



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Enzalutamide

Proprietary Product Name: Xtandi

Sponsor: Astellas Pharma Australia Pty Ltd

November 2014

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

- An Australian Public Assessment Record (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, in that it will provide 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.

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List of the most common abbreviations and definitions of terms used in this AusPAR

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
AE	Adverse event
ALT	Alanine transaminase
AR	Androgen receptor
ARSI	Androgen receptor signalling inhibitor
AST	Aspartate transaminase
AUC _{0-t}	Area under plasma concentration-time curve from zero to time t of the last measured concentration above the limit of quantification
AUC _{0-∞}	area under the plasma concentration-time curve from time of intake until infinity
BP	Blood pressure
CCMG	Caprylocaproyl macroglycerides, or Labrasol
CER	Clinical evaluation report
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C _{max}	maximum plasma concentration
CMI	Consumer Medicine Information
C _{min}	minimum plasma concentration
CRPC	Castration-resistant prostate cancer
CNS	central nervous system
CSR	Clinical Study Report
DBP	Diastolic blood pressure
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group The ECOG performance status has 6 grades. Grade 0: Fully active, able to carry on all pre-disease performance without restriction; grade 1: restricted in physically strenuous activity but ambulatory

Abbreviation	Meaning
	and able to carry out work of a light or sedentary nature (e.g. light house work, office work); grade 2: ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours; grade 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours; grade 4: completely disabled. Cannot carry on any self-care. Totally confined to bed or chair; grade 5: Dead.
EMA	European Medicines Agency
EQ-5D	European Quality of Life 5-Domain Scale. The EQ-5D is a standardised instrument for use as a measure of health outcome. Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each assessed on 3-point categorical scales ranging from “no problem” to “severe problem”. Higher scores reflect worse quality of life (QoL). The EQ-5D was administered only at selected sites in Europe (France, United Kingdom, Germany, Italy, and Spain).
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy-Prostate. The FACT-P pain assessment asks patients to respond to the statement, “I have pain,” using the following scale: 0-Not at all; 1-A little bit; 2-Somewhat; 3-Quite a bit; and 4-Very much.
FDA	Food and Drug Administration
GABA	gamma aminobutyric acid
h	hour/s
GnRH	Gonadotropin-releasing hormone
IC ₅₀	50% inhibitory concentration
ICH	Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
MDV3100	enzalutamide
MedRA	medical dictionary for regulatory activities
mg	Milligram
mL	Millilitre
ms	Millisecond
OS	Overall survival

Abbreviation	Meaning
PD	Pharmacodynamics
PI	Product Information
PFS	progression-free survival
PK	Pharmacokinetic/s
PSA	Prostate specific antigen
QT	<p>QT interval of the ECG.</p> <p>The QT interval is the portion of an electrocardiogram between the onset of the Q wave and the end of the T wave, representing the total time for ventricular depolarization and repolarization. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias such as torsade de pointes and sudden death.</p>
QTc	<p>Corrected QT interval.</p> <p>The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval QTc is often calculated.</p>
RECIST v1.1	<p>Response Evaluation Criteria in Solid Tumors version 1.1</p> <p>The RECIST is a voluntary, international standard using unified, easily applicable criteria for measuring tumor response using X-ray, CT and MRI.</p>
SAE	Serious adverse event
SBP	Systolic blood pressure
SCS	Summary of Clinical Safety
SOC	System Organ Class
t _½	Half-life
TGA	Therapeutic Goods Administration
Tmax	Time to achieve maximum concentration
US	United States
µg	Microgram

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	26 June 2014
<i>Active ingredient:</i>	Enzalutamide
<i>Product name:</i>	Xtandi
<i>Sponsor's name and address:</i>	Astellas Pharma Australia Pty Ltd Level 4,6 Eden Park Drive Macquarie Park NSW 2113
<i>Dose form:</i>	Soft capsule
<i>Strength:</i>	40 mg
<i>Container:</i>	Blister pack
<i>Pack size:</i>	112
<i>Approved therapeutic use:</i>	<i>Xtandi is indicated for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.</i>
<i>Route of administration:</i>	Oral
<i>Dosage:</i>	160 mg (four 40 mg capsules) as a single oral daily dose
<i>ARTG number:</i>	210494

Product background

Prostate cancer is known to be androgen sensitive and its development and progression can be promoted by testosterone. Castration resistant prostate cancer (CRPC) is defined as disease progression despite androgen depletion therapy (ADT¹) and may present as either a continuous rise in prostate specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases.

Treatment methods for prostate cancer have targeted testosterone production or action: gonadotropin-releasing hormone (GnRH) receptor antagonists or analogues, inhibitors of enzymes involved in testosterone production, and antiandrogens. Antiandrogens prevent the activation of the androgen receptor (AR) by endogenous androgens, thereby reducing the stimulation of prostate cancer cells.

¹ Androgen-deprivation therapies include surgical castration or medical therapy with GnRH analogues, anti-androgens (such as bicalutamide, flutamide, and nilutamide), androgen synthesis blockers (such as abiraterone), and/or oestrogenic compounds.

Enzalutamide is a non-steroidal antiandrogen that blocks several steps in the androgen receptor (AR) signalling pathway: binding to the AR, nuclear translocation of the activated receptor, and association of the translocated receptor with nuclear deoxyribonucleic acid (DNA).

This AusPAR describes the application by the Astellas Pharma Australia Pty Ltd (the sponsor) to register Xtandi capsules containing 40 mg enzalutamide for the following indication:

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

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 1 July 2014.

At the time the TGA considered this application, a similar application had been approved in 13 countries including the European Union (21 June 2013), USA (31 August 2012), Canada (29 May 2013) and Switzerland (4 December 2013), and was under consideration in 24 other 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 Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

II. Quality findings

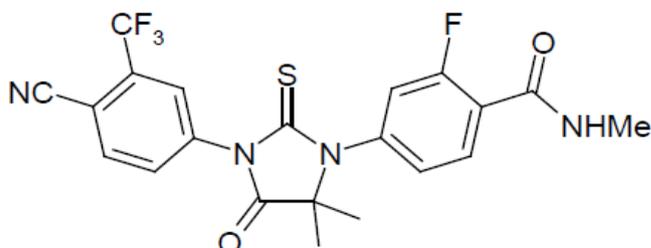
Introduction

Enzalutamide is a non-steroidal antiandrogen; it is a new chemical entity. There are no monographs for enzalutamide.

Drug substance (active ingredient)

Enzalutamide is a synthetic thioxoimidazolidine. The structure is shown in Figure 1:

Figure 1: Structure of enzalutamide



Enzalutamide is not chiral. There is limited structural relationship to other non-steroidal antiandrogens. Enzalutamide drug substance is a white solid powder. It is not ionised in the physiological pH range. Enzalutamide is practically insoluble in aqueous solution, independent of pH. The drug substance is dissolved in solution in the capsules, so that

particle size and polymorphism are not important. Control of the drug substance is considered acceptable.

Drug product

The finished product is an opaque, white to off-white, soft gelatin capsule (approximately 20 × 9 mm) with a liquid fill. The capsules are printed “ENZ” in black ink. The fill consists of enzalutamide (40 mg), caprylocaproyl macroglycerides, and low levels of antioxidants (butylated hydroxyanisole and hydroxytoluene).

Caprylocaproyl macroglycerides

The oily capsule fill dissolves the drug and was chosen on the basis of high enzalutamide solubility. Caprylocaproyl macroglycerides (CCMG) is not an excipient in any currently or previously registered Australian medicine. It is a non-ionic water dispersible surfactant consisting of macrogol (polyethylene glycol) esters and glycerol esters (that is, a mixture of mono-, di- and tri- caprylic (octanoic) and capric (decanoic) acid esters of glycerol, and monoesters and diesters of short macrogols). There are European Pharmacopoeia (Ph.Eur.) and United States Pharmacopoeia (USP) monographs for the excipient. Toxicology data were provided for this excipient and have been reviewed separately (see *Nonclinical findings*, below).

As a relatively complex mixture of esters, differences between batches of caprylocaproyl macroglycerides could potentially affect the drug product performance. There are controls on properties such as viscosity and fatty acid composition for the grade used (Ph.Eur. with nominal 8 ethylene oxide units per molecule). Appropriate controls on impurities in the excipient were discussed with the sponsor.

Although the drug is dissolved in the capsule contents, there is a finished product dissolution test.

The capsules are packed in blister packs of 112 capsules. The only observed change on storage is a small increase in levels of an oxidative degradation product; formation of this is faster if the antioxidants are not included. Stability data support a shelf life of 2 years, store below 25°C.

Clinical trial formulations

The first clinical trial used a hard capsule with a 30 mg enzalutamide formulation. Subsequent trials used soft capsules with a higher fill volume, but the same proportions of fill components, giving 40 mg of enzalutamide per capsule. The formulation of the product proposed for registration is identical to that used in all of the latter clinical trials, except for the quantity of an antioxidant.

Biopharmaceutics

Caprylocaproyl macroglycerides

Caprylocaproyl macroglycerides self-emulsifies in water, forming a microemulsion. It has been reported to enhance bioavailability of some drugs via strong inhibition of the P-glycoprotein (P-gp) enterocytic efflux transporter.

Absolute bioavailability

A human absolute bioavailability study is expected as part of the fundamental pharmacokinetic (PK) characterisation of a new chemical entity. This submission did not include such data. Astellas argues that preparation of a simple intravenous (IV) solution is not feasible because of the low solubility and formulation with Cremophor may pose unacceptable risks to subjects.

Astellas notes that the absolute oral bioavailability of enzalutamide given as a caprylocaproyl macrogolglyceride solution to rats and dogs was high (97% and 73% respectively). Astellas argues that high bioavailability is expected given the high permeability and low hepatic extraction ratio.

Study 9785-CL-0001 showed that most radioactivity from a labelled oral (PO) dose was in urine (71%, primarily as a metabolite). This indicates that absorption is at least high.

Effect of food

Study MDV3100-05 was an open, single dose, parallel design study of the effect of food on the bioavailability of the capsules in healthy males. A parallel design was chosen because of the long half-life (approximately 90 h). Doses (four 40 mg capsules) were taken fasted or with a standard high-fat, high-calorie breakfast. Dosing with food slows absorption (median time to reach maximum concentration (T_{max}) 2.0 h versus 1.0 h) and markedly reduces peak plasma levels (maximum concentration (C_{max}) 3.6 µg/mL versus 5.1 µg/mL), but with similar exposure (area under the concentration-time curve over time zero to infinity (AUC_{0-∞}) 276 versus 279 µg.h/mL: 90% confidence interval (CI) within standard bioavailability range).

Advisory committee considerations

As no significant pharmaceutical chemistry issues were identified, the submission was not referred to the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).

Quality summary and conclusions

Registration is recommended with respect to quality and biopharmaceutic aspects if appropriate controls on impurities in the excipient are negotiated.

III. Nonclinical findings

Introduction

The submitted nonclinical (Module 4) data were in general accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline: *ICH guideline on the nonclinical evaluation of anticancer pharmaceuticals* (ICH S9; EMA/CHMP/ICH/646107/2008). The clinical formulation of Xtandi contains the excipient Labrasol (CCMG) to increase the oral bioavailability of enzalutamide. Labrasol is not contained in any currently registered product in the ARTG. Data to support the safety of this excipient were submitted and evaluated separately (see below). The formulations of enzalutamide used in the safety studies included this excipient.

One limitation of the submitted dossier is that the major active human metabolite (M2, N-desmethyl metabolite) is only a minor metabolite in animals. The toxicity profile of this

metabolite has not been adequately addressed by the data provided. Ideally, a general toxicity study with this metabolite should have been conducted but a comprehensive assessment of the toxicity of a major human metabolite may not always be expected for an anticancer drug (ICH S9).

Pharmacology

Primary pharmacology

Testosterone promotes the development and progression of prostate cancer. Treatment methods for prostate cancer have targeted testosterone production or action: gonadotropin-releasing hormone receptor antagonists or super agonists, inhibitors of enzymes involved in testosterone production and antiandrogens. Antiandrogens prevent the activation of the androgen receptor (AR) by endogenous androgens, thereby reducing the stimulation of prostate cancer cells. First generation antiandrogens often fail due to enhanced activity at the AR, either as a result of over-expression of the wild-type AR which results in agonistic activity with the “antiandrogen” or enhanced activity due to a mutant AR responding to a broader range of compounds. Enzalutamide is a second generation antiandrogen, specifically selected to have no agonistic activity at the human AR and to have activity against mutant ARs.

In vitro studies

Enzalutamide was a competitive inhibitor at the AR, preventing the binding of AR agonists with a notable inhibition of dihydroxytestosterone (DHT)-induced nuclear translocation of the AR. Inhibition of DHT-induced proliferation of human prostate cancer cells (containing the T877A AR mutation) was also seen with inhibition constant (K_i) and 50% inhibitory concentration (IC_{50}) values of 0.023 μM and 0.062 μM , respectively (concentrations well below the clinical free minimum plasma concentration (C_{min}) of 0.62 μM). Enzalutamide (1 μM , 2–4 days) reduced the viability of human prostate cancer cells, which correlated with increases in the level of caspase-3, an indicator of apoptosis. Enzalutamide showed inhibitory activity on the DHT-induced proliferation of cells expressing the castration resistant ARs (T877A alone or both T877A and W741C mutants).

Other antiandrogens (bicalutamide and hydroxyflutamide) had inhibitory activity at none or only one of the mutant ARs. Bicalutamide inhibited the DHT-induced proliferation of cells expressing T877A-AR but not T877A-AR plus W741C-AR. Hydroxyflutamide did not inhibit the DHT-induced proliferation of either cell. These data suggest that enzalutamide has inhibitory activity against castration-resistant ARs. Unlike other antiandrogens (bicalutamide, nilutamide and hydroxyflutamide), enzalutamide had no agonistic activity at the AR.

Six metabolites of enzalutamide were assessed for the ability to inhibit testosterone binding to the AR (T877A). M2 and M6 had similar inhibitory activity to enzalutamide (IC_{50} 0.155 and 0.135 μM , respectively, compared with 0.130 μM for enzalutamide). M3 and M4 had low inhibitory activity (IC_{50} 2.1 and 1.6 μM), while M1 and M5 had no inhibitory activity. Only M1 and M2 are significant circulating metabolites in human subjects (with AUC values 62% and 89% those of enzalutamide, on a molar basis). Therefore, M2 is likely to contribute significantly to the efficacy of enzalutamide in patients. None of the metabolites (M1, M2, M3 or M4) had agonistic activity at the AR.

In vivo studies

The anti-tumour activity of enzalutamide was examined in mice bearing xenografts of human castration resistant prostate cancer cells (LNCaP cells which express T877A-AR, but also engineered to overexpress the wild-type AR). This is an acceptable animal model for castration resistant prostate cancer. Dose dependent decreases in tumour growth (by

> 62%) were seen at ≥ 10 mg/kg/day PO for 28 days. Bicalutamide (50 mg/kg/day PO) had no significant effect on tumour growth in this model.

Resistance to treatment with enzalutamide

Possible mechanisms for resistance to enzalutamide include AR gene rearrangement, resulting in a constitutively-active AR that lacks a ligand binding domain, and overexpression of CYP17 leading to elevations in testosterone and DHT, which may promote tumour growth (reviewed in Golshayan and Antonarakis, 2013²).

Secondary pharmacodynamics and safety pharmacology

Enzalutamide was assessed for inhibitory activity at approximately 70 receptors, channels and transporters, 16 non-kinase enzymes and > 200 kinases and deacetylases (at 3-10 μ M; at least 4 times the clinical free C_{max} levels). The only notable off-target activity was at the gamma aminobutyric acid (GABA) gated chloride channel (IC₅₀ about 3 μ M; 3 times the clinical free C_{max} levels). Enzalutamide bound tightly to the channel and complete reversibility was not demonstrated.

Metabolites M1, M2, M3 and M4 also had inhibitory activity against the chloride channel (IC₅₀ values of 20.7, 2.3, 4.0 and 1.55 μ M, respectively). The IC₅₀ values for M1 and M2 were 56 and 1.7 times, respectively, the clinical free C_{max} for these compounds.

The in vitro data indicated a seizurogenic potential with enzalutamide. Clonic convulsions and tonic convulsions were seen in 9 out of 10 mice given 200 mg/kg PO enzalutamide. Convulsions were seen between 1 and 24 h post-dose. The minimum plasma concentrations of enzalutamide and M2 in mice with convulsions were 20 and 6 μ g/mL, respectively (similar to the clinical C_{max} value of enzalutamide and 50% of the clinical C_{max} of M2), based on the plasma concentrations measured in the single dose toxicity study. Significant levels of enzalutamide and M2 were detected in the brain (similar to or greater than plasma levels), while lower levels of M1 were seen (5% of plasma levels). Convulsions were also seen in dogs at high oral doses (60 mg/kg/day PO; C_{max} 58 μ g/mL enzalutamide; exposure ratio based on C_{max} (ER_{C_{max}}) 3.5). Seizure was identified as a dose limiting toxicity in clinical studies with enzalutamide (sponsor's clinical overview), confirming the animal studies are predictive of the clinical setting.

Currently registered antiandrogens, nilutamide and bicalutamide also inhibit the GABA gated chloride channel, but only nilutamide caused convulsions in mice (Foster et al., 2011³). Bicalutamide does not significantly cross the blood-brain barrier, therefore reducing the potential to cause convulsions. Given that convulsions occurred at relatively low plasma levels of enzalutamide, combined with the significant inhibitory activity at the GABA gated chloride channel by both enzalutamide and M2, and the significant central nervous system (CNS) exposures to both of these compounds, seizures should be considered as a potential risk in patients taking enzalutamide. Consideration should also be given to patients that may be currently taking GABA-A acting compounds and the potential risk for seizures in the event of withdrawal of these compounds.

Aside from convulsions, other CNS associated findings with enzalutamide included hypoactivity (in mice and dogs), reduced spontaneous movement (in mice) and decreased reactivity to stimuli (in dogs). Some of these may be associated with the activity at the chloride channel. The no observed effect level (NOEL) for CNS findings was 30 mg/kg/day PO in mice (ER_{C_{max}} 1.3), 200 mg/kg PO in rats (estimated ER_{C_{max}} 2 or higher⁷) and 45 mg/kg/day PO in dogs (ER_{C_{max}} 2).

² Golshayan, A.R. and E. S. Antonarakis. Enzalutamide: an evidence-based review of its use in the treatment of prostate cancer. *Core Evidence* 2013;8:27-35.

³ Foster, W.R., B.D. Car, H. Shi et al. Drug safety is a barrier to the discovery and development of new androgen receptor antagonists. *The Prostate* 2011;71:480-488.

The AR is closely related to the progesterone receptor. Both enzalutamide and M2 had significant inhibitory activity at the progesterone receptor (IC_{50} 16 μ M and 6.2 μ M, respectively; 19 and 5 times the clinical free C_{max} for both compounds). This activity is not likely to be clinically relevant. Enzalutamide had no agonistic activity at either the progesterone alpha or progesterone beta receptors, and no activity (agonistic or antagonistic) at the oestrogen receptor.

Both enzalutamide and M2 inhibited the human ether-à-go-go-related gene potassium (hERG K^+) tail current with IC_{50} values of 15.7 μ M and 18.6 μ M, respectively; corresponding to 18 times the clinical free C_{max} for enzalutamide and 14 times the clinical free C_{max} for M2. No abnormalities in electrocardiogram (ECG) parameters were detected in dogs treated with 60 mg/kg/day PO enzalutamide (4 week repeat dose toxicity study⁴; C_{max} 58 μ g/mL enzalutamide; $ER_{C_{max}}$ 3.5). Estimated exposures to M1 were 2 times the clinical C_{max} for this metabolite, while estimated exposures to M2 were subclinical (assuming exposures in dogs to M1 and M2 were 37% and 3%, respectively, those of enzalutamide). Based on the low margin in the in vitro assay (a 30-fold difference between unbound drug concentrations at the C_{max} and the hERG K^+ IC_{50} is generally considered a "safe" margin; Redfern et al., 2003⁵) and the inadequately tested concentrations in the in vivo study, an effect of the M2 metabolite on the QT interval⁶ cannot be dismissed.

In the specialised safety pharmacology study, respiratory function was unaffected in male rats that received 100 mg/kg PO enzalutamide. The estimated C_{max} for enzalutamide would be 30 μ g/mL⁷ ($ER_{C_{max}}$ 2 times for enzalutamide, 1 for M1 and subclinical for M2). However, in the toxicity studies, audible or irregular breathing was seen in rodents and dogs that received enzalutamide in Labrasol. Respiratory distress was a contributing factor in the deaths of a number of animals. The effects on respiration are likely, at least in part, associated with the vehicle, Labrasol, as irregular or audible breathing, along with histopathological changes of pulmonary inflammation and alveolar histiocytosis, have been reported previously in studies with Labrasol.

Labrasol is a non-ionic surfactant that is likely to have an irritating effect on the respiratory tract if inadvertently aspirated. The findings in rodents are consistent with gavage-related reflux (Damsch et al., 2011⁸). However, respiratory tract findings were also seen in dogs that received enzalutamide with Labrasol via capsules, suggesting the finding is not restricted to gavage administration. While the incidences appeared to occur at the higher doses of Labrasol, there was generally (but not always) an enzalutamide dose related response at \geq 30 mg/kg PO in mice, 100 mg/kg/day PO in rats and 60 mg/kg/day PO in dogs, suggesting enzalutamide may also have an irritating effect on the respiratory tract.

