NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Enzalutamide (XTANDI™) for the treatment of adult men with metastatic castrate-resistant prostate cancer whose disease has progressed on or after docetaxel therapy

Submitted by

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Executive summary

Introduction

- Enzalutamide (XTANDI™) is a new treatment for metastatic castrate resistant prostate cancer (mCRPC) (1). This submission compares enzalutamide with the current standards of care, abiraterone and best supportive care (BSC), and demonstrates superior clinical effectiveness and acceptable cost effectiveness versus both.
- Versus abiraterone, enzalutamide has demonstrated: a small benefit in overall survival (OS); statistically significant benefits in radiographic progression free survival (rPFS) and PSA response rate; a reduced need for steroid use and monitoring; [redacted]

Regulatory information

- On the 21st June 2013, XTANDI was approved by the European Medicines Agency (EMA) for the treatment of adult men with mCRPC whose disease has progressed on or after docetaxel therapy.
- Enzalutamide (160 mg) should be administered orally, once a day, in the form of four 40 mg capsules. Enzalutamide offers the flexibility to be prescribed with or without concomitant steroids, requires less routine monitoring for liver toxicity, hypokalaemia, fluid overload, and blood pressure than abiraterone, and can be administered with or without food.
- Enzalutamide has had a patient access scheme (PAS) discount of [redacted] confirmed by the Department of Health [redacted]. These discounted prices are used in our economic base case

Mode of Action

- Enzalutamide (XTANDI™) is a novel oral androgen receptor (AR) signalling inhibitor which acts at three distinct levels of the signalling pathway: 1) it completely inhibits binding of androgens to ARs in the interior of prostate cells (cytosol); 2) it inhibits the nuclear translocation of activated receptors; 3) it inhibits the association of the activated AR with DNA. Enzalutamide demonstrates this activity even when AR is over-expressed in the prostate cancer (PC) cells resistant to anti-androgens (1). Unlike AR antagonists that only inhibit the binding to the AR, enzalutamide is a pure AR antagonist.
- The mechanism of action of enzalutamide is different from the current standard of care – abiraterone which irreversibly blocks cytochrome P17 (an enzyme involved in the production of testosterone), thereby stopping androgen synthesis in the adrenal glands, testes and the prostatic tumour (2). The mechanism of action of abiraterone is associated with side effects which require management via administration of concomitant steroids, which necessitates some additional monitoring.

Clinical Efficacy

- Data on the efficacy of enzalutamide (160 mg) originates from one large randomised double-blind placebo-controlled phase III study (1,199 patients) called AFFIRM (3). Both treatment arms in AFFIRM enrolled patients with well balanced demographics and baseline characteristics. The patient population of this study includes a large number of UK patients (n=132, 11%).

- All primary and secondary endpoints were reached. Enzalutamide has a significantly greater proportion of patients versus placebo experiencing improvements in both life expectancy and quality of life (QoL), whilst being well tolerated.
- The intention-to-treat (ITT) patient population from AFFIRM has been used to inform this submission, and demonstrates that enzalutamide is a highly effective treatment:
    - ◊ Significant median overall survival (OS) benefit versus placebo of 4.8 months: 18.4 months, [17.3-not reached] vs. 13.6 months, [11.3-15.8]; hazard ratio (HR): 0.63, [0.57-0.84]; p<0.0001 (interim analysis, September 2011).
    - ◊ Enzalutamide also demonstrated a significantly improved OS benefit versus placebo of 4.5 months at database lock of the AFFIRM data, 17.8 months versus 13.3 months; hazard ratio (HR): 0.618, [0.523-0.730]; p<0.001 (database lock, December 2011).
    - ◊ Significant improvement in median radiographic progression free survival (rPFS) (8.3 vs. 2.9 months; HR: 0.40, [0.35; 0.47]; p<0.001).
    - ◊ Significantly longer time to first skeletal-related event (SRE) (16.7 vs. 13.3 months; HR: 0.69 [0.57; 0.84]; p<0.0001).
    - ◊ Significantly longer time to prostate specific antigen (PSA) progression (16.7 vs. 13.3 months with placebo; HR: 0.69 [0.57; 0.84]; p<0.0001).
    - ◊ Able to maintain a stable QoL while patients on placebo showed deterioration, as measured by the Functional Assessment of Cancer Therapy – Prostate (FACT-P) questionnaire in the sub-domains “physical”, “functional” and “emotional wellbeing” and the prostate cancer scale, at all time points.
- The AFFIRM study also demonstrated that enzalutamide is a well tolerated treatment:
    - ◊ The incidence and nature of adverse events (AEs) were similar between enzalutamide and placebo.
    - ◊ Serious and grade 3 or higher AEs were more commonly reported for patients on placebo than on enzalutamide despite the markedly longer exposure to study drug in the enzalutamide treatment arm.

