduction in blood phosphorous was reported in two patients receiving combination therapy.

Other reported events occurred in one patient per event in either treatment phase.

> *Comment: The incidence of any grade TEAE was higher during combination therapy than with enzalutamide monotherapy. The small number of patients studied in this trial therapy have not been randomised and compared against patients receiving docetaxel alone, and therefore firm conclusions cannot be drawn. The incidence of TEAEs during combination therapy occurred more frequently for events in multiple system organ classes including neutropenia, gastrointestinal disorders, nervous system disorders and dyspnoea.*

Serious skin reactions

The incidence of skin common adverse events when adjusted for duration of exposure was similar between the two treatment arms (Table 16).

Table 16: Summary of incidence of common events of the SOC skin & subcutaneous tissue disorders, safety population.

	Overall Incidence, n (%)		Events per 100 Patient-Years of Reporting, n (Event Rate)	
	Enzalutamide (N = 871)	Placebo (N = 844)	Enzalutamide (N = 871)	Placebo (N = 844)
Patients with any event of skin disorders[a]	169 (19.4%)	114 (13.5%)	226 (19.2)	141 (26.0)
Rash	28 (3.2%)	21 (2.5%)	30 (2.5)	22 (4.1)
Hyperhidrosis	23 (2.6%)	20 (2.4%)	23 (1.9)	20 (3.7)
Dry skin	18 (2.1%)	10 (1.2%)	18 (1.5)	10 (1.8)
Pruritus	16 (1.8%)	12 (1.4%)	17 (1.4)	12 (2.2)
Alopecia	15 (1.7%)	6 (0.7%)	15 (1.3)	6 (1.1)
Erythema	11 (1.3%)	7 (0.8%)	11 (0.9)	7 (1.3)
Eczema	9 (1.0%)	3 (0.4%)	9 (0.8)	3 (0.6)

The incidence of grade 3, or higher, adverse events was 0.5% in the enzalutamide arm and 0.1% in the placebo arm. Two events in patients receiving enzalutamide were described as having a toxic skin eruption, with "toxidermia"; in one patient the skin eruption was associated with eosinophilia.

Comment: The narrative for one patient describes the onset of a maculopapular rash occurring on over 50% of the skin surface, with a biopsy showing grade 3 'toxidermia' and inflammatory exudate. This patient did not have lymphocytosis or eosinophilia.

The narrative for another patient describes the presence of an erythematous maculopapular rash, with two small pustules and skin peeling of <20% total body surface area, but Nikolsky sign negative. The skin biopsy was reported to be "not inconsistent with a diagnosis of toxidermia".

In both patients, their symptoms abated following temporary discontinuation of enzalutamide.

The term "toxidermia" is used in French medical literature, but given it is written in the dossier in inverted commas, is not sufficiently explained in these patients to derive a specific diagnosis. The sponsor is requested to provide a sufficient explanation of the term 'toxidermia' – see safety questions.

The first patient has no obvious features of SJS/TEN, whereas for the second patient, the description is concerning for SJS/TEN.

Given the description of the second patient, it is recommended that events of desquamating skin rash be included in the RMP, since this may have been an event of SJS/TEN.

Evaluator's conclusions on safety

The assessment of the comparative safety of enzalutamide versus placebo can only be made during study drug monotherapy. A meaningful analysis is rendered impossible by the potential for inclusion of an unspecified number of patients who received concomitant abiraterone while receiving study drug.

First round benefit-risk assessment

First round assessment of benefits

The benefits of enzalutamide in the proposed usage are:

- In androgen deprived males with metastatic CRPC yet to receive chemotherapy, enzalutamide significantly reduces the time to radiographic progression as compared to placebo.
- The observed increased risk of seizures seen in patients in AFFIRM was not replicated in PREVAIL. However, the advice contained in the PI regarding cessation of therapy in individuals in whom seizures occur while on-therapy should remain.
- Co-administration of enzalutamide and docetaxel was shown to not affect the pharmacokinetics of docetaxel. This finding relates to the initial registration submission rather than the current one, in which monotherapy enzalutamide was administered.

First round assessment of risks

The risks of enzalutamide in the proposed usage are:

- Enzalutamide has not been satisfactorily shown to increase the duration of overall survival (all-cause mortality) as compared to placebo due to the effects of concomitant (especially abiraterone) use and treatment switching and crossover.
- The data for PREVAIL is immature, rendering the OS estimate unstable: in the submission, less than 50% of each treatment arm has died.
- Among the patients in PREVAIL who died, the cause of death was progression of prostate cancer in 75% of each treatment arm.
- Despite a longer time to rPFS with enzalutamide in PREVAIL, the difference in median duration of overall survival differed by 2.2 months. This outcome is potentially confounded by the permitted concomitant use of abiraterone prior to study drug cessation.
- The unclear method of reporting safety data precludes the evaluator from forming any firm conclusions as to the safety of enzalutamide in the proposed indication
- The incidence, and severity, of adverse events in pre chemotherapy PREVAIL patients with CRPC appears, notwithstanding the unclear reporting method, non identical to those who are post chemotherapy reported in AFFIRM. This difference in risk needs to be clearly stated in the PI to satisfactorily inform prescribers and patients.
- The proposed indication includes patients who are 'mildly symptomatic'. There is no definition of this term provided.
- The pivotal study compared enzalutamide against placebo. In contemporary practice, the more appropriate comparator would be abiraterone rather than placebo.
- Concomitant use of enzalutamide and abiraterone was permitted in PREVAIL yet the efficacy and safety of this experimental combination has not been separately reported and therefore cannot be endorsed.
- One in 25 patients receiving enzalutamide in PREVAIL had a TEAE leading to death.
- The incidence of treatment related deaths in PREVAIL has not been reported.
- Approximately 30 patients need to be treated with enzalutamide to prevent one death from prostate cancer disease progression.

- Falls occurred twice as commonly in enzalutamide treated patients as compared to placebo in the randomised controlled trial. This finding is consistent with the safety profile described in AFFIRM.
- The data regarding the magnitude of change in PSA concentration, or time to PSA concentration change, in pre chemotherapy CRPC patients has not been confirmed to be a suitable predictive test of duration of survival, time to radiographic progression or time to first skeletal related event.
- A formal QT study has not been performed.
- The incidence of pre existing electrocardiogram (ECG) abnormalities, including prolonged QT interval, reflects the known adverse event profile of androgen deprivation therapies.
- Treatment emergent ECG abnormalities, including bundle branch block and prolonged QTc, were reported in PREVAIL. These new ECG changes can only be identified if patients have had a baseline ECG.
- The risk of adverse cardiac events during enzalutamide therapy has not been reported separately for patients concomitantly receiving GnRH agonists and antagonists, which confer different baseline risks.
- There is an increased risk of amalgamated ventricular conduction adverse events with enzalutamide exposure as compared to placebo
- The incidence of adverse events was shown in a post hoc analysis of the combined PREVAIL and AFFIRM populations to be directly related to increasing age.
- The adverse event profile of docetaxel may be adversely affected by co-administration with enzalutamide (this potential risk is included in the proposed PI, but only for events of neutropenia)
- A case of potential Stevens Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) has been reported, and requires further clarification from the sponsor.

First round assessment of benefit-risk balance

From the data presented in the dossier, the benefit-risk balance of enzalutamide in the proposed usage is unfavourable.

First round recommendation regarding authorisation

There are substantial methodological discrepancies in the data presented to yield a satisfactory demonstration of efficacy and safety of enzalutamide in the proposed indication. Registration is not yet recommended, pending the sponsors' response to the clinical questions.

Clinical questions

Efficacy

1. The sponsor should provide OS data (hazard ratio [HR], median duration, mean duration) for the enzalutamide and placebo arms of PREVAIL for the randomised controlled period alone, and excluding the period of concomitant abiraterone use where this occurred.

2. In PREVAIL, prior to cessation of study drug, what were the additional therapies used in each treatment arm, and what were the number of patients that received each of them?
3. In PREVAIL, what were the criteria for commencing abiraterone as a concomitant therapy?
4. In PREVAIL, what were the criteria for commencing abiraterone as concomitant therapy as opposed to commencing chemotherapy?
5. The sponsor should report the median and IQR of time to commencement of cytotoxic chemotherapy therapy (and therefore cessation of enzalutamide/placebo) for the four treatment arms: (i) enzalutamide only, (ii) concomitant enzalutamide and additional therapy, (iii) placebo alone, (iv) concomitant placebo plus additional therapy.
6. The sponsor should report the median and IQR of time to PSA progression for the four treatment arms: (i) enzalutamide only, (ii) concomitant enzalutamide & abiraterone, (iii) placebo alone, (iv) concomitant placebo plus abiraterone, using the appropriate denominator.
7. The sponsor should report the proportion receiving, and median and IQR of time to antineoplastic use for the four treatment arms: (i) enzalutamide monotherapy, (ii) concomitant enzalutamide and additional therapy, (iii) placebo monotherapy, (iv) concomitant placebo plus additional therapy.
8. The sponsor should report the median and IQR of time to PSA progression for the four treatment arms: (i) enzalutamide monotherapy, (ii) concomitant enzalutamide & additional therapy, (iii) placebo monotherapy, (iv) concomitant placebo plus additional therapy, using the appropriate denominator.
9. The sponsor should report the number of patients and their median time (plus interquartile range) to rPFS event or first skeletal related event, which ever came sooner, for the four treatment groups receiving (i) enzalutamide monotherapy, (ii) concomitant enzalutamide & additional, (iii) placebo monotherapy and (iv) concomitant placebo & additional therapy, according to the table below:

	Enzalutamide only	Enzalutamide + abiraterone / biological therapy	Placebo only	Placebo + abiraterone / biological therapy
rPFS1				
rPFS2				
rPFS3				
rPFS4				

10. What number of patients in each PREVAIL treatment arm were receiving study drug alone at the efficacy analysis point?
11. The sponsor is requested to provide an explanation for the substantially lower time to both rPFS and death for the post-chemotherapy CRPC Japanese patients in Study 9785-CL-0111 as compared to the non-Japanese patients in the AFFIRM study.
12. The reported data on time to PSA progression in PREVAIL included patients with only one PSA measurement. The sponsor is requested to re-calculate the data in the CSR to reflect the correct denominator of only those patients with >1 PSA measurement.