The NOEL for respiratory effects was 100 mg/kg/day PO enzalutamide (in 2.2 mL/kg/day Labrasol) for rats (26 week study) and 45 mg/kg/day PO enzalutamide (in 0.5 mL/kg/day Labrasol) for dogs. The doses of enzalutamide and Labrasol at the NOEL are at least 7

⁴ This study was chosen as exposures to enzalutamide, M1 and M2 were subclinical in the in vivo cardiovascular safety pharmacology study.

⁵ Redfern, W.S., L. Carlsson, A.S. Davis, et al. Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. *Cardiovascular Res.* 2003;58:32-45.

⁶ The QT interval is the portion of an electrocardiogram between the onset of the Q wave and the end of the T wave, representing the total time for ventricular depolarization and repolarization. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias such as torsade de pointes and sudden death.

⁷ Based on data in the toxicokinetic study (9785-TX-0011) in rats at 100 mg/kg, at which enzalutamide was dosed as a solution in Labrasol. Plasma enzalutamide concentrations for the 200 mg/kg dose as a suspension in Labrasol were below those at 100 mg/kg in the toxicokinetic study. In the safety pharmacology studies, enzalutamide was dosed at 200 mg/kg as a solution in Labrasol.

⁸ Damsch, S., G. Eichenbaum, A. Tonelli et al. Gavage-related reflux in rats: identification, pathogenesis, and toxicological implications (review). *Toxicol. Pathol.* 2011;39:348–360.

times the clinical dose (on a mg/kg basis for local effects). However, given the irritancy of the enzalutamide/Labrasol combination, the proposed text in the PI document that states that capsules should be swallowed whole and that they should not be chewed, dissolved or opened seems appropriate.

Pharmacokinetics

Following oral dosing to animals, peak plasma levels of enzalutamide were reached later than that seen in human subjects (3–7 h compared with 1 h in humans). In Labrasol formulations, relatively high oral bioavailabilities were reported in rats (97.4%) and dogs (72.5%). The plasma elimination half-life was shorter in rodents (9–11 h) than non-rodent species (1.4 days in dogs and monkeys and 2.9 to 4.8 days in healthy human subjects). There was no significant evidence of accumulation in any species. In all examined species, the volume of distribution of enzalutamide was higher than total body water.

At low oral doses, peak plasma levels of M1 were seen at 4–8 h in rodents and much later in non-rodent animal species (12–24 h in dogs, 27–40 h in monkeys). Consistent with an earlier T_{max} for enzalutamide, the T_{max} for M1 in humans was earlier than in animal species (3.5 h) and exposures (AUC) to M1 relative to the parent were also higher (62% in humans compared with 8–34% in mice (dose related trend), 27–47% in male rats, 10–19% in female rats, 27–37% in dogs and 8–11% in monkeys on a molar basis). Peak plasma levels of M2 were seen at a similar time in rodents, dogs and humans (4–24 h) and at later time points in monkeys (24–40 h). M2 was only a minor metabolite in animals with exposures (based on plasma AUC) only 6–29% in mice (dose related trend), 6–7% in male rats, 1–1.5% in female rats, 2–3% in dogs and 18–24% in monkeys. In comparison, exposures (AUC) to M2 in human subjects were almost the same as enzalutamide exposures (89%). The difference between animals and humans in exposure to the pharmacologically active metabolite, M2, is a limitation of the submitted dossier for enzalutamide.

No sex differences in PK parameters were evident in mice, dogs or monkeys. Female rats consistently had higher exposures to enzalutamide, but lower exposures to M1 and M2, than their male counterparts. Sex differences were not assessed in humans, given the proposed indication.

Protein binding by enzalutamide was high and similar in the plasma of mice, rats, dogs and humans (94–98%), with no evidence of a concentration dependence seen. Binding in human plasma was largely attributable to albumin (97.1% bound). Plasma protein binding by M1 was high and similar in human and monkey plasma (97–98%) but marginally lower in the plasma of other species (92–95%). Protein binding by M2 was similar in mouse, dog, monkey and human plasma (93–95%) and lower in the plasma from rats and rabbits (86–90%). The extent of binding by M1 and M2 was independent of concentration.

There was no specific affinity of drug-related material to blood cells. Following oral dosing of radiolabelled (¹⁴C)-enzalutamide to male rats, tissue levels of radioactivity were generally similar to plasma levels. There was no specific affinity or retention of radioactivity in any tissue. Aside from tissues involved in absorption/excretion, notably higher levels were seen in fat (5 times the plasma AUC). This is not considered toxicologically significant. Both enzalutamide and M2 partitioned into the brain of mice and rats with concentrations similar to those seen in plasma. M1 had low penetration into the brain with levels 3–6% of those seen in plasma. In rats, cerebrospinal fluid (CSF) levels of enzalutamide, M1 and M2 were low (\leq 5% of those seen in plasma).

Enzalutamide was extensively metabolised in all species with at least 17 metabolites identified across species. Metabolism involved N-demethylation, amide hydrolysis, oxidation reactions, hydrolysis of the nitrile to an amide, conjugation reactions (with glutathione, glucuronic acid, cysteine and taurine) and various combinations of these. Both

enzalutamide and M1 were the main circulating drug-related compounds in male rats and dogs, while M2 was also prominent in human plasma. The combination of enzalutamide, M1 and M2 accounted for 88% of the circulating drug-related material in human subjects, while all other metabolites were present at $\leq 2\%$ (from sponsor's clinical summaries). While M7 was identified as a human-specific metabolite, it is only produced at very low levels and is not expected to significantly alter the toxicity profile. There were no other human specific metabolites identified.

In vitro studies indicated M2 (the N-desmethyl) is formed non-enzymatically from the amide alcohol, M6. CYP3A4, 3A5 and 2C8 appear to be involved in the formation of M6. Enzymes involved in the formation of M1 from enzalutamide were not identified, but this reaction is likely to involve amidases (potentially multiple). Based on clinical drug interaction studies, enzalutamide is mainly metabolised by cytochrome P450 (CYP) enzyme CYP2C8 and to a lesser extent by CYP3A4/5 (sponsor's clinical overview).

Excretion of drug related material was predominantly via the urine in dogs (50% of the dose) and humans (71% of the dose), while both the urinary and faecal routes contributed to the excretion of drug-related material in rats. Studies in bile-duct cannulated rats and dogs showed good oral absorption, extensive biliary excretion (50% of the dose) and enterohepatic recirculation (rat only). Excreted drug-related material (urine, bile and faeces) consisted predominantly of M1 in rats, dogs and humans, though significant levels of unchanged drug were detected in the faeces of dogs. Significant biliary excretion was demonstrated in rats and dogs (50% of dose). Conjugated metabolites of enzalutamide were only seen in bile samples.

Aside from the low levels of M2 formed in animal species, the PK profile of enzalutamide is sufficiently similar in mice, rats, dogs and humans to warrant the use of the chosen animal species in toxicity studies.

Pharmacokinetic drug interactions

As CYP3A4, 3A5 and 2C8 are involved in the metabolism of enzalutamide to form M2, inhibitors or inducers of these enzymes are likely to alter the plasma kinetics of enzalutamide. Enzalutamide is not a substrate of the P-gp, breast cancer resistance protein (BCRP), organic anion-transporting polypeptide 1B1 (OATP1B1), OATP1B3 or organic cation transporter 1 (OCT1). Therefore, inhibitors or inducers of these transporters are not expected to affect the disposition of enzalutamide.

While some inhibitory activity was seen on CYP2B6, 2C8, 2C9 and 2C19 by enzalutamide and M2, and CYP2C8 by M1, the IC_{50} values were ≥ 12 times the clinical free C_{max} levels. Contrary to the in vitro assays, clinical studies showed induction of CYP2C9 and 2C19 and no significant effects on 2C8 (sponsor's clinical overview). The inhibition of CYP2B6 activity was weak (K_i 42 μ M for enzalutamide and 59 μ M for M2). The inhibitory activity of enzalutamide to these enzymes is not likely to be clinically relevant. No significant inhibitory activity was seen on CYP1A2, 2D6 or 3A4/5.

In vitro, enzalutamide was shown to induce CYP3A4 but not CYP1A2 or 2B6. No in vitro studies were conducted to examine induction of CYP2C9, CYP2C19 or UGTs. The draft PI document states that enzalutamide was likely to be an inducer of CYP2C9, CYP2C19 and uridine diphosphate glucuronosyltransferases (UGTs) based on in vivo human data. Together, the data indicate that enzalutamide is likely to decrease the exposure of drugs that are metabolised by CYP3A4, 2C9, 2C19 or UGTs.

No significant inhibitory activity was seen on the transporters multidrug resistance associated protein 2 (MRP2), OCT2 or OAT1 (at concentrations of 50, 30-100 and 25-50 μ M enzalutamide, M1 or M2, respectively, compared to the respective clinical free C_{max} of 0.86, 0.37 and 1.33 μ M). While some inhibition of OATP1B3 transport was seen with enzalutamide, M1 or M2, the IC_{50} values are high (42.6, 26.3 and > 25 μ M,

respectively, and are therefore not likely to be clinically relevant. Some inhibition of OATP1B1 was seen with M1 (IC₅₀ 4.3 µM), and OCT1 and OAT3 with M2 (IC₅₀ 11.7 and 11.5 µM, respectively) at clinically relevant concentrations, and inhibition of these transporters should be considered as possible during clinical use.

Both enzalutamide and M2 inhibited P-gp transport with IC₅₀ values (1.67 and 1.09 µM, respectively) similar to the clinical free plasma C_{max} levels. Concentrations of enzalutamide in the gastrointestinal tract will be significantly higher than plasma levels. Based on the in vitro data, PK drug interactions involving P-gp should be considered likely.

While the IC₅₀ values for inhibitory activity by enzalutamide, M1 and M2 on BCRP were at least 27 times the clinical free plasma C_{max} (based on M2 values), BCRP is expressed in the GI tract. Given the high local concentrations of enzalutamide in the gastrointestinal tract, inhibition of this transporter in the intestines should be considered as possible. Therefore, enzalutamide has the potential to alter the disposition of drugs that are substrates of P-gp, BCRP, OATP1B1, OCT1 or OAT3.

Toxicology

Acute toxicity

Single dose toxicity studies using the oral route were conducted in mice and cynomolgus monkeys. Neither of the studies were compliant with good laboratory practice (GLP) principles. The observation period in the mouse study was relatively short (4 days) compared with the length recommended in the EU guideline for single dose toxicity (3BS1a). While the observation period in the cynomolgus monkey study was adequate, animals were not subject to necropsy, and therefore no target organs for toxicity can be identified from this study. These limitations are not expected to hinder an assessment of the toxicity profile of enzalutamide as sufficient information can be obtained from the combined set of toxicity studies. The maximum non-lethal dose was 200 mg/kg PO in mice and the highest tested dose in monkeys (100 mg/kg PO). The C_{max} for enzalutamide at these doses were 3.7 and 1.3 times the clinical plasma C_{max}. Deaths were seen in mice treated with ≥ 400 mg/kg PO enzalutamide (ER_{C_{max}} 5.6) indicating a relatively high order of acute toxicity. Clinical signs in mice were only seen at lethal doses, with exposures only marginally above those at the maximum non-lethal dose, suggesting a steep dose-response curve for toxicity.

Perimortem clinical signs included decreased movement, clonic convulsions/tremors, irregular respiration, lacrimation and/or prone/lateral position. The convulsions are likely due to off-target inhibition of the GABA gated chloride channel, while irregular respiration may be due to inadvertent aspiration of the test article. The onset of clinical signs was 1–2 h post-dose with some (decreased movement) lasting up to 2 days. Clinical signs in monkeys were muddy stools and vomiting, indicating gastrointestinal disturbance. Dark reddish foci were seen on the mucosa of the glandular stomach of mice treated with ≥ 400 mg/kg PO enzalutamide.

Repeat dose toxicity

Repeat dose toxicity studies were conducted in mice (1 week), rats (up to 26 weeks) and dogs (up to 13 weeks) using the proposed clinical route (PO). All pivotal studies were GLP compliant and were adequately conducted. The duration of the pivotal studies is considered acceptable to support the proposed clinical use (ICH S9), though it is noted that a 39 week repeat dose toxicity study was on-going. The absence of this study should not preclude registration. Both sexes were included in all studies with the exception of the

pivotal 13 week study in dogs in which only males were used. Given the proposed indication, this is considered acceptable.

Enzalutamide was administered in Labrasol in all studies. At lower doses, enzalutamide was applied as a solution in Labrasol, while, due to solubility limits, high doses of enzalutamide were provided as a suspension in Labrasol, which may have compromised bioavailability. Gavage was used in the rodent studies and the 2 week and pivotal 13 week study in dogs, while enzalutamide was provided in capsules in the 4 week dog study. The sponsor's nonclinical overview states that the maximum doses in the pivotal rat and dog studies were the maximum feasible, based on the maximum dose volume for enzalutamide formulated in Labrasol (2.2 mL/kg in rats and 1.0 mL/kg in dogs⁹) and the maximum solubility of enzalutamide in Labrasol about 45 mg/mL. This seems reasonable.

The highest enzalutamide exposures achieved were in the 26 week rat study and 4 week dog study: 3 times the clinical AUC in male rats and dogs, and 5 times the clinical AUC in female rats (Table 1). Exposures in the 13 week dog study were subclinical and were unusually low compared with those achieved in the 4 week study. The reason for this is unknown but might be related to the different methods of dosing used in the studies, which was via gavage in the 13 week study and in capsules in the 4 week study. Based on preliminary toxicokinetic data provided, exposures in dogs in the 39 week repeat dose toxicity study, where administration was via gavage, are not significantly greater than those in the 13 week study.

The highest estimated exposures to M1 in rats and dogs are only 1.2–1.7 those expected in human subjects based on metabolite to parent AUC ratios on day 1. Higher exposures would have been preferable, but such margins are not unusual for anticancer drugs. The highest estimated exposures to M2 were subclinical ($\leq 40\%$ those seen in human subjects; Table 1). Therefore, the toxicity profile of this compound has not been adequately assessed in the submitted toxicity studies. Ideally, at least one toxicity study should have been conducted with this metabolite alone. However, M2 has a similar pharmacological profile to enzalutamide (including off-target effects on the GABA gated chloride channel and progesterone receptor). Therefore, the toxicity profile of M2 is likely to be similar to enzalutamide alone. Relative exposures to pharmacologically active material (enzalutamide and M2) were moderate in the 26 week rat study and 4 week dog study (Table 1).

⁹ While the nonclinical overview states 0.5 mL/kg for dogs, the dose volumes used in the dog studies were generally greater than this value and the dose volume in the pivotal dog study was 1.0 mL/kg/day. Based on the findings in the other dog studies, this can be considered the maximum tolerated dose volume.

Table 1. Relative exposure in repeat dose toxicity studies

Species	Study duration	Dose (mg/kg/day)	AUC _{0-24h} (µg·h/mL)		Exposure ratio (ER)		M2 ^c		Enzalutamide + M2	
			1	2	1	2	AUC _{0-24h} (µg·h/mL)	ER	AUC _{0-24h} (µg·h/mL)	ER
Mouse (CD-1)	1 week	30	359		1.1		65	–	424	0.7
		100	617		2		111	0.4	728	1.2
Rat (SD)	4 weeks	10	56.6	135	0.2	0.4	–	–	–	–
		30	152	303	0.5	0.9	–	–	–	–
		100	290	427	0.9	1.3	–	–	–	–
	26 weeks	10	239	732	0.7	2.3	14.3/7.3	–	253/739	0.4/1.2
		30	655	1346	2.0	4	39.3/13.5	–	694/1360	1.2/2.3
		100	827	1708	2.6	5	49.6/17.1	0.18/0.06	877/1725	1.5/3
Dog (Beagle)	4 weeks ^a	10	390		1.2		7.8	–	398	0.7
		30	765		2.4		15.3	–	780	1.3
		60	1125		3		22.5	0.08	1148	1.9
	13 weeks ^b	4	101		0.3		–	–	–	–
		20	246		0.8		–	–	–	–
		45	269		0.8		–	–	–	–
Human (CRPC patients)	steady state	[160 mg]	322		–		278	–	600	–

Combined data for both sexes for mice and dogs; a dosing was via capsules; b dosing was via gavage; c estimated assuming M2 exposures were 18%, 6%, 2% and 3% the enzalutamide exposures in male rats, female rats and dogs, respectively (not converting to molar values for simplicity); – = not determined.

Major toxicities

The majority of the toxicities observed with enzalutamide were consistent with the pharmacological action of the drug, with effects on the reproductive organs (male and female), pituitary gland and adrenal gland. Additional findings were seen in the liver, kidney and thyroid gland of rats and the lungs of both rats and dogs.

Findings associated with pharmacological action

As expected for this type of drug, findings in the male reproductive tract included atrophy of the prostate gland and seminal vesicles, degeneration of the seminiferous tubules, with hypospermia and decreased secretions at all dose levels (below the clinical exposure). Associated changes in males included pituitary gland hypertrophy/hyperplasia, affecting the *pars distalis*, and mammary gland atrophy. All of these have been reported previously in toxicity studies with agents that affect testosterone production or action (Pinski et al., 1993¹⁰; Iswaran et al., 1997¹¹). All findings were reversible. A NOEL was not established for these findings, but they are not considered to be a toxicological concern for the proposed indication.

Although the proposed indication is for prostate cancer, female animals were included in the majority of the toxicity studies. Pharmacological effects in female rats included uterine dilatation and adrenal gland hypertrophy and hyperplasia, primarily affecting the zona fasciculata. Mammary gland changes (lobular hyperplasia, gland dilatation) were also seen.

¹⁰ Pinski, J., T. Yano, K. Szepeshazi, K. Groot and A.V. Schally. Recovery of pituitary-gonadal function in male rats after long-term suppression induced by a single injection of microcapsules of LH-RH antagonist Cetrorelix (SB-75). *J. Androl.* 1993;14:164-169.

¹¹ Iswaran, T.J., M. Imai, G.R. Betton and R.A. Siddall. An overview of animal toxicology studies with bicalutamide (ICI 176,334). *J. Toxicol. Sci.* 1997;22:75-88.

Findings not associated with pharmacological action

Deaths in toxicity studies were generally associated with CNS effects as a result of off target action on the GABA gated chloride channel, or respiratory distress. These are discussed further under *Secondary pharmacodynamics and safety pharmacology*, below.

Clinical signs of excessive salivation, gastrointestinal disturbance and respiratory effects may largely be associated with Labrasol, but enzalutamide might also contribute to the effects. Diffuse hepatocellular hypertrophy and increased cytoplasmic eosinophils were seen in rats treated with ≥ 10 mg/kg/day PO enzalutamide (ER_{AUC} at least 0.5). Elevated liver enzymes (alanine transaminase (ALT) and aspartate transaminase (AST)) were not seen in the toxicity studies and the hypertrophic changes may be associated with increased metabolic capacity and enzyme induction. Follicular cell hypertrophy/hyperplasia was seen in the thyroid gland of female rats treated with ≥ 10 mg/kg/day PO enzalutamide. This was suggested to be associated with the hepatocellular hypertrophy. Similar hepatic and thyroid effects have been observed for bicalutamide. There was no evidence of hepatic and thyroid toxicity in dogs. The hepatic and thyroid findings observed in rats are of low relevance to humans.

Increased incidences and severity of chronic progressive nephropathy (CPN) was seen in rats treated with ≥ 10 mg/kg/day PO enzalutamide for 26 weeks. CPN occurs spontaneously at a high incidence in Sprague Dawley rats (in particular males), and some chemicals exacerbate this condition (Hard et al., 2004¹²). While the increase in CPN may be drug-related, such an effect in rats is not generally considered a predictor of renal toxicity in humans (Hard et al., 2009¹³). There was no evidence of nephrotoxicity in dogs.

Genotoxicity and carcinogenicity

The potential genotoxicity of enzalutamide was assessed in a bacterial mutagenicity assay, an in vitro forward mutation assay in mouse lymphoma cells and a mouse micronucleus assay. The main human metabolites, M1 and M2, were also assessed for mutagenicity in bacteria. Appropriate concentrations were used in the in vitro assays, and the highest dose in the in vivo study (30 mg/kg/day PO; ER_{AUC} for enzalutamide 1.2) was determined to be the maximum tolerated dose in a dose ranging study.

Negative results were obtained in all studies. Therefore, enzalutamide is not considered to pose a genotoxic risk. While M1 and M2 were not mutagenic, the potential clastogenicity of these metabolites has not been adequately assessed as exposures to these compounds were subclinical in the mouse micronucleus assay. This is not considered to be a major deficiency, given the intended patient population.

No carcinogenicity studies were conducted, which is considered acceptable given the indication (ICH S9)

Reproductive toxicity

Reproductive toxicity studies were restricted to a preliminary embryofetal development study in mice. The absence of other reproductive toxicity studies is considered acceptable given the proposed indication (ICH S9). Based on its mode of action and the effects on the male reproductive organs seen in the toxicity studies, enzalutamide is expected to have a reversible negative effect on male fertility.

¹² Hard G. C., Khan K. N. A contemporary overview of chronic progressive nephropathy in the laboratory rat, and its significance for human risk assessment. *Toxicol. Pathol* 2004;32:171-180.