- In AFFIRM, patients who discontinued treatment in either arm may have switched to an alternative active therapy. Since more patients in the placebo arm were prescribed this post-study treatment it is likely that the placebo arm may have over-performed, and that the relative benefit of enzalutamide versus placebo has been under-estimated. To avoid adding additional uncertainty associated with correcting for such effects we have presented all results unadjusted.
- No head-to-head comparison of enzalutamide and abiraterone is available; however an indirect treatment comparison (ITC) has estimated these clinical benefits. Overall survival was shown to be improved with enzalutamide: HR: 0.835, 95% CI [0.668; 1.044] showing a benefit which was at the border of significance. Improvements in rPFS, PSA response, and quality of life scores were all significantly improved.

Cost Effectiveness

- A cost utility analysis (CUA) was performed using a new Markov model based on three health states: stable disease, progressive disease and dead, in which costs and quality of life associated with each health state, AEs and SREs could be captured.

- Key inputs for OS and PFS are derived from the AFFIRM study for enzalutamide and the COU-AA-301 study for abiraterone. The control arms in both studies were considered comparable.
- Time to treatment discontinuation (TTD) was used as the primary indicator of disease progression within the health economic model as suggested by expert opinion (4) and in line with NICE comments during the abiraterone appraisal (5).
- The pairwise results of the base case analysis are presented in Table 1 and Table 2. Enzalutamide has an ICER of **£14,795** per QALY gained versus abiraterone and **£43,587** per QALY gained versus BSC.

Table 1: Base-case pairwise cost-effectiveness results with PAS

	Enzalutamide	Abiraterone	BSC
Technology acquisition cost *	[redacted]	[redacted]	0
Other costs	7,555	7,852	6,970
Total costs	[redacted]	[redacted]	6,970
Difference in total costs	-	[redacted]	[redacted]
LYG	[redacted]	[redacted]	[redacted]
LYG difference	-	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
QALY difference	-	[redacted]	[redacted]
ICER	**-**	**14,795**	**43,587**

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.
[redacted]

Table 2: Incremental cost-effectiveness results with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)	ICER incremental analysis (QALYs)
A: BSC	6,970	[redacted]	[redacted]	0	0	0	Not applicable	Not applicable
B: Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	102,751	102,751
C: Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,587	14,795

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; ICER incremental analysis: compares the treatment in the current row with the last non-dominated treatment option

- Extensive scenario analyses and deterministic sensitivity analyses showed that the model results were robust. The PSA showed an 83% probability of enzalutamide being cost-effective versus abiraterone at a willingness to pay (WTP) of £20,000 per QALY gained, and an 81% probability of being cost-effective versus BSC at a WTP of £50,000 per QALY gained. Enzalutamide versus BSC meets the criteria for appraisal of end of life medicines, which may be relevant in patient for whom abiraterone or steroids are inappropriate or contraindicated.
- Experts suggested that Astellas include a scenario analysis to review the cost effectiveness of enzalutamide and abiraterone assuming equal overall survival, time to treatment discontinuation and drug acquisition cost, while including the difference in monitoring costs and requirement for steroids. This scenario elicits a cost saving of £1,007 compared to abiraterone while resulting in the same number of QALYs.

Conclusion

- Enzalutamide is a new highly effective and well tolerated drug for the treatment of men with mCRPC that progresses on or after docetaxel treatment. Enzalutamide has demonstrated a benefit in OS, and statistically significant benefits in rPFS, PSA response rate and QoL. Enzalutamide may offer financial and administrative benefits by requiring less routine product specific monitoring for liver toxicity, hypokalaemia, fluid overload and blood pressure, therefore avoiding associated hospital visits and clinician contact. [redacted].
- The CHMP report concluded that overall, the benefits of enzalutamide in mCRPC patients who had progressed after one or two chemotherapy regimens at least one containing docetaxel appear clear, are robust and of clinical relevance (6).