13. In PREVAIL, was Radium 223 permitted as an additional agent prior to cessation of enzalutamide/placebo, and if so, how many patients in each arm received this therapy?
14. The sponsor should confirm whether the reported data pertaining to first skeletal event is for the randomised controlled period only, or also includes the period following initiation of additional therapies. If the latter applies, the sponsor should report the outcome for the monotherapy period of study treatment, including standardisation for the duration of study treatment.
15. What proportion of the skeletal related events occurred after commencement of cytotoxic chemotherapy in each PREVAIL treatment arm?
16. The sponsor should confirm that patients who received abiraterone also received prednisone/prednisolone at all stages of the PREVAIL study, as per the currently approved PI for abiraterone.
17. What pharmacokinetic analysis was performed on patients receiving concomitant abiraterone and enzalutamide to ensure the safety of this combination?
18. The sponsor should present the quality of life data for each treatment arm of PREVAIL for the study drug monotherapy period alone.
19. The sponsor should present the efficacy outcomes of OS and time to first skeletal-related event for each treatment arm of PREVAIL, stratified for concomitant additional therapy use.
20. The sponsor should present the PREVAIL subgroup analyses of OS for (i) those patients that only received study drug as monotherapy and (ii) those that received concomitant study drug plus additional therapy, prior to cessation of study drug.
21. What is the prognostic value of achieving a PSA concentration reduction of >50% from baseline for patients fulfilling the criteria to enter PREVAIL?
22. Were patients in PREVAIL who had clinical progression prior to a skeletal-related event or radiographic progression permitted to received concomitant therapy prior to cessation of enzalutamide/placebo?
23. In study 9785-CL-0321, what were (i) the median (IQR) baseline bone mineral bone density t-score, and (ii) the median (IQR) change in bone mineral density t-score over time?

Safety

24. The sponsor should confirm the reporting methods of the safety analysis. A safety analysis reporting only the period during which patients only received the study drug as monotherapy is requested, that is, excluding the period when concomitant use of additional therapies occurred, and excluding the period post-cessation of study drug. Outcomes should be reported including standardisation according to duration of study drug treatment.
25. Can the sponsor explain the difference in incidence of TEAEs leading to death in enzalutamide treated patients in PREVAIL (37/871 = 4.2%) as compared to the incidence of any TEAE leading to death in AFFIRM of 2.9%.
26. What was the incidence of treatment related death (as opposed to treatment emergent) for patients in PREVAIL while receiving monotherapy study drug?
27. The cause of death for 9 enzalutamide treated patients and 4 placebo treated patients in PREVAIL was described as 'general health deterioration'. The sponsor is requested

to provide a more thorough explanation for the actual cause of death for these thirteen patients.

28. The cause of AEs leading to death in 4 enzalutamide treated patients and 1 placebo treated patient in PREVAIL is listed as 'death'. The sponsor is requested to provide a more thorough explanation for the actual cause of death for these five patients.
29. The sponsor is requested to provide a sufficient explanation of the non-specific term 'toxidermia' for the two patients in whom it occurred.
30. The incidence of second malignancies observed in PREVAIL should be included in the PI.
31. In the post marketing safety report, six patients were reported to have either 'neoplasm' or 'neoplasm malignant' or 'lymphangiosis carcinomatosa'. What is the histological diagnosis of the cancer for these six patients, and what was their duration of enzalutamide exposure?
32. In Study 9785-CL-0321 were patients with reported new QTcF prolongation >500 msec a sub-group of those with new prolongation >480 msec?
33. In Study 9785-CL-0321, were the two deaths reported in the safety analysis set treatment related?
34. What proportion of patients in PREVAIL were continuing to receive (i) a GnRH agonist and (ii) a GnRH antagonist, in each treatment arm? What was the incidence of cardiac and ECG TEAEs due to enzalutamide for patients receiving each GnRH treatment modality?

Second round evaluation

The sponsor's response addresses questions that were raised in the first round clinical assessment. For details of the evaluator's assessment of the response, please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of enzalutamide, in addition to those in the first round evaluation, in the proposed usage are:

- A similarity of efficacy in patients dichotomised at age 75 years.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of enzalutamide in the proposed usage are:

- The sponsor has not provided a satisfactory response to establish if a difference in risk of adverse cardiac/ECG events according to type of GnRH agonist/antagonist use exists.
- A positive relationship between duration of enzalutamide exposure and fatal TEAE has been reported by the sponsor, but this has not been quantified further.
- Data from the randomised controlled trial PREVAIL demonstrates a higher incidence of second malignancy for patients exposed to enzalutamide than those exposed to placebo.

- In PREVAIL, the safety profile for patients exposed to enzalutamide aged ≥75 years was worse than for those aged <75 years.
- The occurrence of rash consistent with a diagnosis if toxic epidermal necrolysis has been reported.

Second round assessment of benefit-risk balance

The benefit-risk balance of enzalutamide is unfavourable given the proposed usage, but would become favourable if the changes recommended are adopted.

Second round recommendation

The proposed indication could be supported if the sponsor satisfactorily responds to the relevant PI comments.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a EU-Risk Management Plan (EU-RMP) Version 7.0 (dated 6 October 2014, DLP 16 September 2013 for the Phase 3 Study MDV3100-03 and 1 July 2013 for the remaining studies in the Integrated Safety Population) and Australian Specific Annex (ASA) Version 1.2 (dated 17 October 2014), which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 17.

Table 17: Ongoing safety concerns.

Ongoing safety concerns	
Important identified risks	Seizure Hypertension Fall Hallucination 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
Important missing	Patients with severe renal impairmentPatients with

Ongoing safety concerns	
information	moderate or severe hepatic impairment Reproduction/fertility Patients of non White race[1] 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

CYP: cytochrome P450; ECOG: Eastern Cooperative Oncology Group; PS: Performance Status
1. Excluding Asian patients (primarily of Japanese ethnicity)

RMP reviewer comment

Notwithstanding the evaluation of the nonclinical and clinical aspects of the Safety Specification, there are no definite objections to the list of safety concerns and missing information items provided in the context of this application. However, the following information is required to assess the list of safety concerns and missing information:

- The sponsor should provide information on the post market experience with anti-androgen withdrawal syndrome.
- The sponsor should provide information on the post market experience with resistance to enzalutamide.
- The sponsor should provide information on the post market experience of transporter mediated drug interactions with enzalutamide (including results of studies conducted for this purpose for the FDA).
- The sponsor should provide information on the post market experience of patients with central nervous system conditions that are taking enzalutamide.

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for important identified and potential risks and missing information. Furthermore, additional activities are planned for some of the risks. These activities are summarised in Table 18.

Table 18: Additional pharmacovigilance activities planned by the sponsor.

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
Post authorisation safety study Category: 3 Ongoing	Seizure	The safety of enzalutamide in patients excluded from the pivotal study due to certain baseline factors considered predisposing for	Study completion date: June 2018 Final report submission: March 2019

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
		seizure.	
Clinical study Category: 3 Ongoing at time of RMP sign-off date.	Patients with moderate or severe hepatic impairment (study concerned with severe hepatic impairment)	Assess, in subjects with normal hepatic function and patients with pre-existing severe hepatic impairment, the effect of severe hepatic impairment on the pharmacokinetics of enzalutamide and N-desmethyl enzalutamide	Study completion date: May 2014 Final report submission: November 2014
Clinical study Category: 3 Planned at time of RMP sign-off date; now ongoing	Patients with moderate or severe hepatic impairment (study concerned with moderate hepatic impairment)	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	Draft protocol submission: February 2014 Final report submission: December 2015
Post-authorisation efficacy study Category: 3 Ongoing	Data on the efficacy of enzalutamide in patients with metastatic CRPC previously treated with abiraterone (not a safety concern)	Data on the efficacy of enzalutamide in patients with metastatic CRPC previously treated with abiraterone	Report of interim Analysis: June 2015 Final report submission: December 2016

RMP reviewer comment

There is no definite objection to the pharmacovigilance plan proposed by the sponsor in the context of this application.

Risk minimisation activities

The sponsor states the following:

> *The product information is sufficient to mitigate the current identified and potential risks of enzalutamide. The necessary information to ensure appropriate use of the*

product will be included in the relevant sections of the SmPC to avoid or prevent any severe and life threatening consequences. No additional measures for risk minimisation are considered necessary by the MAH at this time.