¹³ Hard G. C., Johnson K. J., Cohen S. M. A comparison of rat chronic progressive nephropathy with human renal disease - Implications for human risk assessment. *Crit. Rev. Toxicol.* 2009;39:332-346

Placental transfer of enzalutamide and/or its metabolites has not been assessed. Teratogenicity and embryofetal lethality were evident in mice that received ≥ 10 mg/kg/day PO enzalutamide during the period of organogenesis; based on toxicokinetic data in non-pregnant animals at higher doses, the systemic exposure to enzalutamide and M2 at 10 mg/kg/day was below the clinical exposure based on AUC. The teratogenic effects included cleft palate (with absent palatine bone), cervical rib and decreased anogenital distance. The latter finding is consistent with malformations seen with other antiandrogens (Iswaran et al., 1997¹⁴). Given the critical role of androgens in male fetal development, teratogenic effects would be expected with this type of drug.

Pregnancy classification

The sponsor has proposed Pregnancy Category X. This category is defined as *drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy*. In light of the teratogenic effects seen in mice, this pregnancy category seems acceptable.

Phototoxicity

Enzalutamide was not phototoxic in a standard in vitro assay in Balb/c 3T3 cells.

Excipients

The proposed formulation of Xtandi contains the novel excipient, Labrasol. All toxicity studies with enzalutamide included Labrasol as an excipient. The highest dose of Labrasol was 10.6 g/kg/day PO in mice, 2.65 g/kg/day in rats and 4.77 g/kg/day in dogs. Toxicities associated with Labrasol were evident in some of the studies and included excessive salivation and respiratory effects (audible or difficulty in breathing with pulmonary inflammation evident during post-mortem analyses).

Respiratory distress was a cause of death of a number of animals, both rats and dogs. The respiratory effects were probably attributed to an induction of reflux by Labrasol leading to local irritation effects and accidental aspiration of the excipient, Labrasol. The clinical signs of excessive salivation are also an indicator of reflux (Damsch, et al., 2011¹⁵). In general, the incidence and severity of respiratory effects were higher in animals that also received enzalutamide, suggesting a contribution of enzalutamide in the irritancy effect, though the reflux may be associated with Labrasol alone. No adverse respiratory effects were seen in rats that received 2.2 mL/kg/day Labrasol (equal to about 2.3 g/kg/day) for 26 weeks or in dogs that received 0.5 mL/kg/day Labrasol (equal to about 0.53 g/kg/day) for 13 weeks. These doses are adequately higher than the proposed clinical dose of Labrasol (on a mg/kg basis). Therefore, the likelihood of respiratory effects in patients is low. The proposed text in the PI document that states that capsules should be swallowed whole and that they should not be chewed, dissolved or opened seems appropriate.

Impurities

Three impurities/degradants in the drug substance and drug product specifications have been specified at levels above the qualification thresholds in the relevant ICH guidelines. The proposed limits for these impurities/degradants have been adequately qualified in the submitted toxicity studies.

¹⁴ Iswaran, T.J., M. Imai, G.R. Betton and R.A. Siddall. An overview of animal toxicology studies with bicalutamide (ICI 176,334). *J. Toxicol. Sci.* 1997;22:75-88.

¹⁵ Damsch, S., G. Eichenbaum, A. Tonelli et al. Gavage-related reflux in rats: identification, pathogenesis, and toxicological implications (review). *Toxicol. Pathol.* 2011;39:348-360.

Paediatric use

No specific studies in juvenile animals were submitted. Such studies are not considered necessary to support the application for the proposed indication.

Nonclinical summary and conclusions

- The submitted Module 4 data were in general accordance with the ICH guideline on the nonclinical evaluation of anticancer pharmaceuticals (ICH S9). Xtandi contains the novel excipient Labrasol. The formulations of enzalutamide used in the safety studies included this excipient while the safety of the excipient was also evaluated separately. The only notable limitation of the submitted dataset is that the toxicity of the major active human metabolite has not been adequately assessed.
- Enzalutamide was a competitive inhibitor at the wild-type AR and its castration-resistant mutant variants, T877A and W741C. No agonistic activity was detectable at the AR. One major human metabolite, M2, also had inhibitory activity at the AR and is likely to contribute significantly to the efficacy of enzalutamide in patients. Decreased tumour growth was seen in a mouse model bearing a castration-resistant prostate cancer cell line.
- Both enzalutamide and M2 had significant inhibitory activity at the GABA gated chloride channel and readily crossed the blood-brain barrier. Convulsions were seen in both mice and dogs with plasma concentrations of enzalutamide similar to or marginally above the clinical C_{max}. Both enzalutamide and M2 inhibited the hERG K⁺ tail current. Insufficient data were provided to exclude a potential for QT prolongation during clinical use. Audible or irregular breathing was seen in rodents and dogs that received enzalutamide in Labrasol. Respiratory distress was a contributing factor in the deaths of a number of animals. The respiratory effects are partly due to reflux and inadvertent aspiration with a consequent local irritation effect of enzalutamide/Labrasol. The NOELs for respiratory effects are at least 7 times the clinical dose. The likelihood of respiratory effects in patients is low provided the capsules are taken as directed and not chewed or broken prior to swallowing.
- Oral absorption was high in rats and dogs. M1 was a moderate metabolite and M2 a minor metabolite in animal species. Both of these are significant metabolites in humans. No significant inter-species differences in plasma protein binding were evident. Both enzalutamide and M2 partitioned into the brain of mice and rats with concentrations similar to those seen in plasma. CYP3A4, 3A5 and 2C8 appear to be involved in the formation of M2. Enzymes involved in the formation of M1 from enzalutamide were not identified.
- In vitro studies indicated a number of potential PK drug interaction possibilities:
 - Inhibitors or inducers of CYP3A4/5 and 2C8 are likely to alter the plasma kinetics of enzalutamide.
 - Enzalutamide is likely to decrease the exposure of drugs that are metabolised by CYP3A4, 2C9, 2C19 or UGTs (also based on in vivo human data).
 - Enzalutamide has the potential to alter the disposition of drugs that are substrates of P-gp. An effect on substrates of BCRP, OATP1B1, OCT1 or OAT3 cannot be excluded.
- Repeat dose toxicity studies were conducted in mice (1 week), rats (up to 26 weeks) and dogs (up to 13 weeks). The toxicities observed were associated with the pharmacology of the drug (effects on the reproductive organs, pituitary gland, mammary gland and adrenal gland), off-target effects on the GABA gated chloride

channel (convulsions) or associated with Labrasol (respiratory effects, salivation and gastrointestinal disturbance). Deaths in toxicity studies were generally associated with CNS or respiratory effects. Findings in the liver, thyroid gland and kidney of rats were considered to be either adaptive or species-specific effects.

- Enzalutamide was not genotoxic in the standard battery of tests. No carcinogenicity studies were submitted, which is considered acceptable.
- Reproductive toxicity studies were restricted to a preliminary embryofetal development study in mice. Teratogenicity and embryofetal lethality were evident at low relative doses.
- Enzalutamide was not phototoxic in a standard in vitro assay.
- The safety of the excipient, Labrasol, has been adequately assessed.

Conclusions and recommendation

- The pharmacology studies support the proposed indication.
- 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.
- In vitro studies indicate a large number of potential PK drug interactions are possible.
- The only toxicity of clinical relevance is the potential to cause CNS effects (for example, seizures). Other findings are expected with this type of drug or are not clinically relevant.
- Local irritation effects in the oesophagus and respiratory tract are not expected to occur clinically provided the capsules are taken as directed and not chewed or broken prior to swallowing.

There are no objections on nonclinical grounds to the proposed registration of enzalutamide for the proposed indication.

Recommended revisions to the nonclinical text in the draft PI are beyond the scope of the AusPAR.

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

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

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

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

Clinical rationale

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

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

Clinical treatment of advanced prostate cancer is also limited by the development of resistance to currently available antiandrogen therapies. In addition, overexpression of the AR has been documented in upwards of 50% of CRPC specimens and is believed to contribute to tumour progression. Currently approved antiandrogens, including bicalutamide and flutamide, have been found to stimulate AR signalling in the setting of AR overexpression, thereby potentially exacerbating or accelerating castration-resistant tumour growth. In clinical practice, most patients receive 2 or more hormonal manipulations and are then offered chemotherapy (for example with docetaxel or cabazitaxel) as their disease continues to progress.

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

Evaluator comments: The clinical rationale is sound. Abiraterone (Zytiga) is currently approved in Australia and is *“indicated with prednisone or prednisolone for the treatment of metastatic advanced prostate cancer (castration resistant prostate cancer) in patients who have received prior chemotherapy containing a taxane”*¹⁶.

Guidance

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

¹⁶ Australian PI for Zytiga, March 2012

Contents of the clinical dossier

The submission contained the following clinical information:

Module 5:

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

Module 2:

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

Paediatric data

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

Good clinical practice

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

Pharmacokinetics

Studies providing pharmacokinetic data

Table 2 shows the studies relating to each PK topic.

Table 2: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	9785-CL-0001	To evaluate the PK, metabolism, and excretion of enzalutamide in plasma, urine, and faeces after a single oral 160 mg (100 µCi) dose of ¹⁴ C-enzalutamide.

PK topic	Subtopic	Study ID	*
	Bioequivalence † - Single dose	MDV3100-05	To evaluate the bioequivalence of two oral formulations of enzalutamide following a single 160 mg dose in healthy male subjects under fasted and fed conditions; and to assess the effects of food on the rate and extent of absorption of the two oral formulations following a single 160 mg dose in healthy male subjects.
	Food effect	MDV3100-05	See above
PK in special populations	Target population§ - Single dose and multi-dose	S-3100-1-01	To determine the safety and tolerability profile of enzalutamide (30, 60, 150, 240, 360, 480, and 600 mg), including the dose limiting toxicities, and the maximum tolerated dose when administered orally to patients with CRPC.
	Hepatic impairment	9785-CL-0009	To compare the single-dose PK of enzalutamide (160 mg; four 40 mg capsules) in subjects with mild and moderate hepatic impairment to matched control subjects with normal hepatic function
PK interactions	Gemfibrozil; itraconazole	9785-CL-0006	To investigate the effect of multiple oral doses of 600 mg gemfibrozil twice daily on the PK of a single oral dose of 160 mg enzalutamide; and to investigate the effect of multiple oral doses of 200 mg itraconazole once daily on the PK of a single oral dose of 160 mg enzalutamide.
	Pioglitazone; drug cocktail of S-warfarin, omeprazole and midazolam	9785-CL-0007	To determine the effect of multiple once daily administration of enzalutamide (160 mg; four 40 mg capsules) on the PK of a single dose of pioglitazone (CYP2C8 substrate), S-warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate) and midazolam (CYP3A4 substrate) in patients with CRPC.
Population PK analyses	Healthy subjects	Study report 9785-PK-0002	To assess the extent of drug-drug interaction of gemfibrozil and itraconazole on single dose enzalutamide PK, using data from study 9785-CL-0006.

PK topic	Subtopic	Study ID	*
	Target population	Study report 9785-PK-0001	To develop a population PK model of enzalutamide, and population PK-PD models for its effect on PSA concentration (a biomarker for prostate cancer progression) and spontaneously reported fatigue (the most frequently reported adverse event), using data from Study S-3100-1-01.
		Study report icon2147020	To investigate potential factors that may cause increases in plasma concentrations of enzalutamide metabolite M1 (also referred to as MDCP0001) in CRPC patients in Study CRPC2.
		Study report icon2147016	To document the relationship(s) of enzalutamide and its major active metabolite M2 (also referred to as MDPC0002) steady-state pre-dose plasma concentrations (C _{min}) with study efficacy and safety outcomes in Study CRPC2.
	Both healthy and target population	Study report icon2147014	To build a population PK model of enzalutamide after oral administration of enzalutamide liquid-filled capsules in healthy male subjects and in patients with CRPC, including cofactors that contribute to inter-individual variability in enzalutamide PK, using PK data from studies S-3100-1-01, MDV3100-05, and CRPC2.

* Indicates the primary aim of the study.

† Bioequivalence of different formulations.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

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

Evaluator's summary and conclusions on pharmacokinetics

Overall, the PK data is adequate with respect to evaluation of this application. Enzalutamide was absorbed rapidly after oral administration in patients, with C_{max} observed 1 to 2 h after administration. Based on a mass balance study in healthy human subjects, oral absorption of enzalutamide was estimated to be at least 84.2%. Food effect study showed that food had no clinically significant effect on the extent of absorption. The mean apparent volume of distribution (V/F) of enzalutamide in patients after a single oral dose was 110 L (29% coefficient of variation, CV).

Enzalutamide and its metabolites M1 and M2 were found to be highly bound to plasma proteins (96% to 98%). Enzalutamide was found to be extensively metabolised. There

were two major metabolites in human plasma: M2 (N-desmethyl enzalutamide; active metabolite) and M1 (a carboxylic acid derivative; inactive metabolite).

Drug interaction studies showed that CYP2C8 played an important role in the metabolism of enzalutamide and the formation of M2, while CYP3A4 played a more minor role. The mean apparent clearance (CL/F) of enzalutamide in CRPC patients was 0.564 L/h after single dose and 0.614 L/h after multiple dosing.

Following oral administration of ¹⁴C-enzalutamide, 84.6% of the radioactivity was recovered by 77 days post dose: 71.0% was recovered in urine (primarily as M1, with trace amount of enzalutamide and M2), and 13.6% was recovered in faeces (0.39% of dose as unchanged parent enzalutamide). Based on this result, renal excretion appeared to be a minor elimination pathway for unchanged parent enzalutamide and the active metabolite M2.

The PK of enzalutamide were examined in subjects with baseline mild (n = 6) or moderate (n = 8) hepatic impairment (Child-Pugh Class A and B¹⁷, respectively) and in 14 matched control subjects with normal hepatic function. Results showed that following a single oral 160 mg dose of enzalutamide, exposure parameters for enzalutamide increased by up to 1.24 fold and 1.29 fold in subjects with mild and moderate hepatic impairment, respectively, compared to healthy control subjects. Based on the study results, no dose adjustment was considered necessary for patients with baseline mild or moderate hepatic impairment.

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

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

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

Pharmacodynamics

Studies providing pharmacodynamic data

The studies relating to pharmacodynamics included the following:

¹⁷ The Child-Pugh score is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease (encephalopathy, ascites, serum bilirubin, serum albumin and prothrombin time). Each measure is scored 1-3, with 3 indicating most severe derangement. Assessment as good operative risk (A or mild) if 5 or 6 points; moderate risk (B or moderate) if 7 to 9 points; and poor operative risk (C or severe) if 10 to 15 points (developed for surgical evaluation of alcoholic cirrhotics.).

Table 3: Submitted pharmacodynamic studies.

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

* Indicates the primary aim of the study. ‡ And adolescents if applicable.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

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

Mechanism of action

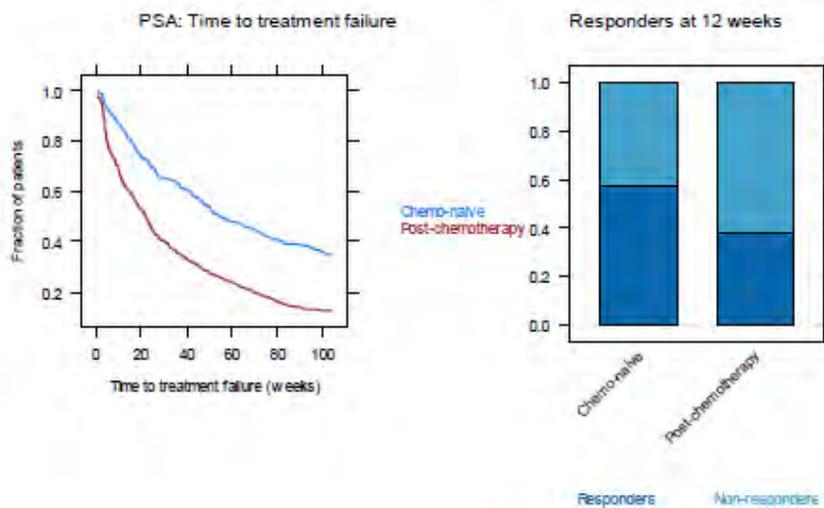
Mechanism of action was studied in Study CRPC-MDA-1, a single centre, single arm, open-label study of patients with metastatic progressive CRPC treated with oral enzalutamide (160 mg/day). Immunohistochemistry for AR in bone marrow samples was performed and subcellular distribution of AR was recorded (membranous, cytosolic, nuclear, or combination).

Of the 16 patients who were evaluable for assessment of bone marrow AR expression by immunohistochemistry, 5 were prostate specific antigen (PSA) responders (defined by a $\geq 50\%$ reduction from baseline in PSA at Week 9) and 11 were PSA non-responders. Of the evaluable 5 PSA responders, all 5 showed reduction in nuclear AR localisation. Of the evaluable 11 PSA non-responders, 2 showed reduction in nuclear AR localisation and 9 showed no change or increase in nuclear AR localisation. Statistical correlation was not assessed due to low numbers of evaluable patients.

Secondary pharmacodynamic study

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

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



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

Evaluator's conclusions on pharmacodynamics

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

Dosage selection for the pivotal studies

Dose selection of enzalutamide for the pivotal study was based on the results of a Phase I dose escalation study, S-3100-1-01. With regards to dose selection for the pivotal study, the maximum tolerated dose in this study was determined to be 240 mg daily, based upon the occurrence of dose limiting toxicities as well as adverse events (AEs) of fatigue leading to dose reductions at higher doses. There were 5 dose limiting toxicities reported in Study S-3100-1-01, all occurring at doses of 360 mg daily or higher (3 events of seizure, and 1 each of rash and confusion). There was also a dose-dependent increase in AEs of fatigue leading to dose reduction, with a 2.9% incidence at 240 mg daily, 7.5% incidence at 360 mg daily, and 20.0% incidence at 480 mg daily.

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

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

Evaluator comment: The rationale for the dose selection in the Phase III study is sound.

Efficacy

Studies providing efficacy data

Pivotal study

Pivotal efficacy Study CRPC2 (AFFIRM) was a multi-centre, randomised, double blind, placebo controlled, Phase III study evaluating the efficacy and safety of enzalutamide in patients with progressive CRPC who had been previously treated with 1 or 2 chemotherapy regimens, at least 1 of which was docetaxel-based. The primary objective was to determine the benefit of enzalutamide compared to placebo as assessed by overall survival (OS).

Other efficacy studies

Study S-3100-1-01 was a multi-centre, Phase I, open-label, uncontrolled, dose escalation safety and PK study of enzalutamide with dose expansion at the tolerated doses, in patients with CRPC. The primary objective was to determine the safety and tolerability profile of enzalutamide, including the dose limiting toxicities, and the maximum tolerated dose when administered orally to patients with CRPC. The study was ongoing at the time of this submission.

Study CRPC-MDA-1 was a single centre, single arm, open-label study of patients with metastatic progressive CRPC treated with oral enzalutamide (160 mg/day), evaluating the tumour micro-environment. The primary objective was to explore the effect of treatment with enzalutamide on AR signalling and expression of survival/resistance pathways in the bone marrow metastases of CRPC patients in correlation with measures of anti-tumour activity to identify predictors of response or resistance to therapy. The study was ongoing at the time of this submission.

Evaluator's conclusions on efficacy

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

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

In terms of effect on bone and soft tissue disease, study results showed that the time to radiographic progression was statistically significantly longer in enzalutamide treated patients compared with placebo treated patients (median duration of radiographic progression-free survival (PFS) of 8.3 months with enzalutamide versus 2.9 months with

placebo; $p < 0.0001$). The stratified hazard ratio for time to radiographic progression in the enzalutamide group relative to the placebo group was 0.404, indicating a 60% decrease in the risk of radiographic progression with enzalutamide compared to placebo. The time to first skeletal-related events was also statistically significantly longer among enzalutamide treated patients compared with placebo treated patients (median time to first skeletal-related events of 16.7 months with enzalutamide versus 13.3 months with placebo; $p = 0.0001$). The stratified hazard ratio for time to first skeletal-related event in the enzalutamide group relative to the placebo group was 0.688, indicating a 31% decrease in the risk of skeletal-related events with enzalutamide compared to placebo. The proportion of patients for whom the best overall soft tissue radiographic response was complete or partial response was 28.9% in the enzalutamide group compared with 3.8% in the placebo group (difference of 25.08%; $p < 0.0001$).

With regards to the effect on pain, the rate of pain palliation at Week 13 was 44.9% among enzalutamide treated patients, compared to 6.7% among placebo treated patients (difference of 38.2%; $p = 0.0079$). The proportion of patients with pain progression at Week 13 was 27.8% in the enzalutamide group compared to 39.0% in the placebo group (difference of 11.2%; $p = 0.0018$). In terms of effect on QoL, the Functional Assessment of Cancer Therapy–Prostate (FACT-P) response rate was 43.2% with enzalutamide compared to 18.3% with placebo (difference of 24.9%; $p < 0.0001$). However, the European Quality of Life Five-Domain Scale (EQ-5D) scores were generally comparable between both treatment groups, although analyses on the QoL over time using the EQ-5D were difficult to interpret due to the small sample size of evaluable patients and the large decrease in the number of patients completing the questionnaire over time. In terms of effect on functional status, analyses on the Eastern Cooperative Oncology Group (ECOG) performance status over time showed that the mean ECOG performance status deterioration from baseline was greater in the placebo group compared with the enzalutamide group, across all assessed time points (Weeks 9, 17, 25, 37 and 49).

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

Safety

Studies providing safety data

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

- General AEs
- Adverse events of special interest were not pre-specified in the protocol. Based on analyses of AEs in Study CRPC2, additional analyses were performed by the sponsor looking at AEs in study CRPC2 of fatigue, diarrhoea, hot flush, musculoskeletal pain, and spinal cord compression
- Laboratory tests, included haematology and routine blood chemistry

- Vital signs and 12-lead ECG. A thorough QT/QTc evaluation was embedded into the study, in which all ECGs were read centrally at an independent and blinded ECG laboratory.