RMP evaluator comment

The sponsor's conclusion with regard to the need for additional risk minimisation activities is considered acceptable in the context of this submission.

Reconciliation of issues outlined in the RMP report

The following section summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Recommendation #1 in RMP evaluation report

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.

Sponsor response

No response required.

Evaluator's comment

N/A

Recommendation #2 in RMP evaluation report

The sponsor should provide information on the post-market experience with anti-androgen withdrawal syndrome.

Sponsor response

A search of the sponsor's global safety database retrieved 1 reported case with the preferred term "anti-androgen withdrawal syndrome". This case is a literature report based on an investigator conducted study in post docetaxel metastatic CRPC patients, which describes 1 patient (out of 30) with a confirmed PSA response of ≥ 50% after discontinuing enzalutamide treatment. According to the authors, despite the withdrawal PSA response observed in the study, no symptomatic benefit or radiological responses were noted after enzalutamide withdrawal.[12]

Evaluator's comment

The sponsor's response has been noted.

Recommendation #3 in RMP evaluation report

The sponsor should provide information on the post market experience with resistance to enzalutamide.

Sponsor response

A search of the sponsor's global safety database retrieved 15 reported cases with the preferred term "drug resistance" (Table 19). Twelve of these cases are literature reports and originated from the American Association of Cancer Research (AACR) conference

[12] Rodriguez-Vida A, et al. (2015) Is there an antiandrogen withdrawal syndrome with enzalutamide? *BJU Int.* 115: 373-380.

presentation regarding an investigator-sponsored study of 31 prostate cancer patients treated with enzalutamide; it was noted that none of the 12 patients with a detectable androgen receptor splice variant (AR-V7) achieved PSA response. Three more cases originated from spontaneous reporting and no biomarker known to be associated with enzalutamide resistance was reported in these cases.

Table 19: Overview of drug resistant cases in the global safety database.

Source	Events reported (PTs)	Case description	Presence of resistance biomarkers
Literature	Drug resistance, drug ineffective	It was reported that the patient might have had a primary resistance to enzalutamide; no PSA response	AR-V7
Comp. use	Drug resistance, drug ineffective	The patient was reported to have experienced "therapeutic escape and/or resistance (modification of PSA)" during enzalutamide treatment, which was considered as lack of efficacy and drug resistance	-
Spont.	Drug resistance, drug ineffective	After approx. 3 months of enzalutamide treatment, there was no PSA decrease and bone and MRI scans showed metastases and increased tumour size. Enzalutamide was discontinued.	-
Spont.	Drug resistance, drug ineffective	The patient "showed some resistance 6 months into therapy. They were then switched to abiraterone for a couple of months	-

Source	Events reported (PTs)	Case description	Presence of resistance biomarkers
		and switched back to enzalutamide on an unspecified date because they were "not doing well" while on abiraterone.	

AR-V7: androgen receptor splice variant; MRI: magnetic resonance imaging; PSA: prostate specific antigen; PT: preferred term

Evaluator's comment

The sponsor's response has been noted.

Recommendation #4 in RMP evaluation report

The sponsor should provide information on the post market experience of transporter mediated drug interactions with enzalutamide (including results of studies conducted for this purpose for the FDA).

Sponsor response

A search of the sponsor's global safety database for preferred terms "Drug interaction" and "Labelled drug-drug interaction medication error" retrieved 55 cases of drug interaction, all received via spontaneous reporting. Most of the drug interactions reported are described in the current labelling information for enzalutamide (interactions with strong inhibitors or inducers of CYP2C8 and interactions with medicinal products that are substrates of CYP3A4, CYP2C9 or CYP2C19), such as drug interaction with fentanyl (12 cases), warfarin (7 cases), digoxin (4 cases) and omeprazole (3 cases). The less frequent drug interactions reported included interactions with atorvastatin, simvastatin, bisoprolol, palladon, tramadol, paracetamol, phenprocoumon, duloxetine hydrochloride, zoledronic acid, unspecified beta blocker and unspecified proton pump inhibitor. It should be noted that in many cases only a "suspected drug interaction was reported" or the consumer requested that the sponsor provide information on the use of enzalutamide with specific drugs. In 7 cases an unspecified drug interaction was reported.

Drug interaction cases are summarised (available in the sponsor response document).

Evaluator's comment

The sponsor's response has been noted.

Recommendation #5 in RMP evaluation report

The sponsor should provide information on the post market experience of patients with central nervous system conditions that are taking enzalutamide.

Sponsor response

Information regarding AEs in a special patient population (that is, patients with central nervous system conditions treated with enzalutamide) is not collected in the sponsor's safety database.

The sponsor is currently conducting a post authorisation safety Study 9785-CL-0403, a multicentre, single arm, open label, post marketing safety study to evaluate the risk of seizure in patients with metastatic CRPC treated with enzalutamide who are at potential increased risk of seizure. The primary objective of the study is to examine the incidence of

seizure events. As of the cut-off date of 31 March 2015, 241 patients were enrolled in the study. Of the 241 patients enrolled, 239 patients had started enzalutamide treatment on or prior to the cut-off date. There have been 4 confirmed seizure cases (in 3 patients). Within 4 months of treatment, the seizure rate was 2/139 (1.4%) (95% CI: 0.2, 5.1). The total seizure rate as of 31 March 2015 was 3/239 (0.8%).

Evaluator's comment

The sponsor's response has been noted.

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

It is considered that the sponsor's response to the TGA Section 31 request has adequately addressed the non PI issues identified in the RMP evaluation report. Outstanding issues include administrative issues and PI recommendations not addressed in the Section 31 response.

Outstanding RMP issues

- As a result of the events described in the clinical evaluation report, the sponsor should update the RMP/ASA to include 'Severe skin reactions (including SJS and TEN)' as an Important Potential Risk (Reference: Round 2 recommendation).
- As a result of the events described in the s31 response, the sponsor should update the RMP/ASA to include 'Posterior reversible encephalopathy syndrome (PRES)' as an Important Potential Risk (Reference: Round 2 recommendation).

Comments on the safety specification of the RMP

Clinical evaluation report

The clinical evaluator made the following first round comment in regard to safety specifications in the draft RMP:

> *The Safety Specification in the draft RMP is not entirely satisfactory and should be revised, having regard to the comments below.*
>
> *It is recommended to the RMP evaluator to include a potential risk of desquamating skin rash in association with enzalutamide, in the RMP, given the described occurrence in one patient.*

Furthermore the clinical evaluation report contained the following comment on skin reactions:

> *The narrative for one patient describes the onset of a maculopapular rash occurring on over 50% of the skin surface, with a biopsy showing grade 3 'toxidermia' and inflammatory exudate. This patient did not have lymphocytosis or eosinophilia.*
>
> *The narrative for another patient describes the presence of an erythematous maculopapular rash, with two small pustules and skin peeling of <20% total body surface area, but Nikolsky sign negative.*
>
> *The skin biopsy was reported to be "not inconsistent with a diagnosis of toxidermia".*
>
> *In both patients, their symptoms abated following temporary discontinuation of enzalutamide.*
>
> *The term "toxidermia" is used in French medical literature, but given it is written in the dossier inverted commas, is not sufficiently explained in these patients to derive a*

specific diagnosis. The sponsor is requested to provide a sufficient explanation of the term 'toxidermia' – see safety questions.

The first patient has no obvious features of SJS/TEN, whereas for the second patient, the description is concerning for SJS/TEN.

Given the description of the second patient, it is recommended that events of desquamating skin rash be included in the RMP, since this may have been an event of SJS/TEN.

The clinical evaluator made no second round comment in regard to safety specifications in the draft RMP.

RMP evaluator comment

As a result of the events described in the clinical evaluation report, the sponsor should update the RMP/ASA to include 'Severe skin reactions (including SJS and TEN)' as an Important Potential Risk.

Nonclinical evaluation report

The nonclinical evaluator made the following comment in regard to safety specifications in the draft RMP:

No new information has been provided that would warrant a change to the Nonclinical Safety Specification of the Risk Management Plan.

Key changes to the updated RMP

Not applicable. No updated RMP has been submitted.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

Implement EU-RMP Version 7.0 (dated 6 October 2014, DLP 16 September 2013 for the Phase 3 Study MDV3100-03 and 1 July 2013 for the remaining studies in the Integrated Safety Population) and Australian Specific Annex (ASA) Version 1.2 (dated 17 October 2014) and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Nonclinical

The nonclinical evaluator had no objections on nonclinical grounds to registration of enzalutamide for the proposed indication.

The following comments were noted at the time of registration of this product:

The safety of the excipient, Labrasol, has been adequately assessed.

The toxicity of the major active human metabolite, M2, has not been adequately assessed, but given the similar pharmacological profiles of M2 and enzalutamide, M2 is likely to have a similar toxicity profile to enzalutamide.

The nonclinical submission consisted of additional toxicity data that were noticeably absent from the original submission for Xtandi(toxicity of the M2 metabolite and definitive embryofoetal development studies in two species), as well as additional information regarding possible pharmacokinetic drug interactions.

- New nonclinical studies were submitted, but none directly related to support the new indication.
- *In vitro* pharmacokinetic data indicated:
- Drug interactions involving displacement from protein binding sites are not anticipated.
- Enzalutamide administration may decrease the exposure of drugs that are metabolised by CYP2B6, CYP3A4, UGT1A1 or UGT1A4.
- Exposures to drugs that are Pglycoprotein substrates may be altered with enzalutamide co-administration.
- *In vitro*, M1, the pharmacologically inactive carboxylic acid metabolite of enzalutamide, was a substrate for OAT3. The clinical relevance of this finding is uncertain.
- The sponsor has presented pilot toxicity studies in mice and rats to aid in the selection of doses for future carcinogenicity studies, and 4 and 39 week repeat dose toxicity studies in mice and dogs, respectively. In general, the toxicities observed in the newly submitted studies were similar to those observed previously. The new toxicity studies do not alter the toxicity profile of enzalutamide, with the exception of Leydig cell changes (hypertrophy/hyperplasia) observed in the testes of both mice and dogs. These changes are suggestive of proliferative effects in this tissue.
- Definitive embryofoetal development studies in mice and rabbits were submitted. No adverse embryofoetal effects were observed in rabbits. Embryofoetal lethality and toxicity were observed at subclinical exposures in mice. Enzalutamide was teratogenic in the latter species (consistent with previously submitted data.
- Two repeat dose toxicity studies with the pharmacologically active metabolite, M2, were submitted. In general, the toxicity findings were similar to those observed in repeat dose toxicity studies with enzalutamide, with changes in the male reproductive organs (decreased prostate and epididymal weights and Leydig cell hypertrophy in the testes; consistent with the pharmacological action of M2 [and enzalutamide]), liver (increased weight and enlargement correlating microscopically with centrilobular hypertrophy), adrenal gland (eosinophilic change in the zona fasciculata) and gastrointestinal tract (perforation, erosion and mucosal thickening of the forestomach). The newly submitted toxicity data with M2 suggest a possible risk of hepatotoxicity and cardiotoxicity in patients receiving Xtandi. The risk is not considered to be greater for the new indication.

Clinical

The clinical evaluator recommended that subject to the satisfactory amendment of the PI the sponsor's proposed usage could be supported.

Pharmacokinetics/pharmacodynamics

The sponsor provided information about the PSA and testosterone inhibition in hormone-naïve patients. This indicates that enzalutamide, in the absence of castrate levels of both measures has a degree of efficacy in lowering overexpression of PSA, but it does not

support enzalutamide being used without prior orchidectomy or GnRH analogues. The PI appropriately contains no information drawn from this.

Bone mineral density

Enzalutamide results in lowered androgen levels, below that with orchidectomy or GnRH analogues alone. The bone mineral density (BMD) data should be presented as T-scores at baseline, and changes in those with treatment duration. This should be included in the PI to encourage proactive management of any osteoporosis. This is important clinical information given the increase in falls observed with enzalutamide treatment in the pivotal studies associated with this submission (PREVAIL) and that for initial registration (AFFIRM).

Pharmacokinetics in Japanese patients

Based on a pharmacokinetic study in 9 Japanese patients (3 patients/cohort, receiving 80 mg, 160 mg and 240 mg), the Sponsor proposes to include a statement in the PI that there are no differences between Caucasian and Japanese patients.

> *Delegate comment: there are too few patients, particularly for a very common cancer and the potentially wide use of enzalutamide, for such a generalisation so this information should be removed from the PI.*
>
> *Delegate comment 31 August 2015: in the draft response to the Delegate report of 26 August 2015 note 31 August 2015, the sponsor has agreed to this request (see Appendix 1).*

Efficacy

MDV3100-03 (PREVAIL) was a phase III, randomised, double blind, placebo controlled multicentre trial performed in North America, Europe, Australia and Asia to assess the efficacy and safety of enzalutamide in 872 patients versus placebo in 845 patients with metastatic prostate cancer that progressed on androgen deprivation therapy. Patients must have been asymptomatic or mildly symptomatic due to prostate cancer at study entry and must not have previously received cytotoxic chemotherapy.

Patients were randomised to enzalutamide 160 mg daily or placebo, with continued testosterone suppression (GnRH agonist/antagonist or following orchidectomy). The median age of the patients enrolled was 71 years and more than one third were over the age of 75.

The study drug was to continue until confirmed radiographic disease progression or a skeletal related event **and** either the initiation of cytotoxic chemotherapy or an investigational agent, for treatment of prostate cancer (see comments below).

Co-primary endpoints (Table 20):

- OS: pre-specified interim analysis 16 September 2013, anticipated 765 deaths
- rPFS in ITT population (although data missing for 84 patients for rPFS due to late randomisation) pre-specified analysis May 2012)

Table 20: Summary of planned interim analyses for the two co-primary endpoints.

Analysis	Number of Events for Analysis	P-Value (2-Sided)
Interim overall survival	Approximately 516 (67%)	0.012
Final overall survival	765 (100%)	0.045
Final rPFS	≥ 410 (100%)	0.001

Secondary efficacy endpoints:

- time to first skeletal related event (ITT)
- time to initiation of cytotoxic chemotherapy (ITT)
- time to PSA progression (ITT)
- PSA response ≥ 50% (where evaluable)
- best overall soft tissue response (where evaluable)
- the safety of enzalutamide cf placebo

Exploratory outcomes included Health Related Quality of Life (HRQoL) assessments, time to any additional therapy and various pharmacokinetic and pharmacodynamic parameters

Delegate comments on study design, wording:

- At the time of study design, randomisation to placebo was acceptable as there was no established standard of care in this population; participation in a clinical trial or consideration of chemotherapy was the standard. However, during the course of the study, abiraterone was approved (demonstrating rPFS and OS advantage in this population), providing a proven therapy that was neither cytotoxic nor investigational for patients to access upon progression. Protocol amendments to the PREVAIL trial were made reflecting this study outcome (for example, rPFS and OS became the co-primary endpoints). A more meaningful comparison now would be a head-to-head study with an active comparator, for example abiraterone or chemotherapy.
- Thus this study addresses the question of whether enzalutamide demonstrates activity when used first line in the metastatic CRPC setting, and is more effective than no initial active treatment (placebo) until progression, as judged by rPFS; the availability of a range of efficacious treatments and extensive treatment switching in both arms from that point onwards, means that the longer term efficacy outcomes of the trial overall test whether early use of enzalutamide is more efficacious than delayed introduction of other efficacious therapies; as such, the ability to demonstrate longer term efficacy outcomes (for example, OS) with enzalutamide is limited by the extensive treatment switching occurred. The relative efficacy of enzalutamide cannot be established and would require a separate head to head comparisons with these treatments.
- Quality of life outcomes should have been a secondary endpoint, rather than an exploratory endpoint. While OS and rPFS are highly meaningful to patients, this is a palliative treatment being introduced earlier in the treatment pathway, and treatment goals should be improvement in or maintenance of quality of life. This information is important for patients and clinicians to make an informed choice.

rPFS (defined according to PCWG2 criteria)

For the primary analysis of rPFS, the 439 independently reviewed rPFS events exceeded the 410 pre-specified. These occurred less frequently in the enzalutamide arm as compared with placebo: 118 (14.2%) versus 321 (40.1%) respectively. The Kaplan-Meier estimate of median duration of rPFS was not met in the enzalutamide arm (IQR 9.5, not reached), as compared to 3.9 months (IQR 1.9, 8.3). It is notable that the majority of events were soft tissue progression, which might reflect the entry criteria of being asymptomatic or only mildly symptomatic. The extent of improvement was consistent across both bony and soft tissue metastases.

This was supported by a second analysis at the interim OS cut-off of 16 Sept 2013, the median duration of rPFS was 19.7 months (95% CI: 18.1, 22.3) in the enzalutamide arm versus 5.4 months (95% CI: 4.2, 5.6) for the placebo group. HR = 0.307, 95% CI: 0.267, 0.353, p< 0.0001).

The estimated hazard ratio of rPFS, with treatment as the only covariate, was 0.186 (95% CI 0.149, 0.231), p<0.0001, in favour of enzalutamide.

Subgroup analyses supported a consistent benefit from enzalutamide.

> *Delegate comment: updated rPFS analysis is required to confirm the benefit observed (data from 84 patients were missing) and is a condition of registration. It is noted, that longer term data however, will be affected by treatment switching.*

Table 21: MDV3100-03 Duration of rPFS: co-primary 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	

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.

OS

At the pre-specified interim OS analysis, 540 deaths had occurred. The estimated median duration of OS was 32.4 months (IQR 22.0, not reached) in the enzalutamide arm compared to 30.2 months (IQR 17.2, not reached). There were 241 deaths in the enzalutamide arm (27.6%) as compared to 299 in the placebo arm (35.4%) after a median duration of follow-up time of 22.2 months and 22.4 months respectively.

In the Section 31 response, the sponsor provided an updated exploratory data analysis (cut-off 15 January 2014) after 656 deaths, that is, still yet to meet the pre-specified number of deaths. There were no supporting data for evaluation and the Assessment

report downloaded from the European Medicines Agency (EMA) website comments that "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". This information has not been included in the PI.

The unstratified Cox regression HR for death, with treatment as the only covariate, was 0.706 (95% CI 0.596, 0.837), p<0.0001, in favour of enzalutamide treatment.