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

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

Comments: The sponsor had provided within the SCS safety results in 3 safety populations: the safety population from the pivotal Phase III study CRPC2, the integrated safety populations of 3 open-label uncontrolled studies (S3100-1-01, CRPC-MDA-1, and 9785-CL-0111¹⁸), and the integrated safety populations of all 4 studies (Studies CRPC2, S3100-1-01, CRPC-MDA-1, and 9785-CL-0111). In addition, the SCS contains the individual presentation of the safety results of 5 Phase I PK studies (9785-CL-0007, 9785-CL-0009, 9785-CL-0001, MDV3100-05, and 9785-CL-0006), as well as updated safety information (serious AEs (SAEs) and deaths) for 2 ongoing, Phase II, open-label studies (9785-CL-0121 [open-label extension of the DDI study 9785-CL-0007] and 9785-CL-0321 [open-label single-arm, efficacy and safety study in patients with hormone-naïve prostate cancer]).

The safety results in the pivotal Phase III study (CRPC2) and the integrated results of the 3 open-label uncontrolled studies (S3100-1-01, CRPC-MDA-1, and 9785-CL-0111) are presented in the clinical evaluation report (see Attachment 2 of this AusPAR). The individual safety results of studies S3100-1-01 and CRPC-MDA-1, the integrated safety results of CRPC2 and the 3 open-label uncontrolled studies, the individual safety results of the 5 Phase I PK studies stated above and the updated safety information of the 2 ongoing Phase II open-label studies stated above, were evaluated for the purpose of this submission and no major safety concerns were raised.

Patient exposure

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

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

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

¹⁸ The CSR of study 9785-CL-0111 was not submitted in this application dossier. According to the sponsor, Study 9785-CL-0111 was an ongoing Phase I-II multi-centre, open-label, uncontrolled, dose-escalation study in Japanese patients with CRPC. At the time of the 07 October 2011 cut-off date for safety analyses, 27 of the anticipated 46 patients (9 patients in dose escalation cohorts and 37 patients in dose expansion cohorts) were enrolled into the study. Study objectives include a determination of the safety and PK of single doses of 80, 160, and 240 mg of enzalutamide in Japanese patients, safety and PK of multiple daily doses of 160 mg enzalutamide in Japanese patients, and efficacy measures such as PSA response, circulating tumour cell counts, disease progression, and markers of bone turnover.

Safety issues with the potential for major regulatory impact

- Haematological effect
- Neuropsychiatric effect
- Cardiovascular safety

These are discussed below.

Evaluator's conclusions on safety

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

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

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

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

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

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

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

First round benefit-risk assessment

First round assessment of benefits

The benefits of enzalutamide in the proposed usage are:

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

Efficacy results in the pivotal study (CRPC2) showed that there was a statistically significant increase in the duration of OS among patients treated with enzalutamide compared with patients treated with placebo (median survival duration of 18.4 months with MDV3100 versus 13.6 months with placebo; $p < 0.0001$), and a 37% decrease in the risk of death for patients receiving enzalutamide compared to those receiving placebo. There was also a statistically significant increase in time to PSA progression among enzalutamide treated patients compared with placebo treated patients (median time to PSA progression of 8.3 months with enzalutamide versus 3.0 months with placebo; $p < 0.0001$).

The time to radiographic progression was statistically significantly longer in enzalutamide treated patients compared with placebo treated patients (median duration of radiographic PFS of 8.3 months with enzalutamide versus 2.9 months with placebo; $p < 0.0001$), as was the time to first skeletal-related events was also statistically significantly longer among enzalutamide treated patients compared with placebo treated patients (median time to first skeletal-related events of 16.7 months with enzalutamide versus 13.3 months with placebo; $p = 0.0001$). The proportion of patients for whom the best overall soft tissue radiographic response was complete or partial response was 28.9% in the enzalutamide group compared with 3.8% in the placebo group (difference of 25.08%; $p < 0.0001$).

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

First round assessment of risks

The risks of enzalutamide in the proposed usage are:

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

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

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

With regards to effect on BP, analyses of the vital signs in Study CRPC showed that there appeared to be an association of enzalutamide treatment with increased BP, with mean SBPs and DBPs observed to be slightly higher than baseline at post-baseline timepoints up through the Week 49 visit. However, the maximum mean increase from baseline was small (SBP: maximum mean increase of 2.1 mmHg from baseline [observed at Week 5]; DBP: maximum mean increase of 1.2 mmHg from baseline [observed at Week 9]). There was also no incidence of AE of hypertensive crisis in the enzalutamide group versus 0.3% (1/399) in the placebo group in Study CRPC2. In addition, the majority of AEs of hypertension among enzalutamide treated patients in Study CRPC2 were of Grades 1 and 2, there was no incidence of SAE of hypertension in the enzalutamide group, and the incidence of AE of hypertension leading to discontinuation of study drug was low in the enzalutamide group (0.1%). It also needs to be taken into consideration that this AE can be monitored by routine BP measurements.

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

Of clinical concern was the potential risk of seizures. Seizure was a known potential toxicity of enzalutamide, based on nonclinical findings, and had been identified as a dose limiting toxicity in the dose escalation study, Study S-3100-1-01. Analysis in Study CRPC2 of the incidence of seizures showed that the incidence in the enzalutamide group was low (0.8% [6/800] versus 0% with placebo), although it is noted that Study CRPC2 excluded patients with medical conditions that could predispose them to seizures and medications known to decrease the seizure threshold. Five of these AEs of seizures were considered serious AEs (preferred terms of convulsion [n=2], partial seizure [n=2], or status epilepticus [n=1])¹⁹. The sponsor had observed that dose appeared to be an important predictor of the risk of seizure, based on findings of dose-dependent convulsions observed in mice, that seizure was a dose limiting toxicity in Study S-3100-1-01, occurring only at doses \geq 360 mg, and that of the 5 patients who experienced a seizure in CRPC2, 4 patients had PK data available, and their enzalutamide C_{min} plasma concentrations were in the upper two quartiles (Study icon2147016). It is noted that the potential risk of seizure has been clearly indicated in the proposed PI under the heading of “Precautions”, that “*Caution should be used in administering XTANDI to patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, stroke, primary brain tumours or brain metastases, or alcoholism. In addition, the risk of seizure may be increased in patients receiving concomitant medicines that lower the seizure threshold*”. This is considered appropriate.

First round assessment of benefit-risk balance

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

¹⁹ The remaining AE was that of a patient in the enzalutamide group with an event term of syncope but with several features suggestive of seizure, and included in the incidence calculation by the sponsor following an additional review of the AEs of seizures.

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

Safety result showed that common AEs associated with enzalutamide were fatigue, hot flush and headache. In Study CRPC2, these AEs were mostly of Grades 1 or 2 in severity, with low incidences of SAEs. Enzalutamide appeared to be associated with an increase in BP and a decrease in leukocyte and neutrophil counts. However, the effect on BP appeared to be small (maximum mean increase from baseline in SBP and DBP of 2.1 mmHg and 1.2 mmHg, respectively). The majority of AEs of hypertension among enzalutamide treated patients in Study CRPC2 were of Grades 1 and 2 in severity, and there was no incidence of SAE of hypertension in the enzalutamide group. In addition, this effect on BP can be monitored by routine BP measurements. The effect on leukocyte and neutrophil counts also appeared to be small (maximum mean decline of approximately 800/ μ L and 700/ μ L in leukocyte counts and neutrophil counts, respectively). Neutropenia was not implicated in any SAEs in study CRPC2, and the overall incidence of AEs of leucopenia and neutropenia in the enzalutamide group was low (\leq 1.3%). In addition this effect on leukocyte and neutrophil counts can be monitored by routine clinical laboratory tests.

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

First round recommendation regarding authorisation

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

Clinical questions

Safety

Please provide analysis of the results for SBP and DBP measurements study S3100-1-01 according to the dose groups.

Analyses of SBP and DBP in the integrated safety results of the 3 open-label studies did not show any obvious dose relationship. However, as noted by the sponsor, the interpretation of dose relationships in the integrated analysis was limited by the method of assigning patients to dose group. An attempt to look at possible dose-related trend in the dose escalation study S3100-1-01 could not be done as SBP and DBP in different dose groups in Study S3100-1-01 was not presented in the clinical study report (CSR) of the study.

Second round evaluation of clinical data submitted in response to questions

Sponsor's response: The sponsor assessed the SBP and DBP measurements from Study S3100-1-01, a Phase I, open-label, uncontrolled, dose escalation safety and PK study with dose expansion at the tolerated doses for patients with progressive CRPC, both pre- and post-chemotherapy.

In this study, the dose of any individual patient could have changed after week 13 (as described in the study report). Therefore, analyses of SBP and DBP measurements, as requested by the TGA, have been conducted from baseline through Week 13 of enzalutamide treatment. As pre-specified in the protocol, only a small number of patients were included in each dose group during this study. A summary of the mean change in BP measurements is presented by dose groups in Table 4.

Table 4: Mean change in systolic and diastolic blood pressure measurements from Baseline to Week 13

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

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

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

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of enzalutamide in the proposed usage are unchanged from those identified under *First round assessment of benefits*, above.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of enzalutamide in the proposed usage are unchanged from those identified under *First round assessment of risks*, above.

Second round assessment of benefit-risk balance

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

Second round recommendation regarding authorisation

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

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU-RMP Version 4.0, dated 25th April 2013 with an Australian Specific Annex Version 1.0, dated 23rd May 2013 which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 5.

Table 5: Important identified risks, potential risks and areas of missing information

Safety concerns	
Important Identified Risks	Seizures Hypertension Falls Hallucination Neutrophil count decreased Non-pathologic fracture Interactions with strong inhibitors or inducers of CYP2C8 Interactions with medicinal products that are substrates of CYP3A4, CYP2C9 or CYP2C19
Important Potential Risks	Cognitive/memory impairment
Important Missing Information	Patients with severe renal impairment Patients with moderate or severe hepatic impairment Reproduction/fertility Patients of non-White race Patients with ECOG PS \geq 2 Patients with severe cardiovascular disease Patients with brain metastases or with baseline

Safety concerns	
	<p>factors predisposing for seizure</p> <p>Patients with metastatic castration-resistant prostate cancer previously treated with abiraterone acetate.</p>

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for all important identified and potential risks and missing information.

Additional pharmacovigilance activities, comprising 3 clinical studies, are planned to further elucidate the risks of seizure, severe hepatic impairment and moderate hepatic impairment, respectively. There is an additional planned study proposed described by the sponsor as *“a post-authorisation efficacy study to collect data on the efficacy and safety of enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with abiraterone acetate”*.

Risk minimisation activities

Sponsor’s conclusion in regard to the need for risk minimisation activities

The sponsor makes the following statement in the RMP regarding the need for risk minimisation activities: *“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.”*

OPR reviewer comment: The sponsor’s conclusion is acceptable and is consistent with other drugs of similar indication.

Planned actions

The sponsor proposes routine pharmacovigilance and risk minimisation activities for all important identified risks and important potential risks and important areas of missing information.

Reconciliation of issues outlined in the RMP report

This section summarise the recommendations in 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 in RMP evaluation report

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated TGA request for information and/or the nonclinical and clinical evaluation reports. 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, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

Sponsor’s response

The sponsor will provide the information as requested.

OPR evaluator's comment

This is acceptable.

Recommendation in RMP evaluation report

The TGA appreciates the sponsor supplying the evaluation reports from the US. To further assist the evaluation process, it would be appreciated if the sponsor could also consider providing the full evaluation reports from Canada and the EU.

Sponsor's response

The full evaluation reports from Canada and the EU are provided.

Of note, for the Australian RMP, the sponsor proposed not to include 'moderate hepatic impairment' as Important Missing Information and to include only severe hepatic impairment. The PK of enzalutamide were examined in subjects with baseline mild or moderate hepatic impairment (Child-Pugh Class A and B, respectively) and no dose adjustment is necessary for this patient population. The revised *Hepatic impairment* section in the *Precautions* [section of the PI] provides appropriate guidance for the use of enzalutamide in patients with moderate or severe hepatic impairment.

OPR evaluator's comment

The EU-RMP includes 'moderate hepatic impairment' as Important Missing Information. The OPR accepts the EU-RMP with ASA.

Recommendation in RMP evaluation report

The "use of concomitant QT interval prolonging medication" should be added as important missing information.

Sponsor's response

The clinical findings suggest that enzalutamide is not associated with an increased risk of QT prolongation. Patients on concomitant QT interval prolonging medications were excluded from the Phase III trial as is standard for studies including a thorough ECG assessment. Inclusion of these patients could potentially have limited the ability to detect a treatment effect on QT prolongation; they were not excluded due to a potential safety concern. The available data from Study CRPC2, based on the results of a comprehensive ECG (in triplicate) evaluation analysed by a validated ECG core laboratory, do not suggest that enzalutamide is associated with clinically meaningful effects on QTcF²⁰, including predicted changes in QTcF at maximum concentrations of enzalutamide and the active metabolite, M2.

In Study CRPC2, there were few placebo corrected mean changes from baseline in QTcF greater than the clinically relevant increase of 5 ms; however, for the increases at these time points and the analyses of predicted QTcF changes at C_{max}, the upper bound of the CI did not exceed 10 ms. Therefore these increases are not considered clinically meaningful. In addition, there were no AEs of torsade de pointes and no difference between treatment groups in the frequencies of AEs that were potentially related to torsade de pointes/QT prolongation.

Although hERG inhibition was demonstrated (using hERG-expressing human embryonic kidney [HEK] cells), the sponsor considers this to be of little pharmacological significance at the therapeutic plasma levels of enzalutamide and the active metabolite, M2 in patients. The sponsor does not consider the use of enzalutamide in patients taking medications known to prolong QT interval as meaningful missing information, and therefore not appropriate to include in the RMP.

²⁰ QTc Fridericia's correction

OPR evaluator's comment

This is acceptable.

Recommendation in RMP evaluation report

"Atrial fibrillation" should be included as an important identified risk. As stated by the sponsor in the RMP: "*Compared to enzalutamide-treated patients younger than 75 years, enzalutamide-treated patients 75 years and older were more likely to experience atrial fibrillation...*". Considering the serious nature of atrial fibrillation (including risk of death) and the substantial proportion of prostate cancer diagnosis in men aged over 75 years, it is reasonable to include this as an ongoing safety concern.

Sponsor's response

The sponsor does not agree with adding atrial fibrillation (AF) as an identified risk based on the information stated in the RMP. In the general population, the risk factors for AF include advancing age, European ancestry, body size, electrocardiography features like left ventricular hypertrophy, diabetes, hypertension, cardiovascular disease, hyperthyroidism, chronic kidney disease, heavy alcohol consumption, and family history (Go et al., 2013²¹). In the general practice setting in Australia, AF patients are disproportionately older and male (Fahrudin et al., 2007²²). This observation is consistent with the inpatient setting.

Based on the analyses from Australian National Hospital Morbidity Dataset, the rates of hospitalisations with a principal diagnosis of AF were 140 per 10,000 males > 80 years of age, 110 per 10,000 males 70 to 79 years of age, 75 per 10,000 males 60 to 69 years of age, and 35 per 10,000 males < 60 years of age in 2007 (Wong et al., 2012²³). Data from the rest of the world consistently show that the incidence rates of AF are higher in males and increase with age (Jensen et al., 2013²⁴; Piccini et al., 2012²⁵; Stefansdottir et al., 2011²⁶).

Age is also a risk factor for AF in the CRPC2 Study population. The incidence rates of AF are higher in patients aged ≥ 75 years compared to patients aged < 75 years in both the enzalutamide arm (2.5% versus 0.7%) and the placebo arm (1.9% versus 1.0%). Other known risk factors for AF were also common in patients treated with enzalutamide, such as history of cardiovascular disease (18.1%) and history of hypertension (55.5%). Overall, the incidence rate of treatment-emergent AF is lower in the enzalutamide arm compared to the placebo arm (1.1% versus 1.3%); thus, treatment-emergent AF is not a risk associated with enzalutamide treatment.

Of note, the majority of the reported treatment-emergent AF events were Grade 1 or 2 in both the enzalutamide arm (3 Grade 1, 4 Grade 2, 2 Grade 3) and the placebo arm (4 Grade 1, 1 Grade 2). Furthermore, the incidence rate of all cardiac disorders is lower in the enzalutamide arm compared to the placebo arm (6.1% versus 7.5%).

In summary, data from the randomised Phase III CRPC2 Study do not support adding AF as an identified risk for enzalutamide.

²¹ Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics-2013 update: a report from the American Heart Association. *Circulation*. 2013;127:e6-e245.

²² Fahrudin S, Charles J, Miller G. Atrial fibrillation in Australian general practice. *Aust Fam Physician*. 2007;36:490-1.

²³ Wong CX, Brooks AG, Lau DH, Leong DP, Sun MT, Sullivan T, et al. Factors associated with the epidemic of hospitalizations due to atrial fibrillation. *Am J Cardiol*. 2012;110:1496-9.

²⁴ Jensen PN, Thacker EL, Dublin S, Psaty BM, Heckbert SR. Racial differences in the incidence of and risk factors for atrial fibrillation in older adults: the cardiovascular health study. *J Am Geriatr Soc*. 2013;61:276-80.

²⁵ Piccini JP, Hammill BG, Sinner MF, Jensen PN, Hernandez AF, Heckbert SR, et al. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries: 1993 -2007. *Circ Cardiovasc Qual Outcomes*. 2012;5:85-93.

²⁶ Stefansdottir H, Aspelund T, Gudnason V, Arnar DO. Trends in the incidence and prevalence of atrial fibrillation in Iceland and future projections. *Europace*. 2011;13:1110-17.

OPR evaluator's comment

This is acceptable.

Recommendation in RMP evaluation report

It is recommended that the sponsor provide the full study protocol for the “*post- authorisation efficacy study to collect data on the efficacy and safety of enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with abiraterone acetate*”.

Sponsor's response

A copy of the requested Study 9875-CL-0410 Protocol is provided.

OPR evaluator's comment

This is acceptable.

Recommendation in RMP evaluation report

Subject to the review of the full study protocol, the pharmacovigilance plan does not appear adequate to further elucidate the ongoing safety concerns associated with enzalutamide. It is recommended that the sponsor consider an Australian safety study or registry. It is anticipated that advice will be sought from the Advisory Committee on the Safety of Medicines (ACSOM) regarding the adequacy of the pharmacovigilance plan and suggestion of an Australian based study.

Sponsor's response

The sponsor has completed 2 clinical trials with enzalutamide in Australia at 39 sites in 325 patients. There are currently 2 studies enrolling patients in Australia, with a total of 32 sites and planned enrollment of 172 patients. Due to this significant participation by Australian patients and the similar racial group demographic between Australia and the US, the sponsor does not believe that an Australian based study is warranted.

OPR evaluator's comment

This is acceptable.

Recommendation in RMP evaluation report

The sponsor should update RMP sections III.4.1 and III.4.2 with the post marketing requirement requests from the FDA.

Sponsor's response

The sponsor agrees to include the following information [reproduced in part]:

III.4.1 Imposed Mandatory Additional Pharmacovigilance Activity, and III.4.2 Mandatory Additional Pharmacovigilance Activity:

- Perform an in vitro screen to determine if N-desmethyl enzalutamide is metabolised by the major human CYP450 isozymes. Based on results from the in vitro screen, clinical drug-drug interaction trials may be needed.
- Convene a panel of experts in oncology and neurology to obtain recommendations regarding which patients, if any, who were excluded from the randomised clinical trial because of increased risk of seizure should be evaluated in a post marketing safety trial. Following the panel's recommendations, conduct a single-arm safety trial to assess the risk of seizure with enzalutamide 160 mg/day in at least 350 patients with metastatic castrate-resistant prostate cancer who are at increased risk for seizure.

- Conduct a clinical trial in patients with normal hepatic function and patients with pre-existing severe hepatic impairment to assess the effect of severe hepatic impairment on the PK of enzalutamide and N-desmethyl enzalutamide.
- Conduct a drug interaction trial to evaluate the effect of rifampin (a strong CYP3A inducer and a moderate CYP2C8 inducer) on the PK of enzalutamide and N-desmethyl enzalutamide.
- Conduct a drug interaction trial to evaluate the effect of enzalutamide at steady state on the PK of CYP2D6 substrates.
- Conduct a drug interaction trial to evaluate the effect of enzalutamide at steady state on the PK of CYP1A2 substrates.

OPR evaluator's comment

This is acceptable.

Recommendation in RMP evaluation report

Recommendations were made in relation to revisions to product literature (PI and Consumer Medicine Information, CMI) with regards to proposed routine risk minimisation activities. Details of these are beyond the scope of the AusPAR.

Summary and recommendations**Outstanding issues**

There are no outstanding issues in relation to the RMP for this submission.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

Ratified advice from the ACSOM Meeting Number 21 was pending and would be provided to the Delegate prior to this application being finalised.

Comments on the safety specification of the RMP***Clinical evaluation report***

The clinical evaluator made the following statement regarding the safety specification of the RMP: *"The Safety Specification in the draft Risk Management Plan is satisfactory."*

Nonclinical evaluation report

The nonclinical evaluator made the following comment on the safety specification of the RMP in the first round report:

There are some notable differences in the interpretation of the toxicity data for enzalutamide between the TGA nonclinical evaluator and the results and conclusions detailed in the sponsor's draft RMP.