Treatment switching after progression or discontinuation of study drug was extensive: the sponsor reports 76% in the placebo arm, 43.8% in the enzalutamide arm, with most subsequent therapies having a potential survival benefit. It is noted by the Clinical Evaluator that this did not include the permitted usage of Radium 223, also known to improve survival. Thus, these figures should be amended, both for post baseline treatment switching as well as to the sponsor's further breakdown of the treatments taken concomitantly with the study drug in the Section 31 response. The revised figures in the enzalutamide arm are that 2.9% of patients received concomitant treatment with at least 1 antineoplastic therapy, and 5.7% in the placebo arm. Given the survival benefit seen with Radium 223, the sponsor is requested to update Table 22 (below) and the PI for treatments with demonstrated OS benefit (see PI changes).

Table 22 Post baseline antineoplastic therapy use at the 16 September 2013 cut-off (*note that as of January 2014, all remaining patients in the placebo arm were offered enzalutamide). **The sponsor has been requested to update this table to reflect Radium 223 usage and insert updated figure in the PI to reflect treatment switching that might affect OS.**

Table 22: Post baseline antineoplastic therapy use at the 16 September 2013 cut-off.

	Enzalutamide N= 872	Placebo N=845
Patients taking any post baseline antineoplastic therapy	382 (43.8%)	642 (76.0%)
Patients taking any of the following post baseline antineoplastic therapies with demonstrated OS benefit	351 (40.3%)	594 (70.3%)
Docetaxel	286 (32.8)	479 (56.7%)
Abiraterone	179 (20.5%)	385 (45.6%)
Cabazitaxel	51 (5.8%)	110 (13%)
Sipuleucel-T	12 (12%)	10 (1.2%)
Enzalutamide	9 (9 %)	37 (4.4%)*

Delegate comments:

The OS data are substantially affected by treatment switching to the large number of agents that are known to have a survival benefit.

The OS data are immature still, with the prespecified number of deaths still not reached, including in the latest update provided in the Section 31 response (an exploratory analysis prior to formal unblinding and crossover of the placebo arm to enzalutamide after January 15 2014). It is not clearly stated in the PI that the data are immature, and the consequent estimated median survival figures are fluctuating as a result. Wherever, "median OS" is mentioned in the PI, it should be preceded by the word "estimated", including in the heading.

There is excessive and wordy information in the PI which obscures key information including the treatment switching. The Delegate proposes that the first statement in the paragraph beginning "At the pre-specified interim analysis…" be that the overall survival data are immature, a brief mention of the estimated median survival and then the numbers receiving therapies post baseline with a demonstrated survival benefit. Re-insertion of the table with the data from the pre-specified interim analysis (but not the updated survival analysis that has not been evaluated) will restore clarity as long as the information is not duplicated in the text as with the previous draft of the PI.

Table 23: Overview of use of abiraterone and/or chemotherapy (ITT population) in PREVAIL.

	Enzalutamide (n = 872) n (%)	Placebo (n = 845) n (%)
No use of abiraterone or chemotherapy	517 (59.3)	244 (28.9)
Use of abiraterone only	47 (5.4)	86 (10.2)
Use of chemotherapy only	176 (20.2)	214 (25.3)
Use of chemotherapy followed by abiraterone	108 (12.4)	279 (33.0)
Use of abiraterone, followed by chemotherapy	24 (2.8)	22 (2.6)

Results for other efficacy outcomes

Time to first skeletal related event

First skeletal related events are new events requiring either: radiation to bone, bone surgery, pathological fracture, spinal cord compression or initiation/change in antineoplastic therapy to treat bone pain from prostate cancer

Despite delaying rPFS significantly, which might be expected to result in a similar reduction in skeletal related events, there was only an absolute 4.7% difference in the number of patients experiencing a skeletal related event. This may reflect in part that a smaller proportion of relapses were in bone in the whole population, as well as the treatment switching in the placebo arm to an effective therapy, and the use of therapies such as bisphosphonates, rank ligand inhibitors and palliative radiation. When the analysis is restricted to the treatment emergent period (that is, from the day of commencement until 28 days after discontinuation or <28 days of cytotoxic or investigational therapy commenced, whichever is sooner), there were 3.1% more events in the enzalutamide arm.

Delegate comments:

The Delegate agrees with the Clinical Evaluator that the 4.7% absolute difference figure should be included in the PI, as the hazard ratio does not adequately reflect the relatively modest absolute benefit observed (see PI changes).

This observation of improved rPFS but a higher overall of AEs in the enzalutamide arm was also noted in the pivotal trial for initial registration for use with

progression following chemotherapy. It may be explained by the longer treatment duration in the enzalutamide arm (the sponsor is requested to provide data according to treatment duration of exposure to clarify this) but also that with extended survival, there is possibly a greater total disease burden over time and window for such adverse events.

There is an increased risk of osteoporosis and fracture with severe androgen depletion, and all patients had been on Androgen Deprivation Therapy (ADT) prior to enrolment. The sponsor presented data showing median change in bone density from baseline with treatment over time. This does not inform of their bone density and fracture risk against standardised controls. As requested by the clinical evaluator, the sponsor is requested to provide these as a median change (with range, and interquartile ranges) **in T scores from baseline** rather than percentage change to provide meaningful clinical information for inclusion in the PI (see Questions for sponsor and PI changes). It is also noted that although 83% of patients had bony metastases at enrolment, only 51% were on bisphosphonate therapy: so there is a risk of both iatrogenic osteoporotic and cancer related fracture, particularly with the falls related to enzalutamide seen in this and the AFFIRM trial (metastatic CRPC post docetaxel).

Table 24: Estimated incidence and time to first skeletal related event.

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	

[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.

Time to initiation of cytotoxic therapy

As of the data cut off, more patients in the placebo arm received subsequent cytotoxic chemotherapy (60.9 versus 35.3%). The estimated median time to commencement of additional cytotoxic chemotherapy was longer in the enzalutamide arm (median 28.0 months (IQR 15.3, not reached)) compared with placebo (10.8 months (IQR 4.9, 28.8)). Based on a median follow-up time of 19.6 months for the enzalutamide arm and 19.4 months for the placebo arm, the Cox regression hazard ratio, based on a single covariate of treatment arm, was 0.35 (95% CI 0.30, 0.40) in favour of enzalutamide.

Delegate comment:

The wording of the trial design implies the study drug was continually taken by patients until the commencement of cytotoxic or another study therapy; however, the study drug was discontinued on established progression, and other therapies could be initiated. There was little concomitant usage of enzalutamide and other agents (2.3%), and the study drug was discontinued when other therapies commenced, including abiraterone. As previously mentioned, the time to chemotherapy in both arms is confounded by treatment switching.

- *Influences on time to chemotherapy:*
  - *The approval of abiraterone may have come too late for those who enrolled early and/or progressed early; especially likely in the placebo arm.*
  - *Even if abiraterone was available, the continued blinding upon progression might have biased the choice to commence chemotherapy rather than try abiraterone, particularly in the context of rapid progression.*

Time to PSA progression (not a definition of disease progression for the study)

The estimated median time to PSA progression was 11.2 months (95% CI 11.1, 13.7) and 2.8 months (95% CI 2.8, 2.9) for the enzalutamide and placebo arms respectively. The associated hazard ratio was 0.17 (95% CI 0.14, 0.20), p<0.0001.

Best overall soft tissue response

In those with measurable disease at baseline (45.4% in the enzalutamide arm, 45.0% placebo), the investigator assessed soft tissue response was higher in the enzalutamide arm (Table 25).

Table 25: Best overall soft tissue response in the population with measurable disease.

	Enzalutamide N=396	Placebo N=381
Patients with evaluable post-baseline assessment	382 (96.5%)	353 (92.7%)
Complete response (CR)	78/382 (20.4%)	4/353 (1.1%)
Partial response (PR)	155/382 (40.5%)	15/353 (4.2%)
CR or PR	233/382 (61.0)%)	19/353 (5.4%)

Exploratory endpoints

Time to degradation of functional assessment of cancer therapy-prostate (FACT-P) score

The median time to degradation of FACT-P was 11.3 months in the enzalutamide group versus 5.6 months in the placebo group.

Consistent with being on a treatment that affects progression rate, the degradation of the individual components of the FACT-P score (physical wellbeing, social/family wellbeing, emotional wellbeing, functional wellbeing and prostate cancer) demonstrated a consistent difference, of similar magnitude to the overall result, in favour of enzalutamide.

Completion rates of the questionnaires were not as high for the FACT-P for the pain assessments, which is a very relevant measure for a palliative therapy. It would have been reassuring to know that any delay in progression was also accompanied by a delay in the onset of symptoms.

Other efficacy studies

Study 9785-CL-0321: this is not discussed further as the population enrolled were not required to have castrate levels of testosterone, and therefore the findings do not inform regarding the proposed usage.

Efficacy summary

Randomised, unconfounded data are only available to assess rPFS and there was a clear that enzalutamide treatment was superior to placebo in delaying the progression of existing metastases or development of new lesions. It was notable that soft tissue progression exceeded bone progression.

The potential confounding effects of treatment switching are extensive in this trial. A number of therapies with a proven PFS and OS advantage were available to patients upon progression in both arms, including abiraterone which was approved part way through this trial for a similar population. Thus the reported subsequent endpoints will incorporate the effects of a range of treatments, more so in the placebo than the enzalutamide arm.

Unblinding was allowed only if such information would guide emergency management. A consequence of continued blinding is that sequencing of treatment choices are likely to have been biased by uncertainty regarding the treatment allocation e.g. the potential benefit of targeting the androgen pathway with abiraterone. In particular, this might have meant patients with early treatment failure (as occurred predominantly in the placebo arm) were given chemotherapy rather than offered additional androgen pathway blockade; the corollary is that patients in the enzalutamide arm could be given a further anti-androgen.

In addition to the effects of treatment switching, there were fewer events than predicted so at the scheduled interim reporting of OS, the co-primary endpoint, was based on immature data. This needs to be conveyed clearly in the PI and the sponsor has been requested to state categorically when reporting medians for any endpoints whether the data presented are estimated. The estimated benefit in OS is modest, especially compared with the large improvement in rPFS which may be due at least in part to the 76% treatment switching in the placebo arm. The apparent narrowing of the observed benefit in OS cf rPFS also confirms that essentially delaying efficacious treatment is associated with a poorer outcome (which occurred in this trial design through using a placebo), and the current clinical algorithm no longer supports this approach. The development of any agents in the future for this population would require an active comparator. However, it is not possible to rule out a more rapid relapse once resistance to enzalutamide develops, especially as this may potentially confer resistance to other proven treatments including abiraterone and docetaxel.

Accepting the limitations with such extensive treatment switching in both arms, the remainder of the secondary endpoint analyses were generally supportive of a sustained benefit with enzalutamide treatment over no active treatment (placebo) until first progression. It is noted that the time to chemotherapy question was compromised by the addition of potentially a series of treatments including abiraterone to treatment options, and relevance somewhat lessened by the active investigation of optimal scheduling and combinations with chemotherapy.

Safety

Safety data (with patient numbers in brackets) for evaluation were provided from the following trials: randomised data from the pivotal Study MDV3100-03 (1715) and non randomised from 9785-CL-0007 (evaluated for the initial registration, 14 patients), S-3100-1-01 (evaluated for the initial registration, 140 patients), MDV3100-06 (22), 9785-CL-0321 (67). The safety profile of enzalutamide had been described in the initial application for registration supported by data from the AFFIRM study, and in addition Periodic Safety Update Reports (PSURs) were supplied for further review to the Delegate upon request.

In the pivotal PREVAIL study, the median duration of exposure to enzalutamide was 16.6 months (range 0.2, 35.6) versus 4.6 months (0.1, 31.7) for the placebo. Half of the patients in the treatment arm received 12-24 months of treatment. Dose interruptions (11.4%) were more common than dose reductions (2.2%) indicating this was relatively well tolerated, and similar to that reported for the AFFIRM study.

Key adverse events occurring more frequently with enzalutamide treatment in the AFFIRM study after correcting for the longer treatment duration were seizures, falls, headache, hot flushes, visual hallucinations and hypertension.

In the PREVAIL study, consistent with the advanced nature of the disease and the ageing population affected, there were high rates of TEAEs in both arms of the study. With enzalutamide treatment, fatigue (35.6% in enzalutamide arm with 0.5% were reported as an SAE; 0.7% required dose interruption or discontinuation) and asthenia which are very similar events were again prominent, as were falls. The rate of non-pathological fractures occurring indicates the importance of falls (0.8%, and of managing baseline and treatment induced osteoporosis proactively (the sponsor has been requested to present T-scores and add information to the PI regarding osteoporosis). Headaches, hot flushes and hypertension also occurred more commonly, and were attributed by investigators as being likely related to treatment. Visual hallucinations occurred less commonly (0.1% each arm) which may be due to the earlier stage of disease compared with the higher rates reported in the AFFIRM study. Insomnia was reported as more frequent in the enzalutamide arm. Dysgeusia, peripheral oedema and both diarrhoea and constipation were reported more commonly as treatment-related. When standardised per 100-patient years hot flushes, hypertension, falls and dysgeusia were more frequent with enzalutamide (see comment below regarding standardisation).

The absolute incidence figures for adverse events are difficult to interpret given the large differences in treatment duration. Standardising for treatment exposure with enzalutamide provides a way of adjusting for the inevitably higher number of adverse events due to data collection over a longer treatment period in the treatment arm. However, where the treatment is considered to be causative, or the risk of the event increases over time due to a cumulative effect, this reduces the likely attribution to treatment. In addition, it does not take into account the severity of the event, which may be treatment-related. Event rates such as for falls, osteoporosis, and non-pathological fracture risk are likely to increase with exposure and would be underreported with standardisation.

There was a slight increase in the number of deaths unrelated to progression in the enzalutamide arm compared with the placebo (37 deaths in total: 17 from disease progression, 16 causes other than disease progression and in 4 instances, the cause of death was unknown). This compared with 32 treatment emergent deaths in the placebo (18 due to disease progression, 13 due to other causes, and 1 unknown cause). There did not appear to be a treatment related explanation for the difference in the number of deaths. This was also the finding of the EMA in their assessment report.

Hypertension

This was increased in the enzalutamide arm (13.9% versus 4.7%) with Grade 3 events occurring in 6.8% versus 2.3%. This signal was seen in the AFFIRM study also, and was most likely to occur within the first 90 days of commencing treatment. Given the frequency of the event, and the easy monitoring the Delegate considers it should be moved to the Precautions section as it is likely to be missed where it is currently placed and requires clinician awareness.

Falls

These are a significant hazard in this population and are reported as an SAE in 0.8% with 0.6% in the enzalutamide having a serious adverse event (SAE) of femoral neck fracture (0.6% versus 0%) in the placebo. The higher rates of syncope (0.7% versus 0% in the placebo arm reported as an SAE) may also contribute to the falls and fracture rate. Similarly, this should be moved to the Precautions section of the PI to ensure awareness and preventative interventions, and the heading changed to "Falls and Fall-related injuries" to raise awareness, as in the Canadian Product Monograph.

Seizures

Seizures were a dose limiting toxicity and are identified as a recognised risk, but were uncommon in the PREVAIL study (0.1% in each arms) which permitted patients with a prior stroke and medicines potentially lowering the seizure threshold, unlike the AFFIRM study where they were excluded. The Sponsor reports the PREVAIL events as follows:

> *The enzalutamide treated patient experienced nonconvulsive status epilepticus from complex partial seizures followed by a generalized seizure. The placebo-treated patient experienced 2 separate events of complex partial seizure.*

The sponsor stated in the Section 31 response: "To further evaluate the risk of seizure associated with enzalutamide 160 mg/day, the sponsor is conducting Study 9785-CL-0403, a single-arm safety trial in at least 350 patients with metastatic CRPC who are at increased risk for seizure. As of 08 Apr 2015, 139 patients have been administered enzalutamide for at least 3 months (protocol defined seizure risk evaluation set). Of these, 2 (1.4%, 95% CI: 0.2%, 5.1%) patients experienced a confirmed first seizure within the first 4 months of treatment… Pending the results of Study 9785-CL-0403, the PI will be reviewed to determine what, if any, additional information should be provided regarding the risk factors associated with enzalutamide treatment and seizure."

> *Delegate comment: these data were not presented for evaluation, and submission of the study for evaluation by the TGA is a condition of registration. It is considered essential that this information be added to inform prescribers, regardless of the outcome of the trial. It is noted that there have been seizures reported already by the 4 month stage but the PI is currently more restrictive so new information needs to be added at this stage, based upon what has been presented.*

Posterior reversible encephalopathy syndrome (PRES)

The sponsor indicated in the Section 31 response that "a cumulative review of the safety data from clinical trials and the global safety database identified 3 confirmed non fatal cases of PRES. An association of enzalutamide with PRES cannot be excluded based on the

2 non-fatal post-marketing PRES cases assessed as possibly associated with enzalutamide due to plausible temporal relationships, absence of alternative etiologies (sic), and positive dechallenges. Therefore, based on the available information, it is concluded that the signal of PRES is confirmed."

> *Delegate comment: the sponsor has included appropriate text in the PI but PRES also needs to be added as an Important Identified Risk in the RMP/ASA.*

Second malignancy

The clinical evaluator noted the increased frequency of second malignancies in the enzalutamide arm. When standardised against treatment duration, the rate was 1.9 events/100-patient years compared with 0.7 events in the placebo arm. Whether this is causally linked to enzalutamide is not clear. Information has been included in the PI, and this should also be included in the Identified Risks section of the ASA of the RMP to ensure post marketing data are captured.

Electrocardiograph/cardiovascular

ECG abnormalities were reported at a higher rate in the enzalutamide arm, which are difficult to interpret due to the differences in exposure. The clinical evaluator sought information regarding the incidence of cardiac and ECG TEAEs for each GnRH treatment modality, essentially to inform about the risks of using agents such as leuprorelin and goserelin in conjunction with enzalutamide vs orchidectomy and enzalutamide. It would be acceptable to include the wording from the SmPC regarding the risks of QT prolongation with androgen deprivation. Alternatively, if the sponsor does not wish to include this information, the data requested by the clinical evaluator about cardiac/ECG abnormalities by GnRH analogue versus orchidectomy and enzalutamide should be provided (as indicated was possible in the response to the Round 2 clinical evaluation (see PI changes and if necessary, Questions for Sponsor).