- In contrast to what is stated in the *Nonclinical Safety Specification*, some inhibition of OATP1B1 by M1 was seen at clinically relevant concentrations and interactions involving this transporter cannot be excluded. The *Nonclinical Safety Specification* should be amended to reflect this.
- In Section SII.1.2. Pro-convulsive Potential, it is stated *"enzalutamide causes dose-dependent convulsions in mice. The plasma exposures (C_{max} and AUC_{24h}) for doses that are associated with convulsions in mice (200 mg/kg) are at least 3.3 fold higher than plasma exposures in patients receiving 160 mg/day enzalutamide."* The safety margin

for convulsions is overstated. The minimum plasma concentrations of enzalutamide and M2 in mice with convulsions were similar to the clinical C_{max} value of enzalutamide and 50% of the clinical C_{max} of M2. The text should be amended accordingly.

The sponsor acknowledged that an interaction at OATP1B1 cannot be dismissed and modified the Nonclinical Safety Specification of the RMP accordingly.

With regard to *Pro-convulsive Potential*, the sponsor stated that it is unclear how the nonclinical evaluator came to the conclusion “*The minimum plasma concentrations of enzalutamide and M2 in mice with convulsions were similar to the clinical C_{max} value of enzalutamide and 50% of the clinical C_{max} of M2*”, claiming the exposure margin in the *Nonclinical Safety Specification* (3.3 for enzalutamide and ≤ 0.7 for M2) was extrapolated from data in single dose and 1 week repeat dose toxicity studies and no toxicokinetic data were collected in a safety pharmacology study (Study 9785-PT-0005). The nonclinical evaluator considered the latter statement was not correct. While no toxicokinetic data were reported in Study 9785-PT-0005, levels of enzalutamide, M1 and M2 were determined in plasma and brain samples from these animals at the time of convulsions with data reported in Study 9785-ME-5016. The minimum plasma concentration of enzalutamide and M2 in mice with convulsions was 20.6 µg/mL and about 6 µg/mL, respectively (from individual data of the report for Study 9785-ME-5016). These values are approximately equivalent to the clinical C_{max} for enzalutamide (which is 16.6 µg/mL) and approximately 50% of the clinical C_{max} for M2 (which is 12.7 µg/mL). Therefore, the exposure margins calculated by the nonclinical evaluator are considered correct. For convulsant activity, C_{max} is considered a better comparator than AUC. Therefore, the nonclinical evaluator recommended this section of the *Nonclinical Safety Specification* in the RMP should be amended accordingly.

Suggested condition of registration

- Implement EU-RMP Version 4.0, dated 25th April 2013 with Australian Specific Annex Version 1.0, dated 23rd May 2013 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:

Introduction

Castration resistant prostate cancer is defined as disease progression despite androgen depletion therapy (ADT²⁷) and may present as either a continuous rise in PSA levels, the progression of pre-existing disease, and/or the appearance of new metastases. Thus it represents a spectrum of disease ranging from asymptomatic patients without metastases with rising PSA levels despite ADT, to those with metastases and significant debilitation due to cancer symptoms. The median survival of patients with CRPC is approximately 18-24 months.

²⁷ Androgen-deprivation therapies include surgical castration or medical therapy with GnRH analogues, anti-androgens (such as bicalutamide, flutamide, and nilutamide), androgen synthesis blockers (e.g. abiraterone, ketoconazole; the latter is no longer available for this indication in Australia), and/or oestrogenic compounds.

The management of all patients with CRPC, including those without overt metastases, follows the same treatment algorithm aiming to prolong survival, minimise complications and maintain quality of life.

There are three pharmaceutical agents approved for the treatment of CRPC in Australia with a demonstrated survival advantage: docetaxel with prednisone as front-line chemotherapy; once patients progress on docetaxel and require second-line therapy, the options included cabazitaxel plus prednisone or abiraterone plus prednisone. Cabazitaxel is a taxane administered IV, with potential side effects of febrile neutropenia, and serious gastrointestinal side effects including diarrhoea. Abiraterone is an oral inhibitor of androgen biosynthesis and treatment requires the co-administration of prednisone, with potential side effects of mineralocorticoid excess (hypertension, hypokalaemia, and fluid overload), hepatotoxicity, and adrenal insufficiency.

Other novel approaches include immunotherapies such as sipuleucel-T dendritic cell vaccine, the anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) monoclonal antibody ipilimumab, anti-programmed death 1 (anti-PD1) or anti-PD1 ligand monoclonal antibodies and the PROSTVAC-VF vaccine against the PSA gene. These agents are in the development phase.

Enzalutamide is an orally administered, potent AR signalling inhibitor that blocks several steps in the AR signalling pathway: binding to the AR, nuclear translocation of the activated receptor, and association of the translocated receptor with nuclear DNA. In nonclinical studies, enzalutamide treatment decreased the growth of prostate cancer cells. Enzalutamide, by targeting the AR signalling pathway, has a novel mechanism of action with the potential to overcome resistance (especially that mediated by up-regulation of the AR) to androgen-deprivation therapy.

Quality

Registration is recommended with respect to quality and biopharmaceutic aspects if appropriate controls on impurities in the excipient are negotiated (see *Quality findings*, above, for details).

Nonclinical

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

Enzalutamide was a competitive inhibitor at the wild-type AR and its castration-resistant mutant variants, T877A and W741C. No agonistic activity was detectable at the AR. One major human metabolite, M2, also had inhibitory activity at the AR and is likely to contribute significantly to the efficacy of enzalutamide in patients. Decreased tumour growth was seen in a mouse model bearing a castration-resistant prostate cancer cell line.

Both enzalutamide and M2 had significant inhibitory activity at the GABA gated chloride channel and readily crossed the blood-brain barrier with concentrations similar to those seen in plasma. Convulsions occurred in both mice and dogs with plasma concentrations of enzalutamide similar to or marginally above the clinical C_{max}.

Both enzalutamide and M2 inhibited the hERG K⁺ tail current. Insufficient data were provided to exclude a potential for QT prolongation during clinical use.

Respiratory distress was a contributing factor in the deaths of a number of animals. The respiratory effects are partly due to reflux and inadvertent aspiration with a consequent local irritation effect of enzalutamide/Labrasol. The NOEL for respiratory effects is at least

7 times the clinical dose. The likelihood of respiratory effects in patients is low provided the capsules are taken as directed and not chewed or broken prior to swallowing.

Oral absorption was high in rats and dogs. CYP3A4, 3A5 and 2C8 appear to be involved in the formation of M2.

In vitro studies indicated a number of potential PK drug interaction possibilities:

- Inhibitors or inducers of CYP3A4/5 and 2C8 are likely to alter the plasma kinetics of enzalutamide.
- Enzalutamide is likely to decrease the exposure of drugs that are metabolised by CYP3A4, 2C9, 2C19 or UGTs (also based on in vivo human data).
- Enzalutamide has the potential to alter the disposition of drugs that are substrates of P-glycoprotein. An effect on substrates of BCRP, OATP1B1, OCT1 or OAT3 cannot be excluded.

Enzalutamide was not genotoxic in the standard battery of tests. No carcinogenicity studies were submitted, which is considered acceptable. Teratogenicity and embryofetal lethality in mice were evident at low relative doses.

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.

Clinical

The clinical evaluator has reviewed the submitted data, which included:

- 5 clinical pharmacology studies, including 5 that provided PK data.
- 5 population PK analyses.
- 1 pivotal efficacy/safety studies (AFFIRM study [CRPC2]).
- 1 dose-finding study (Study S-3100-1-01).
- 2 other efficacy/safety studies (Study S-3100-1-01 and Study CRPC-MDA-1).
- Statistical Analysis Plan for the SCS; which includes integrated safety results across studies).

The submission did not include paediatric data.

The submitted data was evaluated using TGA adopted EMA Guidelines as follows:

Guideline on the evaluation of anticancer medicinal products in man Points to consider on application with 1. Meta-analyses; 2. One pivotal study.

Additional sources and references considered by the Delegate:

- Joelle El-Amm, MD, Jeanny B. Aragon-Ching. The changing landscape in the treatment of metastatic castration-resistant prostate cancer. *Ther Adv Med Oncol*. 2013;5:25-40.
- <www.uptodate.com> [website on evidence-based clinical decision support resource, for healthcare practitioners]
- Saad, F, Hotte, S.J. Guidelines for the Management of castrate-resistant prostate cancer. *Can Urol Assoc J* 2010;4(16);380-4
- Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone:

recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 2008;26:1148-59.

- Caffo O, Gernone A, Ortega C et al. Central nervous system metastases from castration-resistant prostate cancer in the docetaxel era. *J. Neuro-oncol.* 2012;107:191–196.
- <<http://www.nsa.org.au/documents/item/48>> Brain Tumours and Driving a guide for clinicians [Brochure prepared for use by medical professionals].

Pharmacokinetics/pharmacodynamics

Absorption

Enzalutamide is a small molecule that has no ionic forms over the physiologic pH range with low solubility and high permeability. It is absorbed rapidly after oral administration, with a T_{max} of 1.75 h after a single dose of 160 mg. An absolute oral bioavailability study was not conducted as an IV formulation of enzalutamide for humans was not available because of its limited aqueous solubility. PK data from animals support the high oral bioavailability estimated from the ¹⁴C human mass balance study (≥ 84.2%), with 71% excreted in the urine as mostly unchanged parent compound, confirming that this is the minimum absorbed.

Results showed that a high fat meal reduced the rate of enzalutamide absorption (C_{max} reduced by 30%; T_{max} 1 h later) but that the extent of absorption was unaffected (adjusted geometric mean ratios for AUC_{0-t} and AUC_{0-∞} 99.61% and 98.98%, respectively). Thus enzalutamide liquid-filled capsules can be taken with or without food: this is included in the PI and the clinical trials doses were taken without regard to food intake.

There was no major deviation from dose proportionality or linearity after single or multiple dose administration over the dose range of 30 to 600 mg.

The mean apparent volume of distribution (V/F) in healthy subjects ranged between 62.7 to 117 L. Results of the hepatic impairment study (9785-CL-0009) indicated that enzalutamide and its metabolites M1 and M2 were highly bound to plasma proteins. The protein binding, irrespective of hepatic function, was 98%, 98%, and 96% for enzalutamide, M1, and M2, respectively. A red blood cell partitioning study indirectly indicated that the radioactivity (enzalutamide) was preferentially retained in the plasma component of blood.

Metabolism

Sites of metabolism and mechanisms/enzyme systems involved:

- A total of seven Phase I metabolites were identified in plasma, urine, and faeces of healthy subjects. These were formed via demethylation, oxidation, and hydrolysis reactions. No Phase II conjugation products were observed. Metabolites M1 (inactive; a carboxylic acid derivative) and M2 (active; N-desmethyl enzalutamide) were the major metabolites in plasma.
- The major ¹⁴C components in plasma were parent compound enzalutamide, M1 (inactive), and M2 (active). The main component in urine was M1 (62.7% of radioactive dose), with small amounts detected of inactive metabolites in faeces.
- In-vitro studies showed that enzalutamide was metabolised by CYP2C8 and CYP3A4/5, all of which played a role in the formation of the active metabolite. A clinical drug-drug interaction study in healthy volunteers (Study 9785-CL-0006) showed that CYP2C8 played an important role in the metabolism of enzalutamide and the formation of M2. In the presence of a strong CYP2C8 inhibitor (gemfibrozil) plasma exposure to enzalutamide increased by 4.26 fold, while M2 exposure decreased by 25%. The same study also showed that CYP3A4 played a minor role in the metabolism

of enzalutamide. The exposure of enzalutamide and its metabolites (M1 and M2) were increased by no more than 41% in the presence of a strong CYP3A4 inhibitor (itraconazole).

Pharmacokinetics of metabolites

After a single 160 mg dose of enzalutamide in healthy subjects, metabolites M1 and M2 were formed slowly (median T_{max} of 96 and 132 h post-dose for M1 and M2, respectively) and eliminated with a mean t_{1/2} of 223 and 186 h, respectively. There were no significant changes in exposures to M1 and M2 when enzalutamide was administered with food.

Excretion

Routes and mechanisms of excretion

In the radiolabel mass balance study, a mean of 84.6% of the orally administered dose (75.4% to 92.0% in individual subjects) was recovered through Day 77 post-dose: 71.0% was recovered in urine (primarily as M1, with trace amount of enzalutamide and M2), and 13.6% was recovered in faeces (0.39% of dose as unchanged parent enzalutamide). Based on this result, renal excretion is a minor elimination pathway for unchanged parent enzalutamide and the active metabolite M2.

The averaged mean apparent clearance (CL/F) of enzalutamide was between 0.596 to 0.753 L/h in healthy subjects. The mean t_{1/2} of enzalutamide in healthy subjects was 2.9 to 4.8 days. The mean t_{1/2} for M1 and M2 in healthy subjects ranged from 7.8 to 9.3 days, and 7.5 to 8.8 days respectively.

Intra- and inter-individual variability of pharmacokinetics

In Study 9785-CL-0001 (healthy subjects; single dose), the exposure variability was low (AUC_{0-∞}), and in Study 9785-CL-0007 (CRPC patients; multiple dose) inter-subject variability (AUC_{tau}, C_{min} and C_{max}) was also low.

Pharmacokinetics in the target population

Results in Study S-3100-1-01 showed that oral absorption of enzalutamide in patients with CRPC was rapid across dose range of 30 mg to 600 mg, when administered as single or multiple doses, with peak concentrations of enzalutamide achieved in about 1 to 2 h post-dose. The mean V/F of enzalutamide in CRPC patients was 110 L indicating extensive extravascular distribution. The mean CL/F of enzalutamide in CRPC patients across combined doses of 30 mg to 600 mg was 0.564 L/h after single dose and 0.614 L/h after multiple dosing, or approximately 1% of the liver plasma flow rate (48.7 L/h), suggesting that enzalutamide is a low extraction ratio drug. The mean t_{1/2} of enzalutamide in CRPC patients was 139.6 h (5.8 days) after a single dose. The t_{1/2} did not appear to be affected by dose, and it took approximately 1 month to reach steady state, with daily administration.

Due to its slow clearance from plasma, the daily fluctuations in steady-state enzalutamide concentrations after multiple dosing were low.

Pharmacokinetic interactions

Hepatic impairment

The PK of enzalutamide were examined in subjects with baseline mild (n = 6) or moderate (n = 8) hepatic impairment. It is noted that the patients with “moderate” hepatic impairment did not have significant synthesis dysfunction and therefore may not be fully representative of this population. The modest increased exposure of enzalutamide may be an underestimate for patients with a greater degree of impairment still classified as moderate (no dose adjustment advised). Those with severe hepatic dysfunction were excluded from clinical trials. The PI contains information about a potentially larger effect where there is more significant dysfunction.

Renal impairment

No formal renal impairment study for enzalutamide had been conducted. Based on the results of a population PK analysis (icon2147014) which showed that CrCL (≥ 30 mL/min estimated by the Cockcroft and Gault formula) did not have clinically meaningful influence on the exposures to enzalutamide, no dose adjustment was considered necessary for patients with CrCl values ≥ 30 mL/min. Patients with CrCl < 30 mL/min were excluded from clinical studies.

Gemfibrozil (potent CYP2C8 inhibitor) and itraconazole (potent CYP3A4 inhibitor)

After multiple oral doses of gemfibrozil, and subsequent modelling and simulation in a population PK study (Study 9785-PK-0002) there was a 1.39 fold (AUC_{0-432h}) and 2.17 fold ($AUC_{0-\infty}$) increase respectively in of the sum of enzalutamide and M2. The potent CYP3A4 inhibitor itraconazole resulted in a 28% increases in the sum of enzalutamide and M2, respectively. These results suggest that CYP2C8 plays a more important role in the metabolism of enzalutamide and the formation of M2, compared with CYP3A4.

Delegate's comment: appropriate prescribing advice is included in the PI regarding dose adjustments of enzalutamide if use of strong CYP2C8 inhibitors (such as gemfibrozil). The advice is extrapolated to avoid inducers (such as rifampicin) but there are no data to demonstrate the effects or whether a higher enzalutamide dose is required with concomitant inducers to avoid loss of efficacy. The PD dose selection studies showed a PSA decrease of 59.3% at enzalutamide 60 mg/day and of 66.7% at 150 mg/day. Thus, any dose adjustment would depend on the observed metabolism of both the parent and active metabolite. In response to this Overview, the sponsor was requested to advise whether such a study has been performed (and if so, provide the results) or is planned (see *Questions for the sponsor*, below).

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

Study 9785-CL-0007 showed that enzalutamide is a strong inducer of CYP3A4, and moderate inducer of CYP2C9 and CYP2C19. After a single oral dose of 2 mg midazolam in the presence of 160 mg enzalutamide at steady state, AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} of CYP3A4 substrate midazolam decreased by 86%, 86% and 77%, respectively, compared with administration of 2 mg midazolam alone. After a single oral dose of 10 mg warfarin in the presence of 160 mg enzalutamide at steady state, AUC_{0-t} and $AUC_{0-\infty}$ of CYP2C9 substrate S-warfarin decreased by 55% and 56%, respectively. After a single oral dose of 20 mg omeprazole in the presence of 160 mg enzalutamide at steady state, AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} of CYP2C19 substrate omeprazole decreased by 72% and 70%, and 62%, respectively.

Delegate's comment: The PI for enzalutamide includes the potential interactions with drugs which are substrates of CYP3A4, CYP2C9, and CYP2C19.

Pharmacodynamic effects

In Study CRPC-MDA-1, a single-centre (the US), single arm, open-label study of patients with metastatic progressive CRPC treated with oral enzalutamide (160 mg/day), immunohistochemistry for AR in bone marrow samples was performed and subcellular distribution of AR was recorded (membranous, cytosolic, nuclear, or combination). Paired baseline and Week 9 specimens were evaluable from 16 patients (26.7%): 5 patients who were PSA responders (defined by a $\geq 50\%$ reduction from baseline in PSA at Week 9) showed reduction in nuclear AR localisation and of 11 PSA non-responders, 2 showed reduction in nuclear AR localisation and 9 showed no change or increase in nuclear AR localisation.

Secondary pharmacodynamic effects

A population PK/PD model (Study report 9785-PK-0001) was developed to examine the effect of enzalutamide exposures on PSA concentrations, using data from Study S-3100-1-01. Results supported an enzalutamide effect of decreasing initial PSA concentrations, and slowing the rate of PSA concentration increase during treatment. Simulation results suggested that chemo-naïve patients appeared to have a greater treatment benefit than post-chemotherapy patients.

Dose selection

The 160 mg dose for the pivotal study was chosen after dose limiting toxicities (fatigue, seizures were observed > 240 mg daily (Phase I dose escalation Study S-3100-1-01). Efficacy (no progression by any means: PSA, radiographic, or clinical at 24 weeks) was shown to be similar for the 150 mg/day dose and 240 mg/day cohort. There was a dose-dependent improvement in the number achieving > 50% decrease in PSA, but not beyond 150 mg daily.

Based on a 40 mg capsule formulation, a dose of 160 mg/day was selected for the CRPC2 Study.

Efficacy

Study CRPC2 was a multi-centre (156 sites, 15 countries in North & South America, Europe, Australia, and South Africa), randomised, double-blind, placebo controlled, Phase III study evaluating the efficacy and safety of 160 mg daily of enzalutamide in patients with progressive CRPC who had been previously treated with 1 or 2 chemotherapy regimens, at least 1 of which was docetaxel-based. Subjects were randomised stratified by baseline ECOG performance status score (0-1 versus 2) and baseline mean Brief Pain Inventory-Short Form Question #3 score. Patients were randomised 2:1 ratio to receive either enzalutamide (160 mg daily) or placebo until unacceptable toxicity, or confirmed disease progression and the patient was scheduled to initiate a new systemic antineoplastic therapy, death, or withdrawal. A QT/QTc evaluation was embedded into the study, in which all ECGs were read centrally at an ECG laboratory.

Progression was determined by radiological evidence of (> 2 new bone metastases on bone scan or soft tissue progression) or by occurrence of an adverse skeletal event. PSA progression was not a criterion to discontinue treatment. As per the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) guidelines, progression detected at the first scheduled reassessment at Week 13 required a confirmatory scan > 6 weeks later showing progressively worsening disease (for example, additional new lesions on bone scan) without study medication discontinuation in the interim. Study medication was not discontinued until there was confirmatory evidence and the patient was scheduled to initiate another systemic antineoplastic therapy.

Delegate's comment: the entry and exit criteria from the study differ in that patients were eligible to enrol with just a rising PSA (defined progressive disease for 41% enrolled in the study) but this was not used as a marker of progression to discontinue the study treatment. In response to this Overview, the sponsor was requested to provide a breakdown of the distribution of these patients in each arm and separately for those with no metastatic disease ever diagnosed (see *Questions for the sponsor*, below).

The primary objective was OS (death due to any cause) with enzalutamide versus placebo.

Secondary objectives included:

- radiographic PFS

- time to first skeletal-related event
- quality of life
- time to PSA progression
- pain palliation
- circulating tumour cell count conversion rate (data not submitted in this submission)
- safety
- ECG changes
- PK parameters, and to develop a PK model linking enzalutamide exposure with efficacy, safety outcomes.

Inclusion and exclusion criteria

Subjects enrolled in the study were men with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features, who had ongoing androgen deprivation therapy with a GnRH analogue or orchidectomy (that is, surgical or medical castration), with serum testosterone level < 1.7 nmol/L (50 ng/dL) at screening, who had progressive disease by rising PSA levels alone or imaging after docetaxel-based chemotherapy (median number 8 cycles was similar in both arms) in the setting of medical or surgical castration, and who had no more than 2 prior chemotherapy regimens with at least 1 regimen containing docetaxel.