Safety discussion

Overall the safety profile was consistent with that identified in earlier trials. Significant additional information regarding the risk of PRES has emerged from the postmarketing data collection, and in the PREVAIL study, there was an increase in second malignancies. Seizures were less common in this chemo-naïve population. Appropriate information is included in the PI about the risks of treatment although relocation of some of the information to the Precautions section will increase the chance of it being seen by prescribers.

The two pivotal trials in those with metastatic CRPC have different AE rates, with the more advanced disease having generally higher rates of AEs. The Delegate is in agreement with maintaining separate reporting of the AE tables to ensure accurate advice is provided about risks and benefits in the different populations.

There are still some outstanding issues with regard to the PI, including provision of information about osteoporosis. The sponsor is requested to include a section on osteoporosis risk and non-pathological fractures related to treatment. This includes provision of information about T scores and changes over time with treatment. It is noted that bisphosphonate usage was lower than perhaps expected given the frequency of bony metastases, and this is an area where increased awareness and proactive management could improve outcomes.

With resolution of these outstanding PI issues, the application is considered approvable.

Risk management plan

A number of recommendations for the RMP have been provided by the RMP evaluator and the sponsor should address these matters and follow up where appropriate with the Office of Product Review (OPR).

Specifically:

- As a result of the events described in the clinical evaluation report, the sponsor should update the RMP/ASA to include 'Severe skin reactions (including SJS and TEN)' as an Important Potential Risk (Reference: Round 2 recommendation).

  Delegate note 31 August 2015: The Delegate notes that in the draft response of 31 August 2015, the sponsor has declined to do this. In the PSUR covering the period 31 August 2014 to 28 February 2015, that the PRAC are investigating a case of severe adverse cutaneous reaction. The sponsor is requested to state whether this is one of the 2 cases for which details were provided in the Section 31 response, or an additional case. The Sponsor is required as a standard condition of registration, to provide an update to the TGA via a safety related request if this results in a change to the SmPC and to update the RMP/ASA if a change is made to the RMP as a result of this investigation.

The sponsor should update the RMP/ASA to include 'Posterior reversible encephalopathy syndrome (PRES)' as an Important Potential Risk (Reference: Round 2 recommendation). This is listed in the PI precautions section.

Delegate note 31 August 2015: In the draft response of 31 August 2015 to the Delegate report of 26 August 2015, the sponsor has agreed to include this as an Important Identified Risk in the RMP/ASA.

The Delegate considers that second malignancies should also be added to the list of Identified Risks in the RMP/ASA, consistent with its inclusion in the Precautions section of the PI.

Delegate note 31 August 2015: In the draft response of 31 August 2015 to the Delegate report of 26 August 2015, the sponsor has agreed to include this as an Important Potential Risk in the RMP/ASA. This is acceptable.

The Delegate notes that in the draft response of 31 August 2015, the sponsor has modified the wording regarding the 'Contraindications' section for use in women. This is acceptable and a revised PI is awaited.

Proposed regulatory action and indication

Subject to satisfactory updating of the PI and acceptance of the Conditions of Registration, the application for Xtandi should be approved for registration for the treatment of patients with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

Data deficiencies/limitations

Quality of life should be reported as at least a secondary endpoint, especially where treatment is being introduced earlier in a patient population with a low symptom burden.

Risk-benefit analysis

Delegate's considerations

The Delegate considers that safety and efficacy have been established for the proposed indication. The draft PI has some outstanding issues and the advice of the committee is sought on the pre ACPM responses to those changes provided by the sponsor.

Proposed action

The Delegate has no reason to say, at this time, that subject to the satisfactory update of the PI and acceptance of the conditions of registration that the application for Xtandi should not be approved for registration for the treatment of patients with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

- The Delegate's proposed PI changes
- The Delegate's proposed conditions of registration

Response from sponsor

Delegate's comment

- The hazard ratio should not be used in isolation to describe any of the efficacy endpoints. All reporting should include the absolute differences observed, and whether these were not directly measured it should be stated that they were estimated or the data extrapolated.

Sponsor's response

The sponsor's position is that the HR is the best estimate for risk for the efficacy endpoints because it accounts for the whole curve instead of a single point. When reporting efficacy endpoints, it is also important to include the context and not the absolute difference in isolation; for example, an absolute difference of 2 months could be reported from either the difference between 2 months and 4 months or 10 months and 12 months. In addition, differences cannot always be calculated when the median has not yet been reached. Stating the HR with the associated medians has been used for other products in Australia, for example, abiraterone.

Delegate's comment

- Given the survival benefit seen with Radium 223, the sponsor is requested to update the table of patients receiving post baseline antineoplastic therapies, and also any references in the percentage of patients receiving treatments with demonstrated OS benefit (please replace all of these as it is mentioned in more than one place).

  Delegate comment 31 August 2015: in the draft response of 31 August 2015 to the Delegate report of 26 August 2015, the sponsor has responded: "The sponsor does not agree to include the Radium 223 data since there are limited data available. (only 2 patients on enzalutamide and 1 patient on placebo)." The Delegate wishes to respectfully point out that the table provided in the s31 responses did not include those receiving radium 223, and a re-analysis of OS data was not requested but a correction of the statement in the Clinical Trials section "In addition, 40.3% of enzalutamide treated patients and 70.6% of placebo treated patients received

subsequent therapies with a demonstrated survival benefit". These figures do not include the patients who received radium 223, as provided by the sponsor in the Section 31 response. Given this agent affects survival, all of these patients should be included in figures in the PI updated. The following is from the clinical evaluation report round 2: "In PREVAIL, Radium 223 was permitted as an additional agent prior to the cessation of enzalutamide or placebo. Radium 223 was used by 5 (0.6%) patients in the enzalutamide group and 9 (1.1%) patients in the placebo group."

Sponsor's response

The sponsor has updated the table to include the Radium 223 data (Table 26) and has revised the PI accordingly

Table 26: Selected post baseline anti neoplastic therapies (ITT Population).

Subsequent Therapy	Enzalutamide n = 872	Placebo n = 845
Number of patients taking at least 1 of the 6 subsequent therapies below[a]	352 (40.4%)	596 (70.5%)
Docetaxel	286 (32.8%)	479 (56.7%)
Abiraterone	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%)
Radium-223	5 (0.6%)	9 (1.1%)

The analysis data cutoff date is 2013-09-16.
[a] Concomitant abiraterone use was allowed before study drug discontinuation in patients with confirmed radiographic progression or a skeletal-related event.

Delegate's comment

- Please include the statement as in the SmPC about the hypersensitivity reactions with a cross reference in the 'Contra-indications' section.

  Delegate note 31 August 2015: the Sponsor requested information about the location of this information in the SmPC. It is under the heading Hypersensitivity Reactions. The Delegate notes that the reference to Section 4.8 does not include mention of this adverse event. The sponsor is requested to provide details of the cases on which this was based.

Sponsor's response

The sponsor agrees to include the following wording in the 'Precautions' section of the PI:

Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, tongue oedema, lip oedema and pharyngeal oedema have been observed with XTANDI (see Contraindications).

As of 28 February 2015, there were 56 localised hypersensitivity cases involving 61 AEs reported in Astellas safety database (30 serious and 31 non serious) with the following types of reactions: face swelling/oedema (18), local swelling/oedema (7), swollen tongue (5), genital swelling/oedema (5), ocular hyperemia (5), lip swelling (4), eye swelling/oedema (4), periorbital oedema (3), scrotal swelling/oedema (3), pharyngeal oedema (2), penile swelling (2), eyelid oedema (1), gingival swelling (1), and mouth swelling (1).

Of the 56 localised hypersensitivity cases, there was one Index case of local hypersensitivity reaction (swelling face) with compatible timelines, positive dechallenge and absence of confounders. Twenty cases were assessed as Informative and 36 cases were assessed as Inadequate. Due to limited information reported, the inadequate cases were excluded from the analysis.

Informative cases

The 20 localised hypersensitivity cases (12 serious and 8 non-serious) contained the following 21 AEs: face swelling/oedema (7), local swelling (2), scrotal swelling (2), pharyngeal oedema (2), lip swelling (2), penile swelling (1), gingival swelling (1), eye swelling (1), swollen tongue (1), periorbital oedema (1), and mouth swelling (1). There were no fatal cases of localized hypersensitivity reactions.

In 7 cases (5 serious and 2 non-serious), the localised hypersensitivity events (pharyngeal oedema, face swelling, lip swelling, swollen tongue, periorbital oedema) were considered possibly related to enzalutamide due to positive dechallenge (6) or positive rechallenge (1 case of periorbital oedema).

In 13 cases (7 serious and 6 non serious), the localised hypersensitivity events (face swelling/oedema, pharyngeal oedema, local swelling, scrotal swelling, gingival swelling, eye swelling, penile swelling, mouth swelling) were assessed as unrelated to enzalutamide due to confounding factors such as concomitant medications (4), concurrent infection (3), radiation therapy (2), negative dechallenge (1), incompatible timelines (1), concurrent renal thrombosis (1), and food allergy (1). One case was considered to be an Index case (swelling face) based on compatible timelines, positive dechallenge and absence of confounders.

Delegate's comment

- The sponsor is requested to include a section on osteoporosis risk and fractures related to treatment. This includes provision of information about T scores and changes over time with treatment. It is noted that bisphosphonate usage was lower than perhaps expected given the frequency of bony metastases, and this is an area where increased awareness and proactive management could improve outcomes. It would be best to place this section under the 'Falls' section in 'Precautions' as the two are linked.

Sponsor's response

It is the sponsor's position that risks pertaining to fractures are adequately described in the section on 'Falls and fall related injuries'. Enzalutamide treatment is not associated with an increased rate of osteoporotic fractures.

Delegate's comment

- As requested by the clinical evaluator the sponsor is requested to provide the median change (with range) in T scores from baseline rather than percentage change to provide meaningful clinical information for inclusion in the PI (see Questions for Sponsor and PI changes).

Sponsor's response

The sponsor's position is that the PI should not include T scores. BMD data are not available from the controlled studies under review to support the proposed indication. Only uncontrolled BMD data from a separate population (non castrate patients with hormone naïve prostate cancer) are available from Study 9785-CL-0321. It is important to note that because there is no comparator; it is difficult to determine the effect of enzalutamide on BMD. Patients who receive ADT to treat advanced prostate cancer have

been reported to lose BMD at a faster rate than age matched controls.[13] The risk of BMD loss increases over time. All patients in the AFFIRM and PREVAIL studies were required to continue ADT with a GnRH analogue or bilateral orchiectomy. The median duration of exposure to study drug in AFFIRM was 8.3 months in the enzalutamide group versus 3.0 months in the placebo group. The median duration of exposure to study drug in PREVAIL was twice as long in the enzalutamide group (16.6 months) and 50% longer in the placebo group (4.6 months) compared with exposure in AFFIRM. In the combined controlled population, the median duration of exposure to enzalutamide was 12.8 months and the median duration of exposure to placebo was 3.8 months. When adjusted for the length of exposure (Events per 100 Patient-Year of Reporting), the rates of pathological fracture and osteoporotic fracture were balanced between treatment groups.

In addition, testosterone may protect against bone loss in men with abnormally low levels of testosterone. In PREVAIL, mean testosterone values increased post baseline in the enzalutamide group although they remained within the castrate range.

As requested, data from the 9785-CL-0321 study are provided in Table 27 below for reference only. Due to the nature of the collection and analysis of these data, these data should not be included in the PI.

Table 27: Exploratory T-score date from 9785-CL-0321.

Summary of T-score (in patients with baseline)

VISITS	n	mean		min	med	max
Baseline	50	-0.218		-3.259	-0.091	2.413
Week 25	43	-0.256		-3.231	-0.222	2.620
Week 49	36	-0.345		-3.275	-0.426	2.121
Week 97	29	-0.246		-3.113	-0.136	2.393
Week 169	26	-0.061		-3.105	0.052	2.183

Delegate's comment

- Request to include the rates of osteoporotic fractures in each arm in the PI.

Sponsor's response

Data for osteoporotic fractures are presented in Table 28 below and the time adjusted analysis is presented in Table 29. It is the sponsor's position that these data do not warrant inclusion in the PI due to the small number of events and no established association with enzalutamide treatment.

[13] Preston DM, et al. (2002) Androgen deprivation in men with prostate cancer is associated with an increased rate of bone loss. *Prostate Cancer Prostatic Dis.* 5: 304-10; Chernichenko OA, et al. (2014) Effect of androgen suppression on bone mineral density in patients with prostate cancer. *Exp Oncol.* 36: 276-8.

Table 28: TEAEs by System Organ Class and Preferred Term (Treated Population).

	MDV3100-03 [1]		CRPC2 [2]		MDV3100-03 + CRPC2 [3]		Pooled [4]	Total [5]
System Organ Class Preferred Term	Enz 160 mg/day (N=871)	Placebo (N=844)	Enz 160 mg/day (N=800)	Placebo (N=399)	Enz 160 mg/day (N=1671)	Placebo (N=1243)	Enz Open Label (N=1001)	Enz (N=2509)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS								
OSTEOPOROTIC FRACTURE	2 (0.2%)	1 0.1%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	1(<0.1%)	1(<0.1%)	3(0.1%)

Note: Footnotes [1] to [5] refer to common footnote document.
Note: Patients with multiple events for a given preferred term, system organ class, or overall are counted once only for each preferred term, system organ class, and overall, respectively. Events are sorted by system organ class alphabetically and then by decreasing frequency of preferred term under the all column in the total group.

Table 29: TEAEs of Interest by Preferred Term Adjusting for Length of Treatment Emergent Period: Events per 100 Patient-Year of Reporting (Treated Population).

	MDV3100-03 [1]		CRPC2 [2]		MDV3100-03 + CRPC2 [3]		Pooled [4]	Total [5]
System Organ Class Preferred Term	Enz 160 mg/day (N=871)	Placebo (N=844)	Enz 160 mg/day (N=800)	Placebo (N=399)	Enz 160 mg/day (N=1671)	Placebo (N=1243)	Enz Open Label (N=1001)	Enz (N=2509)
FRACTURES								
OSTEOPOROTIC FRACTURE	2(0.2)	1(0.2)	0 (0.0)	0(0.0)	2 (0.1)	1 (0.1)	1 (0.2)	3 (0.1)

Note: Footnotes [1] to [5] refer to common footnote document.
[6] Total Treatment Emergent Period in 100 Patient-Years is calculated as the sum of each patient's length of treatment emergent period in days divided by 365.25 Time-adjusted rate per 100 patient-year calculated as number of occurrences of event divided by the number of patient-years of treatment emergent surveillance for each treatment group and then times 100. Patients can have more than one occurrence of each event.

Advisory committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Xtandi capsules containing 40 mg of enzalutamide to have an overall positive benefit-risk profile for the indication**;**

> *Xtandi is indicated for the treatment of patients 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.*

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and advised on the following:

- Was of the view that it was acceptable to omit SJS and TEN as an important potential risk in the RMP/ASA.

Proposed Product Information (PI)/Consumer Medicines Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI/CMI and specifically advised on the inclusion of the following:

- A clear statement that androgen deprivation will cause bone loss rather than the simple inclusion of T scores.
- The 'Clinical Trials' section should include absolute differences observed to describe the efficacy endpoints.
- Include a statement about QT interval prolongation and androgen deprivation therapy under 'Precautions'.
- Remove excessive and wordy information which obscures key information including the treatment switching.
- The statement on OS data should emphasise that these are immature.
- Use 'estimated' before 'median' wherever any efficacy endpoint is being reported based on a Kaplan Meier estimate or extrapolation (including in figures and tables).

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

- The Delegate's proposed PI changes

The ACPM noted that the sponsor had agreed many of the Delegates' proposed changes to the PI.

The ACPM was of the view that the SmPC statements re androgen deprivation and risk of QT prolongation should be included in the PI and noted that this was under consideration by the sponsor. The ACPM noted that a statement on QT interval prolongation and androgen deprivation therapy was included in the PI for goserelin and leuprorelin under 'Precautions'.

The ACPM advised that it agreed with the Delegate that HR should not be used in isolation to describe efficacy endpoints and that all reporting should include the absolute differences. For the time to first skeletal related event, the ACPM advised that the absolute difference with enzalutamide treatment (4.7% fewer patients experienced a skeletal related event), should be included, as the HR does not adequately reflect the relatively modest absolute benefit observed.

The ACPM supported the Delegate's request to remove excessive and wordy information in the PI which obscures key information including the treatment switching and to also emphasise that the overall survival data are immature. The ACPM noted that the sponsor had agreed to re-insert the table with the data from the pre-specified interim analysis and is considering revised language for the PI.

The ACPM noted that the Sponsor proposed to limit to the use of "estimated" before "median" to the median OS for PREVAIL. The ACPM supported the use of 'estimated' before 'median' wherever any efficacy endpoint is being reported based on a Kaplan Meier estimate or extrapolation (including in figures and tables) e.g. the overall survival data are still immature.

The ACPM advised that it was reasonable not to include T scores, as only uncontrolled bone mineral density data are available from Study 9785-CL-0321 from a separate population. However, a clear statement that androgen deprivation will cause bone loss should also be included in the PI.

- The Delegate's proposed conditions of registration

The ACPM advised that the Delegate's proposed conditions of registration were appropriate.

The ACPM advised that is seemed reasonable not to include SJS and TEN as an important potential risk in the RMP/ASA based on the sponsor's response.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Xtandi containing enzalutamide for the new indication:

> *For the treatment of patients with metastatic castration-resistant prostate cancer following failure of androgen deprivation therapy in whom chemotherapy is not yet indicated.*

The full indications are now:

- *For the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.*
- *For the treatment of patients with metastatic castration-resistant prostate cancer following failure of androgen deprivation therapy in whom chemotherapy is not yet indicated.*

Specific conditions of registration applying to these goods

- The Xtandi EU-RMP, version 7.0 (dated 6 October 2014, Data Lock Point 16 September 2013 for Phase III Study MDV3100-03 and 1 July 2013 for the remaining studies in the Integrated Safety Population) and ASA version 1.2 (dated 17 October 2014), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Xtandi at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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