Delegate's comment: It is not possible to establish from the reasons for discontinuing docetaxel how many discontinued docetaxel because of disease progression or toxicity while on active treatment. The CSR states that < 5% of patients in both arms had received fewer than 3 cycles of docetaxel, median number of cycles in both arms was approximately 8. The proposed indication is consistent for patients who have "previously received docetaxel" is consistent with this, that is, have been exposed to, rather than necessarily progressed on, docetaxel.

Key exclusion criteria were previous history of seizures/condition that might predispose to seizures, or who were taking medications known to lower the seizure threshold, as seizure had been identified as a potential enzalutamide associated safety signal in the Phase I Study S-3100-1-01. A full list of inclusion and exclusion criteria is presented in the CSR. Patients were eligible if they had a rising PSA, but this was not a criterion for judging progression.

The 3 main analysis population sets were: the Intent-To Treat (ITT) Population (all randomised patients did receive at least one dose); the Safety Population, defined as all randomised patients who had received at least 1 dose of study drug; and the PK Population, defined as all randomised patients who had received at least 1 dose of enzalutamide and had at least one enzalutamide, M1, or M2 plasma concentration result.

Delegate's comment: there is no Per Protocol patient population; therefore it is not possible to determine the proportion who received treatment as outlined in the protocol or to determine the availability of measurements of the variables.

Baseline demographic and disease characteristics were similar between the two groups: the majority of subjects were Caucasian, median age was 69.0 years in both groups, with 24.9% and 26.1% of patients ≥ 75 years old in the enzalutamide and placebo groups, respectively. The median time from initial diagnosis of prostate cancer to randomisation was 70.9 months, and 41% had PSA progression only at the time of enrolment and 59% had radiographic progression. 62.2% of patients entered the study with both bone and

soft tissue metastases, and 91.2% of patients entered the study with bone metastases. Prior therapy for prostate cancer was similar between treatment groups.

Delegate's comment: 8.8% of patients had CRPC defined by rising PSA alone, that is, did not have metastatic disease at the time of entry. In response to this Overview, the sponsor was requested to confirm the numbers who had never had metastatic disease; given these subjects have potentially both a better prognosis and a longer time to development of metastases (study definition of progression), the sponsor was requested to provide a breakdown of the distribution of these patients across the two arms (see *Questions for the sponsor*, below).

Results for the primary efficacy outcome

At the time of the data cut-off, 38.5% of patients in the enzalutamide group and 53.1% in the placebo group had died. The extrapolated median survival was 18.4 (17.3, estimate not met) months in the enzalutamide group, compared with 13.6 (11.3, 15.8) months in the placebo group ($p < 0.001$). The median time on the study drug was 8.3 months and 3 months for the placebo arm and at the cut-off 29.8% were still on enzalutamide compared with 4.8% on placebo. There was widespread use of other treatments by the whole study population following progression: 42% in the enzalutamide arm and 61.4% in the placebo arm received at least one additional treatment (See Table 6).

Table 6: Subsequent therapies to treat prostate cancer used in ≥ 2 patients: Intent-to-Treat Population

	Enzalutamide (n = 800)	Placebo (n = 399)
Number of Patients Taking at Least 1 Subsequent Therapy to Treat Prostate Cancer	336 (42.0%)	245 (61.4%)
All Other Therapeutic Products	32 (4.0%)	26 (6.5%)
Investigational drug (Undefined)	31 (3.9%)	26 (6.5%)
Antimycotics for Systemic Use	19 (2.4%)	19 (4.8%)
Ketoconazole	19 (2.4%)	19 (4.8%)
Antineoplastic Agents	180 (22.5%)	156 (39.1%)
Cabazitaxel	78 (9.8%)	55 (13.8%)
Docetaxel	68 (8.5%)	57 (14.3%)
Mitoxantrone	21 (2.6%)	32 (8.0%)
Carboplatin	23 (2.9%)	17 (4.3%)
Cyclophosphamide	16 (2.0%)	10 (2.5%)
Etoposide	15 (1.9%)	6 (1.5%)

	Enzalutamide (n = 800)	Placebo (n = 399)
Mitoxantrone hydrochloride	0 (0.0%)	12 (3.0%)
Paclitaxel	4 (0.5%)	4 (1.0%)
Vinorelbine	3 (0.4%)	4 (1.0%)
Cisplatin	5 (0.6%)	1 (0.3%)
Epirubicin	3 (0.4%)	1 (0.3%)
Doxorubicin	1 (0.1%)	2 (0.5%)
Estramustine phosphate	1 (0.1%)	2 (0.5%)
Fluorouracil	2 (0.3%)	1 (0.3%)
Ixabepilone	1 (0.1%)	1 (0.3%)
Corticosteroids for Systemic Use	11 (1.4%)	7 (1.8%)
Prednisone	8 (1.0%)	3 (0.8%)
Prednisolone	3 (0.4%)	2 (0.5%)
Budesonide	1 (0.1%)	1 (0.3%)
Hydrocortisone	0 (0.0%)	2 (0.5%)
Endocrine Therapy	179 (22.4%)	108 (27.1%)
Abiraterone acetate	167 (20.9%)	97 (24.3%)
Diethylstilbestrol	8 (1.0%)	10 (2.5%)
Bicalutamide	3 (0.4%)	4 (1.0%)
Flutamide	3 (0.4%)	1 (0.3%)
Nilutamide	1 (0.1%)	1 (0.3%)
Immunostimulants	2 (0.3%)	2 (0.5%)
Sipuleucel-T	2 (0.3%)	1 (0.3%)

The sponsor has stated that the agents known to prolong survival in CRPC were used more often in the placebo arm after progression and therefore that this would improve survival after study withdrawal for the placebo arm.

Delegate's comment: It is not possible from the combined information provided (Table 6, above) to determine the treatments received in each arm following progression, nor therefore any potential impact of these upon OS in the differing arms. In the response to this Overview, the sponsor was requested to provide this information (see *Questions for the sponsor*, below). The *Clinical Trials* section of the PI needs to state clearly that the median survival data are drawn from a combination of the study drug and potentially any other treatments received following progression.

As the cut-off date was September 2011, the actual median survivals are likely to have been reached for both groups, and the sponsor was also requested to provide these data (see *Questions for the sponsor*).

Results for other efficacy outcomes

Subgroup analyses on the primary efficacy endpoint

The hazard ratio CIs for death crossed 1 for 3 out of 4 subgroups, which were those with poorer prognoses upon study entry: lower ECOG score, visceral metastases and more heavily pre-treated with chemotherapy. The finding of uncertain benefit in those treated outside Europe and North America is difficult to interpret.

Delegate comment: a further confounding factor is that these patients are less likely to be fit for treatment with other agents following progression compared with the rest of the trial participants.

Key secondary endpoints

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

The CSR states that “the lack of follow-up beyond the date of the last study dose also contributed to the censoring of approximately 50% of patients in either arm.” For PSA follow-up, it is stated in the CER “*Patients who were not known to have had PSA progression were censored at date of last assessment showing no evidence of PSA progression*”. Therefore it is not possible to determine whether there has been a treatment effect on PSA levels as data are missing for half the patients in each arm. Given the extent of the missing data, any claims should be removed from the PI.

Delegate's comment: PSA is not recommended by the PCWG2 as a criterion for progression to define treatment failure but was allowed as an entry criterion to define progressive disease.

- Duration of radiographic PFS

At the cut-off, radiographic progression occurred in 49.9% and 61.7% of patients in the treatment arm, respectively. The reported median duration of radiographic PFS was 8.3 (95% CI 8.2, 9.4) in the treatment arm versus 2.9 (2.8, 3.4) months in the placebo arm; hazard ratio (95% CI) 0.404 (0.35, 0.466) p value < 0.0001.

Delegate's comment: The data included those who died without evidence of radiographic progression (15.6% in the treatment and 22.8% in the control arm). There is the potential for cases that died of other causes to be counted as progressing with this approach (for example, one patient in the control arm who underwent euthanasia). In response to this Overview, the sponsor was requested to present the radiographic progression-free data with 95% CI by excluding these subjects (see *Questions for the sponsor*, below).

- Skeletal-related events

Overall at the cut-off date, 35.9% patients in the enzalutamide group and 40.4% patients in the placebo group had a skeletal-related event. While the estimated median time to first skeletal-related events was reported to be delayed by 3 months (16.7 months (95% CI

14.6, 19.1) compared with 13.3 months (95% CI 9.9, estimate not met); hazard ratio 0.688 (0.566, 0.835) $p = 0.0001$), there was no upper limit presented for the placebo arm so statistical significance of this cannot be determined (see Comment below).

The use of other proven therapies in both arms following progression makes attribution difficult without further evaluation of the treatments received (see *Questions for the sponsor*, below).

The nature and seriousness of the events was the same in both arms but occurred at slightly higher rate in the treatment arm for spinal cord compression, pathological fracture and surgical bone interventions (see Table 7 below). These differences are likely to be as a consequence of surviving longer with widespread bony metastases and the reporting system (see *Safety* discussion below).

Table 7: Incidence and time to first skeletal-related event: Intent-to-Treat Population, Study CRPC2

	MDV3100 (n = 800)	Placebo (n = 399)
Status of Skeletal-Related Event Follow-Up		
Events	287 (35.9%)	161 (40.4%)
Radiation to bone	176 (61.3%)	101 (62.7%)
Surgery to bone	6 (2.1%)	1 (0.6%)
Pathologic bone fracture	31 (10.8%)	16 (9.9%)
Spinal cord compression	66 (23.0%)	29 (18.0%)
Change of antineoplastic therapy to treat bone pain	20 (7.0%)	16 (9.9%)
Censored observations	513 (64.1%)	238 (59.6%)
Time to First Skeletal-Related Event (months)		
Median (95% CI)	16.7 (14.6, 19.1)	13.3 (9.9, NM)
25%-75% percentile	7.5-21.6	3.7-NM
Stratified Analysis		
Hazard ratio (95% CI)	0.688 (0.566, 0.835)	
P-value (log-rank)	0.0001	

NOTE: Stratification factors used to derive log-rank p-value and hazard ratio were baseline ECOG performance status and mean Brief Pain Inventory – Short Form score (Question #3).
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; NM, estimate not met.

Delegate's comment: the 95% CI has not been presented for the median time to first skeletal-related event which could be expected to be reached before the treatment arm. Therefore it is not possible to determine the statistical significance of this finding. In response to this Overview, the sponsor was requested to provide this information and if the data are not available this claim should be removed from the *Clinical Trials* section of the PI.

The use of other therapies following progression needs to be mentioned in the paragraph about skeletal-related events in the *Clinical Trials* section of the PI. These findings suggest that as a consequence of extending survival, there is an overall increase in the serious AEs such as spinal cord compression, pathological fracture and orthopaedic surgical intervention. There may be overlap in reporting between the pathological fracture and spinal cord compression group and the surgical intervention group. In addition, there were 4 SAEs of cauda equine syndrome in the treatment group (none in placebo) and whether these were related to bony disease is unclear.

- Other secondary endpoints

Because of the large amount of data missing it was difficult to draw conclusions about the secondary endpoints QoL, PSA response rate, and pain palliation.

Baseline completion rate of the QoL questionnaire (FACT-P) was high in both arms, but 33.2% of the control arm and 14.1% did not complete a post-baseline assessment therefore it is difficult to draw any conclusions about influence of the treatment.

It is not possible to determine the level of data missing for PSA measurements as only the 'at least 1 post-baseline' measurement is presented and there is no Per Protocol population data presented to evaluate this further. PSA measurements were said to be missing for approximately half of the patients in each arm therefore assessments of nadir levels and responses are too limited. The number of patients evaluable for pain palliation in either arm (< 7%) was too low to draw any conclusions about treatment effect.

- Exploratory endpoints

Analyses on the quality of life over time using the EQ-5D were difficult to interpret due to the small sample size of evaluable patients and the large decrease in the number of patients completing the questionnaire over time.

Analyses on the ECOG performance status over time showed the median change in ECOG performance status was not different between the groups while in the study. As the subjects were not followed after progression and study drug discontinuation, the number evaluable drops rapidly especially in the placebo arm.

Other efficacy studies

Study S-3100-1-01 was a multi-centre (5 centres in the US), Phase I, open-label, uncontrolled, dose-escalation safety and PK study of enzalutamide with dose-expansion at the tolerated doses, in patients with CRPC. The primary objective was to determine the safety and tolerability profile of enzalutamide, including the dose limiting toxicities, and the maximum tolerated dose when administered orally to patients with CRPC. Inclusion and exclusion criteria were generally similar to those of Study CRPC2, except that previous docetaxel therapy was not required. Overall, 140 patients were enrolled and analysed: 96.4% were Caucasian, with an overall median age of 68 years.

Efficacy analyses included a description of the changes in PSA, disease progression on imaging, circulating tumour cell counts, and bone turnover markers (serum bone-specific alkaline phosphatase [ALP] and urinary N-telopeptide).

In Study S-3100-1-01, the proportion of patients whose best overall radiographic response was partial or stable was 61.6% in the overall study population. This proportion was 71.0% in patients without previous chemotherapy, and 54.8% in patients with previous chemotherapy. These are not comparable with the Phase III trial outcomes, but findings were generally supportive of the study drug having efficacy in the target population, and determining the optimal dose for the Phase III study.

Study CRPC-MDA-1

This was a single-centre (the US), single arm, open-label study of 60 patients with metastatic progressive CRPC treated with oral enzalutamide (160 mg/day) to evaluate the treatment effect on enzalutamide on the tumour micro-environment. In the absence of unacceptable toxicities, patients were treated until disease progression. Study inclusion and exclusion criteria were generally similar to those of Study CRPC2, except that previous docetaxel therapy was not part of the inclusion criteria. Full inclusion and exclusion criteria are provided in the study report. The demographic of the study population was similar to the other efficacy trials.

Primary objectives were AR signalling and expression of survival/resistance pathways in the bone marrow metastases of CRPC patients in correlation with measures of anti-tumour activity to identify predictors of response or resistance to therapy.

Secondary objectives included serum PSA levels, imaging of soft tissue and bone metastases, and markers of bone metabolism, safety and tolerability of treatment. The

study start date (first patient enrolled) was 18 February 2010 and the last-patient-enrolled date was 01 July 2011. The study was ongoing at the time of this submission. Data cut-off date for the CSR submitted was 26 August 2011.

93.3% were on study drug and participated in the study through the Week 9 visit assessments, and 22% were still on treatment at the cut-off. The median time to treatment discontinuation was 5.0 months. 41.1% and 21.4% of patients had $\geq 50\%$, and $\geq 90\%$ decreases from baseline at Week 9, respectively. It is difficult to determine the nadir based on 'at least one post-baseline visit' measurement and as there is no Per Protocol population, it is not possible to determine the number of patients with >1 measurement. Subgroup analyses of prior treatment effect are limited by the small numbers and lack of control arm.

Of the evaluable 5 PSA responders, all 5 showed reduction in nuclear AR localisation. Of the evaluable 11 PSA non-responders, 2 showed reduction in nuclear AR localisation and 9 showed no change or increase in nuclear AR localisation. Statistical correlation was not assessed due to low numbers of evaluable patients.

Efficacy summary

In the pivotal study, an earlier interim analysis after 520 deaths demonstrated a statistically significant improvement in the radiographic PFS (8.3 months versus 3 months, $p < 0.001$). This finding, although a secondary endpoint, is of clinical importance. Following progression, however, patients were free to commence other therapies and the study drug was discontinued once they commenced another systemic therapy. The extrapolated overall median survival was 18.4 (95% CI 17.4, estimate not met) versus 13.7 (11.3, 15.8) months ($p < 0.0001$), and given the median duration of therapy was defined by the radiographic PFS (that is, 8.3 months for the treatment arm), there was a median 12 month period of survival following cessation of the study drug, during which many commenced other therapies (41%) and therefore the impact of those other therapies upon the observed OS is uncertain. The sponsor was asked to provide the actual median OS values in the response to this Overview, as this is likely to have been reached by now.

While the median time to first skeletal-related events was reported to be delayed by 3 months (16.7 months compared with 13.3 months), the statistical significance of this finding cannot be determined until there is a 95% CI upper limit provided for the placebo arm. Any finding may not be solely attributed to enzalutamide due to the use of other proven therapies in both arms following progression.

The impact upon other factors including PSA progression, pain palliation and quality of life cannot be assessed due to significant levels of missing data.

Safety data

The following ongoing studies provided evaluable, interim safety data (1440 patients: 1041 (enzalutamide) and 399 (placebo); 923 at target dose of 160 mg daily):

- key safety analysis :Phase III CRPCS (1199 patients 160 mg versus placebo); median duration of exposure was 8.3 months, with 61.1% ≥ 6 months, 24.8% ≥ 12 months.
- integrated results for open-label, multi-dose Study S-3100-1-01, Study CPRC-MDA-1, 9785-CL-0007 with dose ranges of 30-600 mg; median enzalutamide exposure was 4.6 months, 37.0% ≥ 6 months, 23.3% ≥ 12 months.

The safety data from Study 9785-CL-0111 (a summary but not the actual report was provided for this study in Japanese subjects) was integrated with the studies above.

In the SCS, the sponsor also provided the safety results of 5 Phase I PK studies (9785-CL-0007, 9785-CL-0009, 9785-CL-0001, MDV3100-05, and 9785-CL-0006), as well as updated safety information (SAEs and deaths) for 2 ongoing Phase II open-label studies

(9785-CL-0121 [open-label extension of the drug-drug interaction Study 9785-CL-0007] and 9785-CL-0321 [open-label single-arm, efficacy and safety study in patients with hormone-naïve prostate cancer]).

The data were presented in a range of ways:

- by AEs occurring within the first 60 days to allow for the different durations of therapy
- as standardised event rates/100 patient-years to allow for the different reporting periods for each arm due to shorter treatment duration in the placebo
- as AEs by absolute or differential frequency rates between the arms, for example, > 2%
- as raw rates unadjusted by any of the above

Delegate's comment: in a population with significant background morbidity, the focus on the frequency of events somewhat dilutes other more important less frequent AEs, for example, seizures, anaphylaxis, cauda equina syndromes. The utility of examining the first 60 days for AEs related to a study drug with a 30-day steady state is limited as there will have only been a small window for clinical efficacy to become apparent and equally, to an underestimate of AEs attributable to the study drug.

Adverse events

In the pivotal trial, AEs occurring more frequently in enzalutamide treated patients than in placebo treated patients ($\geq 2\%$ absolute difference in event frequency) in Study CRPC2 are presented in Table 8:

Table 8: All Adverse Events occurring at a $\geq 2\%$ absolute difference in event frequency between treatment groups by Preferred Term: Safety population, Study CRPC2

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

The following AEs occurred with the greatest imbalance between the treatment arm and placebo: hot flushes (20.3% with enzalutamide versus 10.3% with placebo), headache (11.6% versus 5.5%), fatigue (33.6% versus 29.1%), diarrhoea (21.4% versus 17.5%), hypertension (6.1% versus 2.8%) and musculoskeletal pain (14.5% versus 11.5%). After correcting for the longer treatment duration, by assessing AEs starting within the first 60 days of treatment and the event rates/100 patient-years, hot flush, headache, and hypertension remained elevated in the treatment arm.

In Study S-3100-1-01, 9.8% at the 150/160 mg daily dose discontinued the study treatment due to an AE, most commonly fatigue (2.9%). The maximum tolerated dose of 240 mg/day was defined, based upon the occurrence of seizures at the 600 mg daily dose (2 cases), 480 mg daily (1 possible seizure), and 360 mg daily (1 case). Fatigue was the leading cause of dose reductions overall (7.9%). Overall, the most commonly reported SAE was fatigue (2.9%). There was no obvious dose-dependent trend in the incidences of the SAEs by preferred term.

Treatment-related adverse events (adverse drug reactions)

In the pivotal study, treatment-related AEs occurring at $\geq 1\%$ frequency and with an incidence at least 2% higher in the enzalutamide treated group than the placebo treated group were fatigue, hot flush, and headache (4.5% versus 2.3%).

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

In Study S3100-1-01, total treatment-related AEs were generally comparable among treatment dose groups, with the most commonly reported being fatigue (58.6%), nausea (32.9%) and anorexia (15.0%). In Study CRPC-MDA-1, the most commonly reported treatment-related AEs by preferred term were fatigue (40.0%), constipation (15.0%), anorexia (15.0%), and hot flushes (15.0%).

Deaths and other serious adverse events

In the pivotal study, AEs leading to death occurred in 2.9% and 3.5% in the enzalutamide and placebo groups, respectively) mostly due to infections (0.9% compared with 0.3% placebo) and general physical health deterioration (0.8% treatment compared with 1.3% placebo). There were no reported AEs leading to death reported in any of the 3 open-label studies.

Delegate's comment: it is unclear why "death" is listed as an AE leading to death.

A review of all SAEs in controlled and open-label studies (presented as serious TEAEs by the sponsor) included the following (numbers of patients in brackets): anaphylaxis (1), osteonecrosis of the jaw (2), acute leukaemia (1), acute myeloid leukaemia (1), cauda equine syndrome (4).

In the pivotal study, SAEs occurred at similar rates between treatment groups (33.5% and 38.6% in the enzalutamide and placebo groups, respectively) (see Table 9 below).

The most commonly reported SAE in the treatment arm was spinal cord compression (listed as occurring at rate of 6.0% compared with 3.8% with placebo in SAE list; 6.4% compared with 4.5% in first 60 days of treatment (in sponsor's summary); 9% compared with 7.7% in section on *Spinal Cord Compression and Pathological Fractures*, (in sponsor's overview). Additionally, there are 4 cases of cauda equine in the enzalutamide arm of CRPC2 which appear to have been reported separately as an SAE. In response to this Overview, the sponsor was requested to provide from all the different recording methods, a final total for all cases with spinal cord compression or cauda equina over the whole duration of the trial.

The sponsor had noted that in study CRPC2, skeletal-related events such as spinal cord compression and pathological fracture were not required to be reported as AEs unless

they met the criteria for an SAE. Instead, they were required to be reported on the skeletal-related event case report form (CRF), although many investigators also included them as AEs. This would mean that in only evaluating spinal cord compression and pathological fracture from the AE CRF, many non-serious AEs were not included. The sponsor did additional analyses looking at spinal cord compression and pathological fractures that occurred during the safety reporting period using data from the skeletal-related events CRF. Results showed that the imbalance between treatment groups was smaller (spinal cord compression: 8.3% with enzalutamide versus 7.3% with placebo; pathological fracture: 3.5% versus 3.8%). When the event rates for the AEs of spinal cord compression and pathological fracture were adjusted by AE reporting period, the event rates per 100 patient-years at risk were higher in the placebo treated group than in the enzalutamide treated group (spinal cord compression: 11.9 with enzalutamide versus 18.6; pathological fracture: 6.8 versus 9.1).

Table 9: Serious Adverse Events occurring in >1% patients in Any Treatment Group in Study CRPC2

System Organ Class Preferred Term	MDV3100 160 mg (n = 500)	Placebo (n = 399)
Number of Patients Reporting ≥ 1 Serious Adverse Event	268 (33.5%)	154 (38.6%)
Blood and Lymphatic System Disorders	25 (3.1%)	15 (3.8%)
Anemia	21 (2.6%)	12 (3.0%)
Gastrointestinal Disorders	31 (3.9%)	22 (5.5%)
Vomiting	2 (0.3%)	8 (2.0%)
General Disorders and Administration Site Conditions	32 (4.0%)	25 (6.3%)
General physical health deterioration	17 (2.1%)	8 (2.0%)
Pyrexia	2 (0.3%)	5 (1.3%)
Infections and Infestations	42 (5.3%)	23 (5.8%)
Pneumonia	13 (1.6%)	6 (1.5%)
Urinary tract infection	7 (0.9%)	5 (1.3%)
Musculoskeletal and Connective Tissue Disorders	52 (6.5%)	17 (4.3%)
Back pain	11 (1.4%)	7 (1.8%)
Pathological fracture	12 (1.5%)	2 (0.5%)
Bone pain	11 (1.4%)	4 (1.0%)
Neoplasms Benign, Malignant, and Unspecified (Incl Cysts and Polyps)	33 (4.1%)	21 (5.3%)
Metastatic pain	12 (1.5%)	3 (0.8%)
Cancer pain	8 (1.0%)	5 (1.3%)
Metastases to bone	1 (0.1%)	5 (1.3%)
Nervous System Disorders	89 (11.1%)	33 (8.3%)
Spinal cord compression	48 (6.0%)	15 (3.8%)
Nerve root compression	3 (0.4%)	4 (1.0%)
Renal and Urinary Disorders	35 (4.4%)	23 (5.8%)
Hematuria	12 (1.5%)	5 (1.3%)
Urinary retention	3 (0.4%)	8 (2.0%)
Respiratory, Thoracic, and Mediastinal Disorders	17 (2.1%)	10 (2.5%)
Pulmonary embolism	3 (0.4%)	4 (1.0%)

Note: Events with at least a 0.5% absolute higher incidence in enzalutamide treated patients than placebo patients are shown in bold

Delegate's comment: The Delegate believes that both the spinal cord compression rates (including the 4 cases of cauda equine syndrome) should have been reconciled between the CRFs for this analysis. Similarly, this should also have happened for the pathological fracture rates prior to the analysis by report period.

AEs of spinal cord compression and fracture were reported on a CRF for skeletal-related events and appear to have required a further CRF to be classified as an SAEs. It would therefore seem possible these cases may be recorded on the AE CRF and not the skeletal-related event CRF (and potentially vice-versa) as the sponsor states that spinal cord compression cases were not immediately an SAE "unless

they met the criteria for a serious adverse event” (sponsors summary), leading to two potentially non-overlapping datasets.

The Delegate considers all instances of spinal cord compression are an SAE, as this is an oncology emergency with a highly significant detrimental impact upon the patient’s quality of life and survival. The protocol defined an SAE as an event resulting in “persistent or significant disability/incapacity” or “required inpatient hospitalisation or prolongation of existing hospitalisation” so this appears to be a misclassification. There are also the 4 cases of cauda equina syndrome which appear as an SAE under the neurological AE term, but not skeletal-related events.

This dual CRF AE reporting system is likely to lead to difficulty determining the true rate of events, particularly when they are reported over differing timeframes within the trial.

The higher rate of SAEs with enzalutamide are most likely due to living longer with bony metastases, although treatment effects such as loss of bone density with long term ADT (with enzalutamide contributing) may be a factor. The incidence of spinal wedge compression factors supports this. The absolute number of cases with spinal cord compression needs to be reported for those on enzalutamide, as although this may not be a drug effect, the extended as this is important in forming a risk-benefit analysis of the decision to treat such patients.

Table 10: Spinal Cord Compression and Pathological Fracture in Study CRPC2

	Spinal Cord Compression		Pathological Fracture	
	MDV3100 (n = 800)	Placebo (n = 399)	MDV3100 (n = 800)	Placebo (n = 399)
Total Number of Events Reported as Skeletal-Related Events	72	31	41	15
Total Number of Patients with the Event Reported as a Skeletal-Related Event During the Treatment-Emergent Adverse Event Reporting Period	66 (8.3%)	29 (7.3%)	36 (4.5%)	15 (3.8%)
Events per 100 Patient-Years	11.9	18.6	6.8	9.1

Other significant SAEs are pain which was higher in the treatment arm (3.8% versus 3.1%). This is a significant problem with this malignancy, especially bone pain. The rates may be increased by the reporting time, however, it implies that enzalutamide may prolong OS, PFS and time to first skeletal event, but it does not lead necessarily to an improvement in pain.

Discontinuation due to adverse events

Study drug discontinuation in Study CRPC2 was lower in the enzalutamide group compared with the placebo group (7.6% versus 9.8%) and among enzalutamide treated subjects; fatigue was the most common cause (0.6% with enzalutamide versus 0.5% with placebo).

In the integrated studies S3100-1-01, CRPC-MDA-1, and 9785-CL-0111, the overall incidence of AEs leading to permanent study drug discontinuation was 9.3% in the other studies and a potential dose-dependent relationship was noted for fatigue (1.3%) and convulsion (1.3%) both of these events were occurred at >160 mg daily dose group.

Clinical laboratory tests

There appeared to be an association between treatment with enzalutamide and decreased leukocyte and neutrophil counts. An increase by more than two grades post-baseline for low leucocytes (4.6% versus 1.5%) and low neutrophils (3.6% versus 1.0%) and Grade 3 or 4 abnormalities were seen more commonly with enzalutamide compared with placebo: leucocytes (0.9% versus 0.3%) and low neutrophils (1.1% versus 0.0%). The sponsor reported that neutropenia did not underpin any SAEs in Study CRPC2, but was asked to

provide the neutrophil counts for those who died of infection (see *Questions for the sponsor*, below).

Treatment with enzalutamide did not appear to be associated with significant changes in liver function tests (LFTs) or in renal function tests compared with placebo.

Population PK analyses did not suggest that dose modification for mild or moderate renal impairment was required, nor for mild/moderate hepatic impairment. It was noted in the PK section that the patients with moderate hepatic impairment were at the less severe end of the moderate spectrum.

Electrocardiogram/cardiovascular safety

A QT/QTc substudy, conducted in accordance with ICH E14 guidelines²⁸, was embedded within Study CRPC2, and did not identify a safety signal for enzalutamide. As it would take 30 days for enzalutamide to reach steady-state, it would not be appropriate to conduct the study in a healthy volunteer population.

Results of a thorough QT/QTc study embedded in Study CRPC2 did not raise any safety concerns. However, there appeared to be an association of enzalutamide treatment with mild increases in BP. 6.1% (2.0% with Grade 3 severity) of patients in the pivotal trial on enzalutamide had an AE of hypertension compared with 2.8% of patients in the placebo group, with discontinuation in 0.1% of the treatment arm. When the event rates for the AE of hypertension were adjusted by AE reporting period, the event rates per 100 patient-years at risk remained higher in the enzalutamide group compared with the placebo group (8.4 versus 7.2).

Adverse events considered most important by the delegate

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

Given the occurrence of seizures and fatigue as dose limiting toxicities, and their clinical significance, the Delegate believes these should have been AEs of special interest for the pivotal study. The following occurred at higher rates when standardised against treatment reporting duration: seizures, falls, headache, hot flushes, visual hallucinations and hypertension.

Seizures

Based on the nonclinical data, seizures were a known potential toxicity of enzalutamide, and for all the clinical studies, having any conditions or taking any medications (including significant alcohol consumption) which might predispose to having a seizure were exclusion criteria. In the dose-finding study (Study S- 3100-1-01), seizures and fatigue were dose limiting: no seizures were reported at or below 240 mg per day dose, but there appeared to be a dose dependent effect above that level. The time to seizure was inversely proportional to the dose: 360 mg (Day 49), 480 mg (Day 28) and 600 mg (Day 27). These subjects discontinued the study treatment permanently following the seizure.

In total, 7 of 800 patients (0.9%) treated with 160 mg enzalutamide had a seizure (all 7 were considered SAEs) compared with no patients treated with placebo. Two patients had ongoing seizures, one with status epilepticus (see Table 11 below) and one with seizures over 2 days (this case was reported in the ongoing study and is not included in the Table below and no clinical details were available). Four patients had PK data available, and their enzalutamide minimum plasma concentrations (C_{min}) were in the upper two

²⁸ CHMP/ICH/2/04 ICH Topic E 14 *Note for Guidance on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*

quartiles. The treatment duration range prior to the seizure was Day 31-601 days. It is unclear whether subject 358-05 discontinued the study treatment.

Table 11: Summary of seizure cases, Study CRPC2

Dose/ Study Day	Relevant Medical History	Relevant Concomitant Medications	Seizure Type/ Witnessed	Verbatim Term/ Preferred Term	Potential Contributing Factors	Treatment/ Outcome
160 mg/ Day 52	--	--	Partial/ Yes	Focal Seizures associated with brain metastases/ Partial seizures	Brain metastases, low sodium level	Surgery, dexamethasone, levetiracetam; MDV3100 discontinued/ Resolved
160 mg/ Day 310	--	Intravenous lidocaine Propafenone	Convulsion/ Yes	Lidocaine- induced convulsion/ convulsion	Inadvertent administration of intravenous lidocaine	MDV3100 discontinued/ Resolved
160 mg/ Day 49	--	--	Complex Partial/ Yes	Confusion associated with complex partial status epilepticus/ Status epilepticus	--	Phenytoin, clonazepam, levetiracetam; MDV3100 discontinued/ Resolved
160 mg/ Day 152	--	--	Partial/ Yes	Focal seizure/ Partial seizure	Brain metastases	None/ Ongoing
160 mg/ Day 295	Alcoholism	Haloperidol	Convulsion/ No	Seizure/ Convulsion	Concomitant haloperidol, alcohol use	Haloperidol; MDV3100 discontinued/ Resolved
160 mg/ Day 31	--	--	Not reported/ Yes	Vasovagal syncope/syncope	--	Levetiracetam; MDV3100 discontinued/ Resolved

For the last patient in the list above the reported term was vasovagal syncope but with clinical features suggesting possible seizure activity

[Note: Table above has been modified from the original to remove patient identifier details.]

Delegate's comment: the range of study treatment duration does not suggest any particular at-risk window where seizures were most likely to happen to guide the prescriber or patient about the risk. The PK data are in too few patients to have predictive value. Two patients with seizures on enzalutamide had brain metastases (including 1 at Day 52). The incidence of brain metastases in CRPC is estimated to be 2.3%, and as treatments further prolong survival, this rate is likely to increase. Currently, the PI does not include information about the seizures nor the exclusion of patients with identifiable risk factors for seizures from the clinical trial development program. The seizure rates should be mentioned with a cross reference to the risk with drug-drug interactions.

The rates of seizure in a heavily pre-screened population give rise to concern, and create uncertainty, about determining the risk when treatment is commenced in a broader, non-clinical trial setting. This is an active area of pharmacovigilance and the Sponsor is requested to provide any updated safety information regarding seizures from the development program.

Falls

Falls reported in the CSR were 4% for enzalutamide treated patients compared with 1.3% of placebo treated patients (the incidence is stated as 4.6% versus 1.3% in the PI; the sponsor was requested to explain where the higher PI statistics were obtained), with 0.3% versus 0% reporting a Grade 3 fall for enzalutamide versus placebo, respectively. When the event rates for AEs of fall were adjusted by 100 patient-years at risk, there remained an increase in the enzalutamide treated group as compared with the placebo treated group (5.9 versus 3.0). 34% on enzalutamide were reported to have no other contributing

factors. Potential contributing factors were identified in many and a review of the data in the CSR reveals a range of potential contributing factors but also some significant injuries, including fracture of leg, hip fracture, upper limb fracture, and head injury, which make the classification of just one patient having a Grade 3 (requiring hospitalisation) fall seem unlikely.

Psychiatric conditions

Data in the CSR shows there was a generalised increase in psychiatric AEs. Visual hallucinations occurred in 1.3% of the enzalutamide arm compared with none in the placebo according to the CSR but the rate mentioned in the PI is 1.6% versus 0.3%. The sponsor was requested to explain from where the differing statistics are derived. The sponsor has presented AE rates per 100 patient-years which show, although common, insomnia and anxiety were not increased with enzalutamide.

Headaches

In Study CRPC2, headaches were reported for 11.6 % of patients in the enzalutamide group compared with 5.5% of patients in the placebo group. Most were Grade 1 or 2 and no subjects discontinued the study drug due to headache. The event rates per 100 patient-years at risk remained higher in the enzalutamide group compared to the placebo groups (17.7 with enzalutamide versus 14.4 with placebo).

Adverse events of fatigue and hot flushes have been discussed above. Diarrhoea was reported in 21.4% on study drug compared with 17.5% on the placebo, with 1.1% experiencing Grade 3 severity of diarrhoea and study discontinuation rates were low (0.3% versus 0.0%). Event rates per 100 patient-years at risk were higher in the placebo treated group than in the enzalutamide treated group (36.3 with enzalutamide versus 47.4 with placebo). Musculoskeletal pain was reported for 14.5% in the treatment arm compared with 11.5% in the placebo group. 1.1% were Grade 3 severity but none discontinued the study drug because of it.

Safety discussion

The background rate of AEs is high in this population due to their advanced prostate cancer. The morbidity and loss of quality of life experienced by this population is best exemplified by a patient in the placebo arm who chose euthanasia ahead of pursuing a potential new treatment option.

The following AEs occurred at higher rates with enzalutamide when standardised against treatment reporting duration: seizures, falls, headache, hot flushes, visual hallucinations and hypertension.

The key events of concern were the seizures which occurred sporadically during the treatment period, and not necessarily in subjects with other identified risk factors. In the early Phase studies, these occurred at a higher rate, and in the pivotal study, from the limited PK data available (4 subjects) in those who had a seizure indicated that their drug levels were within the higher range. This underscores the importance of ensuring there are not drug interactions which increase the level of enzalutamide (discussed below). Other cases had additional risk factors such as high alcohol intake, medications administered which lowered the seizure threshold or brain metastases: these are likely risks for the broader target population and the PI and CMI need to inform the prescriber and patient appropriately so risks can be minimised. The Delegate does not believe that this population should be prevented from driving solely on the grounds of the risk of a seizure posed by use of enzalutamide.

However, as the total safety population for enzalutamide was 1041 patients who were screened for risk factors before commencing treatment, of whom 923 were taking the proposed dosage (for a median duration of 8.3 months in the pivotal trial of 800 patients), the seizure risk when used outside of a clinical trial setting is not known. This, together

with the increased risk of seizures with elevated drug levels, and potential for drug interactions that might increase drug levels, merits consideration of a boxed warning²⁹ ('black box warning'). The ongoing need for this may be reviewed if there are sufficient post marketing data provided in the future to provide a clearer estimate of the risk with use in the target population. The advice of the ACPM was sought on this matter. It is noted that the Canadian monograph contains such a warning. Similarly, the risk of anaphylaxis is unknown due to the limited experience with enzalutamide (1041 patients).

There is no clear reason for the increased fall rate in the treated arm but together with the increased reported rates of visual hallucinations and cognitive impairment, it is possible that CNS toxicity is contributing, and cannot exclude a drug-related effect. Similarly, the increased rates of headaches may be a treatment effect and need to be included clearly in the CMI because of their severity and frequency compared with the control arm. The rates of hypertension are increased but this is considered manageable and of less relevance in a palliative setting.

Infections as a cause of death were increased in the enzalutamide arm, and the sponsor has been requested to provide details of the neutrophil counts as decreases were reported as an AE in some patients on enzalutamide.

Another key issue is the potential for enzalutamide to interact with other drugs, resulting in potential changes in the safety and efficacy profile. The metabolism of enzalutamide is reduced in the presence of potent CYP2C8 inhibitors, resulting in increased levels which given the dose-related toxicities of both seizures and fatigue, may lead to an AE. The PI informs prescribers about the risk of CYP2C8 inducers such as rifampicin without advice about dose required, nor was there any data presented in support of this and this needs to be addressed. This has potential implications for efficacy in the target population, and clear prescribing advice needs to be available (see *Conditions of registration*, and *Questions for the sponsor*). Enzalutamide itself inhibits a range of enzymes (CYP3A, CYP2C9, CYP2C19), and is likely to result in significant changes in drugs that are substrates of these enzymes (the PI contains appropriate information).

Issues

There were some general issues with the reporting of AEs which has made evaluating the safety profile of enzalutamide difficult. These centre around the classification and reporting of AEs (including SAEs), and in particular, the use dual reporting system for AEs.

No AEs of special interest were pre-specified. Given that seizures and fatigue were evident in the preclinical setting and were both dose limiting toxicities, the Delegate considers these should have been pre-specified. Several AEs that emerged in Study CRPC2 were examined in more detail with a standardisation against time on treatment to determine whether this was affected by the differing treatment or its duration. This was on the basis of the frequency rather than necessarily the severity of the event although all have potential to detract significantly from quality of life.

- Classification

The Delegate is not in agreement with the sponsor's classification of spinal cord compression and the rationale of spinal cord compression being a skeletal-related event, but not necessarily a SAE. Acute spinal cord compression is an oncology emergency, with a very narrow window of potential reversibility with treatment, requiring emergency investigation and treatment to reduce the risk of permanent disability; despite this, a significant number will have either total or a residual degree of paralysis, with consequent significant functional impairment, of any or all of the following: mobility, bladder and

²⁹ A boxed warning is a succinct warning statement printed at the start of the approved product information, designed to alert prescribers to an important safety issue with a medicine. The warning is highlighted by a bold black surround or "box".

bowel function. The impact for the patient and their carers is enormous. The capacity for even relatively minor residual dysfunction is evident in the table of contributing factors presented for falls.

- Dual CRF reporting system, different safety reporting methods

The use of a dual reporting system with CRFs for SAEs and CRFs for individual events, together with the different ways of presenting the safety data already described, has led to some confusion about the total rates of events, for example, spinal cord compression, dose modifications. It is not possible to determine how many patients experience the AE in total as there may be total overlap or potentially none at all between the two groups. There are differing rates of spinal cord compression reported and it is not possible to determine the total rate. The sponsor was requested to reconcile these various reporting systems for spinal cord compression to provide prescriber and patients with a clear risk associated with extending life with this treatment.

- Limited follow-up data

The analysis of rates per 100 patient years was done using the skeletal event rate within the reporting period which allows for comparison with the placebo for this time period. Patients were no longer followed up beyond 30 days of discontinuing the study treatment after progression other than for radiographic progression (first event only), skeletal-related events (unclear if first event recorded or ongoing record kept), and commencement of new therapies or death. It is unclear whether there are data available for comparison, for example, of spinal cord compression over the same time period in those patients who were in the placebo arm but changed therapy.

Within the study timeframe, a higher percentage of patients had a significant skeletal AE after being treated with enzalutamide, most likely as a consequence of being alive for longer with widespread bony disease rather than any direct effect of the drug. However, the absolute rates of AEs are important as they provide information to the prescriber and patient and form the basis of an informed discussion about the risks and benefits of commencing this palliative therapy. In response to this Overview the sponsor was requested to provide a specific figure for the total number of episodes of spinal cord compression and cauda equina syndrome to include in the PI.

- Lack of Quality of Life data

As stated in the background section of the overview, the aims of treating this population should be to prolong survival, minimise complications and maintain quality of life. This study was carried out in a population hoping to extend their life, but extended survival also increases the window for AEs to occur, such as spinal cord compression. Quality of life data would have been useful to determine whether the increased OS and radiographic PFS were meaningful to the subjects in the trial. It would have been useful to know whether data are available for comparison of radiographic PFS, skeletal events, new treatments and death for the full analysis set/ITT population once they have discontinued treatment as outlined in the protocol (see *Questions for the sponsor*, below).

While there are safety concerns with the use of enzalutamide, in the context of a palliative setting, it is the patient's decision as to whether the risks of treatment outweigh the benefits of longer survival, an increased radiographic PFS and possibly delayed time to an adverse skeletal event. The PI needs to reflect the absolute AEs rates (for example, for spinal cord compression) as currently known as these represent the basis of knowing the risks when commencing this medication, and for making an informed choice.

Clinical evaluator's recommendation

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

Risk management plan

The TGA OPR has accepted the EU-RMP Version 14.0 dated 25 April 2013 with an Australian Specific Annex, dated 23 May, 2013.

The opinion of the ASCOM was sought on 7 March 2014.

A number of recommendations for the RMP have been provided by the RMP evaluator. It was considered that the sponsor's response to the TGA request for further information has adequately addressed all of the issues identified in the RMP report.

The RMP evaluator has made a number of recommendations regarding the PI. Details of these are beyond the scope of the AusPAR.

Risk-benefit analysis

Delegate's considerations

Summary of issues

- The safety set for analysis included 1041 patients treated with any dose of enzalutamide, of whom 923 were treated at the proposed dose of 160 mg daily. Seizures occurred in the preclinical studies so all clinical trials excluded those with any history of, or risk factors for seizures. No post marketing data were available.

Seizures were dose limiting, and in the Phase III trial, 0.9% (7/800) of subjects had a seizure (1 case with status epilepticus; 1 case with seizures over 2 days) on enzalutamide compared with none in the placebo. Exclusion criteria meant predisposing risk factors had been minimised, therefore the risk is unknown use with broader usage.
- One case of anaphylaxis was reported in the Phase III trial.
- Drug-drug interactions are important potential causes of increased and decreased enzalutamide metabolism with potential consequences for safety and efficacy, respectively. In turn, enzalutamide is a strong inducer of CYP3A4, and to a lesser extent 2C9 and 2C19.
- This is a heavily pre-treated population and the majority have significant disease burden, so there were significant adverse event rates including spinal cord compression.
- The median OS and radiographic PFS were statistically significantly improved, although there was use in both arms of other treatments known to increase survival following progression.

Data deficiencies and limitations

- There is no PK data for effect of rifampicin on metabolism of enzalutamide and its active metabolite.
- The QoL data were insufficient due to low completion rates, especially in the placebo arm.

- There are no post marketing data available to assess the risk of seizures and anaphylaxis for the proposed usage.

Proposed action

The Delegate had no reason to say, at this time, that the application for Xtandi should not be approved for registration for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.

Proposed conditions of registration:

The following were proposed as conditions of registration:

- Implementation of the EU-RMP Version 14.0 dated 25 April 2013 with an Australian Specific Annex, dated 23 May, 2013 and any updates as required by the TGA.
- Submission of the following clinical trial(s) as Category 1 submissions within 6 months of completion which were designed to evaluate the effect of rifampicin on the PK of enzalutamide and its active metabolite, and to evaluate the effect of enzalutamide at steady state on the PK of CYP2D6 and CYP1A2 substrates.
- Negotiation of appropriate controls on impurities in the excipient to the satisfaction of the TGA.

The Delegate also proposed revisions to the PI and CMI. Details of these are beyond the scope of the AusPAR.

Questions for the sponsor

In its response to the Delegate's overview, the sponsor was requested to address the following:

1. The advice regarding CYP2C18 is extrapolated to inducers (for example, rifampicin) but there are no data presented to explain likely effects or whether a higher dose is required. The sponsor is requested to advise whether such studies have been done or are underway or are planned and whether a dose modification is recommended.
2. The sponsor is requested to clarify the percentage in CRCP2 for whom data were collected for radiographic PFS, skeletal events (including whether this was for the first event or all events), new treatments and death after treatment discontinuation as per the protocol in both arms (or whether these data were just while on active treatment), and whether this formed the basis of the AE rates per 100 patient-years calculations.
3. The sponsor is requested to provide a breakdown of the numbers in each treatment arm in CRPC2 for the 41% who were enrolled on a rising PSA alone. Please can the sponsor confirm among this group what percentage of subjects had never had metastatic disease diagnosed and the breakdown of these patients across each arm.
4. The sponsor is requested to provide the actual median survival data in each arm and a breakdown of the treatments as received by each arm following progression in Study CRPC2.
5. The sponsor is requested to present the radiographic progression-free data for Study CRPC2 without those who died without evidence of radiographic progression, that is, the known radiographic progression-free interval with 95% CI.
6. The sponsor is requested to provide the upper limit of the 95% CI for the placebo arm for the time to first skeletal-related event as this is currently missing.

7. The sponsor is requested to present the neutrophil count for the 7 patients who died of infection in the treatment arm.
8. The sponsor is requested to provide updated safety reports for SAEs and in particular, seizures and anaphylaxis from the development program and post marketing setting.
9. The sponsor is requested to provide details of the case of anaphylaxis including timing, for reported case in CRPC2.

Request for ACPM advice

The Delegate proposed to seek advice on this application from the ACPM and to request the committee provide advice on the following specific issues:

1. Should seizure risk be a black box warning given the risk is uncertain, and the target population (median age 71 years) are likely to have significant risk factors for the former including structural brain disease, potential medications and drug interactions that might increase this risk beyond that in a screened trial population? Should anaphylaxis be included?
2. To provide advice regarding the drug interactions and any corresponding PI and CMI recommendations.
3. Does the ACPM consider that time to first skeletal event has been statistically significantly improved?

Response from sponsor

Response to delegate's questions

The sponsor provided the following answers to the Delegate's questions:

Response to delegate's question 1:

It is assumed the Delegate means CYP2C8. In the clinical drug-drug interaction Study 9785-CL-0006, the effect of multiple doses of the strong CYP2C8 inhibitor gemfibrozil on the PK of a single dose of enzalutamide was investigated. Co-administration of gemfibrozil resulted in a 2.17 fold increase in the sum of the AUCs of enzalutamide and its active metabolite M2. Since this study clearly showed the relevance of CYP2C8 in the metabolism of enzalutamide, an effect of known CYP2C8 inducers (such as rifampicin) cannot be excluded. A clinical drug-drug interaction study in healthy subjects to evaluate the effect of multiple doses of rifampicin on the PK of a single dose of enzalutamide is underway (study 9785-CL-0405). Depending on the results of this study, dose recommendations would be included in the PI if appropriate.

Response to delegate's question 2:

A total of 272 of 800 (60%) enzalutamide patients and 180 of 399 (40%) placebo patients discontinued study drug due to clinical progression or skeletal-related. A review of the scan data in the window 7 days prior to date of last dose through end of study for each patient indicates that approximately 41% and 44% of the enzalutamide and placebo patients, respectively, had at least one scan. A further dissection of the data shows that most of these scans were conducted very near the time of drug discontinuation with approximately 19% of enzalutamide and approximately 11% of placebo patients in this subgroup having at least 1 scan after date of last dose. The primary pre-protocol reasons for lack of additional scans were radiographic PFS events and initiation of a new antineoplastic therapy. Approximately 50% of enzalutamide patients and 52% of placebo patients in this subgroup started a new antineoplastic therapy within 75 days of stopping study drug.

The majority (61.4%) of these patients received these anti-cancer therapies within 1 month of their last dose of study drug, 28.4% of patients received anti-cancer therapies within 2 months of their last dose of study drug and 10.2% of patients received anti-cancer therapies more than 2 months after their last dose of study drug. The median time from last dose of study drug until first anti-cancer treatment was 29.0 days in the enzalutamide arm and 14.5 days in the placebo arm.

Approximately 30% and 23% of enzalutamide and placebo patients, respectively, died in the same time frame. Given that patients were being assessed radiographically approximately every 3 months, these clinical outcomes contributed significantly to the lack of further radiographic follow-up as outlined above. Ultimately, approximately 51% of the enzalutamide and approximately 54% of the placebo patients in this group of patients experienced a radiographic progression event.

The basis of the AE rates per 100 patient-years calculations was the treatment emergent period defined as the date of the first dose of study medication up to 30 days after the last dose of study medication or the start of subsequent initiation of another systemic antineoplastic therapy, whichever occurred first.

Response to delegate's question 3:

The split for rising PSA alone by treatment arms is provided in the CSR for Study CRPC2. The split is 326 of 796 (41.0%) for enzalutamide and 164 of 398 (41.2%) for placebo.

Only 9 patients in total did not have metastatic disease at entry (8 on enzalutamide and 1 on placebo). The criterion "PSA progression only" means patients progressed on docetaxel based on PSA alone. Most patients had metastatic disease already.

Response to delegate's question 4:

The median OS was 18.4 months (CI: 17.3, estimate not met) and 13.6 months (CI 11.3, 15.8) for enzalutamide and placebo, respectively (data from the CSR for Study CRPC2). Details of the treatments received post-progression were provided.

Response to delegate's question 5:

The sponsor has conducted an analysis on time to radiographic disease progression as requested. In this analysis, death from any cause in absence of radiographic disease progression would not be counted as a progression event. The results are presented below in Table 12:

Table 12: Time to radiographic disease progression (Study CRPC2; without those who died without evidence of radiographic progression)

	Enzalutamide (n = 800)	Placebo (n = 399)
Status of Radiographic Disease Progression		
Radiographic Progression Events	399 (49.9%)	246 (61.7%)
Censor	401 (50.1%)	153 (38.3%)
Time to Radiographic Disease Progression (months)		
Median (95%CI)	10.6 (8.3, 11.0)	2.8 (2.8, 2.9)
25%-75% percentile	4.5 – 17.0	2.7 – 5.6
Stratified Analysis		
Hazard Ratio (95%CI)	0.331 (0.279, 0.393)	
P-value (log-rank)	<0.0001	

The results from the new analysis are consistent with the rPFS analysis results. The treatment effect, as represented by the hazard ratio, is stronger showing a 67% reduction of risk of having a progression event for patients in the enzalutamide group.

Response to delegate's question 6:

This information [the upper limit of the 95% CI for the placebo arm for the time to first skeletal related event] is not missing. The upper limit of the 95% CI was not included because it has not been reached.

Response to delegate's question 7:

There were 7 patients who died of infection in the treatment arm, including 2 events of pneumonia, 2 events of sepsis, 1 event of Escherichia sepsis, 1 event of urosepsis, and 1 event of infection. None of the cases reported neutrophil counts during the hospitalisation for the fatal events of infections, although two cases reported elevated white blood cell count.

Response to delegate's question 8:

Seizures

- Clinical development program

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

An increased incidence of seizure was not observed in chemotherapy-naïve patients with metastatic CRPC treated with enzalutamide in MDV3100-03 despite the longer duration of exposure and less stringent entry criteria in this study (for example, no exclusion for concomitant medications that lower the seizure threshold). In MDV3100-03, none of the 871 enzalutamide treated patients had a seizure before the data cut-off date of 16 September 2013. By comparison, 1 of the 844 placebo treated patients (0.1%) had a seizure before the data cut-off date. After the data cut-off date, 1 enzalutamide treated patient (0.1%) had a seizure.

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

- Post marketing cases

A cumulative review and evaluation of post marketing seizure events for Xtandi (enzalutamide) was performed for all cases reported through 31 October 2013. Twenty nine cases were retrieved using the Convulsion Narrow Standardized MedDRA Query, including 23 spontaneous cases and 6 compassionate use cases.

Of the 29 cases, 10 reported onset latency, ranging from 1 day to 178 days after the initiation of enzalutamide treatment. Four cases reported at least 1 risk factor for seizure, including brain metastases (3 cases), alcohol abuse (1 case), and bilateral subdural hematomas/haemorrhage (1 case). One patient's concomitant medications included levetiracetam and the reporting physician was not sure whether seizure occurred before or after enzalutamide treatment. For another case, the reported verbatim term was "possible seizures or TIA³⁰" and no clinical information was provided for the event(s).

³⁰ transient ischemic attack

Myoclonic movements were reported for 1 case. The remaining cases lacked information on the clinical presentation, duration of episodes, risk factors, or triggers for the reported seizure events. The majority of the patients, for whom event outcome is known, recovered from the events, of which 3 cases reported receiving the corrective treatment of levetiracetam.

Anaphylaxis

- Clinical development program

There were three reports of anaphylaxis in the development program: one patient in the CRPC2 Study developed an anaphylactic reaction to bee/wasp sting. The second case, in a patient on placebo in Study MDV3100-03, had anaphylactic shock to a CT scan contrast agent. The third case was reported as a Grade 1 anaphylactic reaction in a patient on enzalutamide in the MDV3100-03 Study. None of these cases were considered to be related to study drug or placebo.

- Post marketing cases

One post marketing case had severe allergic reactions and associated anaphylactic shock due to glacial sunburn. This case was not related to enzalutamide.

Response to delegate's question 9:

The sponsor provided the full narrative for the single reported case of anaphylaxis in CRPC2 as requested.

Comments on efficacy and safety

The sponsor also provided the following responses to the Delegate's request for ACPM's advice on several issues:

Delegate's question 1 to ACPM: Should seizure risk be a black box warning? Should anaphylaxis or spinal cord compression be included?

- Seizures

The sponsor considers inclusion of a black box warning for seizures is unwarranted. The incidence of seizures observed in the CRPC2 Study and in the clinical development program has been low to date (uncommon < 1.0%). The evaluations by both the FDA and EMA have not required boxed warnings or contraindications. In addition, PIs for other products which may lower the seizure threshold has not included boxed warnings.

An assessment of the incidence of seizure observed in the clinical development program was conducted and was summarised in the dossier. In Study CRPC2, seizure was reported as an AE in 5 patients; no patients in the placebo group experienced seizure. Review of potential cases of seizure identified 1 additional patient in CRPC2 and 1 patient in the open-label study, CRPC-MDA-1, who had events assessed by the sponsor as consistent with seizure, although they were not reported as such by the investigators. In the integrated safety population of patients treated with the proposed dose of 160 mg (including those treated with 150 mg), the incidence of seizure is 0.8% (7/909). One additional patient in the PK study in CRPC (Study 9785-CL-0007) experienced seizure while being treated with enzalutamide. Including the patient in this study, the incidence of seizure is 0.9% (8/923) in all patients with CRPC treated with doses of 150/160 mg. There were a number of factors in several of the cases that could be considered to contribute to the risk of seizure; however, the potential for enzalutamide to lower the seizure threshold cannot be excluded.

During the review of the application by the US FDA the proposed language from the sponsor included in the *Warnings and Precautions* section of the US Package Insert was considered adequate, and at no stage did the FDA communicate that a boxed warning should be considered to inform the patients or prescribing physician of the risk of seizure

with enzalutamide. Similarly, the EMA has no requirement for a boxed warning in the Summary of Product Characteristics (SmPC), and the CHMP has not requested that a contraindication be considered for patients at an increased risk of seizure taking Xtandi. The language agreed with the CHMP, prior to the positive opinion announced on 26 April 2013, and presented in Section 4.4 (*Special warnings and precautions for use*) of the SmPC is: “Caution should be used in administering Xtandi to patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, stroke, primary brain tumours or brain metastases, or alcoholism. In addition, the risk of seizure may be increased in patients receiving concomitant medicines that lower the seizure threshold.”

To further determine whether a boxed warning on the risk of seizures in the Package Insert would be appropriate and helpful for the prescribing physician when evaluating treatment options for the patient and consistent with other approved products, the Sponsor has reviewed PI for other products associated with seizure (for example, Seroquel, Prozac, Clorprax/Prexaton/Zyban, Anafranil, Dexamphetamine). For these products, each of which has a similar incidence of seizure as that observed in the enzalutamide clinical development program (uncommon < 1.0%), the risk of seizures is presented in the *Precautions* section and none have a boxed warning for this risk.

- Anaphylaxis:

There was one reported case of anaphylaxis in a patient using enzalutamide during the Phase III clinical trial, and the anaphylactic reaction was caused by bee/wasp stings. The reaction was not related to the study drug. The full narrative for this case was provided. As such, the sponsor believes that a boxed warning or other additional language concerning anaphylaxis is not warranted.

- Spinal cord compression:

Spinal cord compression is considered an “Oncology Emergency” and a number of cases were reported during the enzalutamide clinical development program, as shown in the table below. However, none of these cases were considered to be drug related by the investigators. A boxed warning is not warranted for spinal cord compression.

Table 13: Spinal cord compression cases

	MDV3100-03 (PREVAIL)		CRPC2 (AFFIRM)		MDV3100-03 + CRPC2		Pooled	Total
SOC	Enz 160mg/day (n = 871)	Placebo (n = 844)	Enz 160mg/day (n = 800)	Placebo (n = 399)	Enz 160mg/day (n = 1671)	Placebo (n = 1243)	Enz Open Label (n = 1001)	Enz (n = 2500)
Spinal Cord Compression	40 (4.6%)	29 (3.4%)	53 (6.6%)	18 (4.5%)	93 (5.6%)	47 (3.8%)	26 (2.6%)	119 (4.7%)

Delegate’s question 2 to ACPM: The drug interactions and any PI and CMI recommendations.

To further simplify the PI wording around CYP2C8, the sponsor suggests revising the text³¹.

Delegate’s question 3 to ACPM: Time to first skeletal event has been statistically significantly improved?

In the CRPC2 Study, data were collected on skeletal-related events, even after study drug discontinuation. At the time of the analysis, 287 (35.9%) of enzalutamide treated and 161 (40.4%) of placebo treated patients had experienced a skeletal-related event. The time to event analysis demonstrated a statistical and clinically significant benefit of enzalutamide over placebo on the time to first skeletal-related event with a median time in the

³¹ Details of the proposed revision are beyond the scope of the AusPAR.

enzalutamide treated arm of 16.7 months versus 13.3 months in the placebo arm (hazard ratio = 0.688, p value 0.0001).

Other related issue

Appropriate controls on impurities

To be negotiated with TGA quality evaluators.

Conclusion

The data from the enzalutamide clinical studies demonstrate a favourable risk-benefit ratio for men with CRPC who have received docetaxel. In particular, the pivotal Study CRPC2 (AFFIRM) has demonstrated an improvement in median OS of 4.8 months (hazard ratio = 0.631 (95% CI: 0.529, 0.752), p value < 0.0001) for the proposed indication. Overall, enzalutamide was also well-tolerated in the studies. Xtandi is orally administered without the need for concomitant corticosteroids and can be taken with or without food. The overseas regulatory progress and priority status granted by many health authorities to date support the significant clinical benefits of enzalutamide to patients with CRPC.

Advisory committee considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new chemical entity for a currently registered product.

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

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

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed PI/ CMI amendments:

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

- The current statement on seizures in the PI is inadequate and should be changed along the lines of the Canadian PI and cross reference to the risk with Interactions with other medicines section.
- A statement in the *Precautions / Contraindications* sections of the PI and relevant sections of the CMI to reflect the post marketing data from the periodic safety update reports (PSURs) on seizures.

Specific advice:

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

1. Should seizure risk be a black box warning given the risk is uncertain, and the target population (median age 71) are likely to have significant risk factors for the former including structural brain disease, potential medications and drug interactions that might increase this risk beyond that in a screened trial population? Should anaphylaxis be included?

The ACPM noted seizure events in the pivotal study were uncommon (< 1%). However, convulsions occurred in studies of both mice and dogs with plasma concentrations of

enzalutamide similar to or marginally above the clinical C_{max}. There is a plausible mechanism for the seizures and data from in vitro studies show that enzalutamide and its active metabolite cross the blood brain barrier, bind to, and inhibit the activity of the GABA-gated chloride channel. There is a dose relationship. The rates of seizure in a heavily pre-screened population give rise to concern, particularly when treatment is given in a broader, nonclinical trial setting.

The ACPM was of the view that, at this stage, a statement in the *Precautions* section of the PI is adequate. However, the current Australian PI statement on seizures is inadequate and should be changed along the lines of the Canadian PI and cross reference to the risk with Interactions with other medicines section.

A statement in line with the EMA statement, as suggested by the sponsor, may be sufficient. Post marketing surveillance will be critical in this regard and may modify this advice. The PI should also include mention of the number of post-marketing cases from PSURs.

The statement currently proposed for the PI includes *...Because of the risk of seizure associated with XTANDI use, patients should be advised of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.*

The latter comment does not really help clinicians. The ACPM thought more practical suggestions might be of more use.

The ACPM was of the view that a black box warning was unnecessary for anaphylaxis as this was reported in only one case and was unrelated.

2. To provide advice regarding the drug interactions and any corresponding PI and CMI recommendations.

The ACPM noted the PI has extensive information on drug interactions; approximately 2.5 pages. As the issue of drug interaction is significant and complex it was felt this section needed to be made clearer and perhaps more succinct.

The *Interactions with other medicines* section seems to be a mix of providing data in some cases and giving advice on what to do, for example, avoid Warfarin + E or increase international normalised ratio (INR) monitoring.

The list of potential drugs to consider, which is already in PI, was considered very useful for the clinician, who may not be able to bring to mind that list easily. However, statements like *...In vitro data indicate that enzalutamide is not a substrate for the organic anion transporting polypeptide 1B1 (OATP1B1), OATP1B3, organic cation transporter 1 (OCT1), or P-glycoprotein...* probably are not as immediately useful to a clinician.

The CYP2C8 inhibitors and inducers paragraph could usefully include a table of potent inhibitors and inducers.

3. Does the ACPM consider that time to first skeletal event has been statistically significantly improved?

The ACPM was of the view that time to first skeletal-related event was longer with enzalutamide but considered the OS data more compelling.

The ACPM advised that the 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 capsule containing enzalutamide 40 mg, indicated for:

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

Specific conditions of registration applying to these goods

- The Xtandi EU Risk Management Plan (EU-RMP), version 14.0, dated 25 April 2013 with an Australian Specific Annex dated 23 May 2013, included with submission PM-2013-01155-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The Product Information approved for Xtandi at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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