Abbreviations

Abbreviation	Definition
ABI	Abiraterone
Abiraterone	Abiraterone acetate
ABPI	Association of the British Pharmaceutical Industry
ACD	Appraisal Consultation Document
ADT	Androgen Deprivation Therapy
AE	Adverse Event
AFT	Accelerated Failure Time
AIC	Akaike Information Criterion
ANCOVA	Analyses of covariance
AR	Androgen Receptor
ASCO	American Society of Clinical Oncology
ASCO-GU	American Society of Clinical Oncology-Genitourinary
AST	Aspartate Aminotransferase
AUA	American Urological Association
BIC	Bayesian Information Criterion
BID	Twice Daily
BNF	British National Formulary
BPI	Brief Pain Inventory
BPI-SF	Brief Pain Inventory-Short Form
BSC	Best Supportive Care
CA	Capecitabine
CAB	Cabazitaxel
CDF	Cancer Drug Fund
CEAC	Cost-Effectiveness Acceptability Curve
CEBM	Centre of Evidence Based Medicine
CET	Cetuximab
CG	Clinical Guideline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIC	Commercial in Confidence
CIX	Cixutumumab
CRD	Centre for Reviews and Dissemination
CRF	Case Report Form
CRPC	Castration-Resistant Prostate Cancer
CSR	Clinical Study Report
CT	Computed Tomography
CUA	Cost Utility Analysis
CUS	Custirsen
CVZ	*College voor Zorgverzekeringen* (Dutch health care insurance board)
CYP17	Enzyme Cytochrome P450 17
DARE	Database of Abstracts of Reviews of Effects
DB	Double Blind
DHT	Dihydrotestosterone

DNA	Deoxyribonucleic Acid
DTX	Docetaxel
EAU	European Association of Urology
ECCO	European CanCer Organisation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ERG	Evidence Review Group
EMA	European Medicines Agency
ENZA	Enzalutamide
eMit	Electronic Market Information Tool
EoL	End of Life
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life Five-Domain Scale
ESMO	European Society for Medical Oncology
EWB	Emotional Well-Being
Ext. Dom.	Extended Dominance
FACT	Functional Assessment of Cancer Therapy
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FACT-G	Functional Assessment of Cancer Therapy – General
FDA	Food and Drug Administration
FAD	Final Appraisal Determination
FBC	Full Blood Count
FBW	Functional Well-Being
G-CSF	Granulocyte Colony-Stimulating Factor
GABA	Gamma-Aminobutyric Acid
GEE	Generalised Estimating Equations
GnRH	Gonadotropin Releasing Hormone
HR	Hazard Ratio
HRG	Healthcare Research Group
HRQoL	Health-Related Quality of Life
HRU	Health Resource Utilisation
HTA	Health Technology Assessment
IA	Interim Analysis
ICER	Incremental Cost-Effectiveness Ratio
INR	International Normalised Ratio
IPD	Individual Patient Data
IR	Irofulven
ISOQOL	International Society for Quality of Life Research
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect Treatment Comparison
ITT	Intention To Treat
IVRS	Interactive Voice and Web Response services
LFT	Liver Function Tests
LH	Luteinising Hormone
LHRH	Luteinising Hormone-Releasing Hormone
LOS	Length of Stay
LS	Least Squares Mean
LY	Life Years

LYG	Life Years Gained
mCRPC	Metastatic Castrate-Resistant Prostate Cancer
mPFS	Modified Progression Free Survival
MMRM	Mixed Models with Repeated Measures
MRI	Magnetic Resonance Imaging
MS	Manufacture Submission
MTZ	Mitoxantrone
MUGA	Multi-Gated Acquisition Scan
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NYHA	New York Heart Association
OD	Once Daily
OL	Open-Label
OPC	One Prior Chemo
OR	Odds Ratios
ORR	Objective Response Rate
OS	Overall Survival
PAS	Patient Access Scheme
PC	Prostate Cancer
PCS	Prostate Cancer Scale
PCTFE	Polychlorotrifluoroethylene
PCWG2	Prostate Cancer Clinical Trials Working Group
PDis	Progressive Disease
PFS	Progression Free Survival
PLA	Placebo
PO	Per os (oral)
PP	Per Protocol
PS	Performance Status
PSA	Prostate-Specific Antigen
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PRED	Prednisone
PRO	Patient Reported Outcomes
PVC	Polyvinyl Chloride
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
QTcF	QT interval by the Fridericia correction formula
RAM	Ramucirumab
RCT	Randomised Controlled Trial
RD	Rate Difference
RECIST	Response Evaluation Criteria In Solid Tumors
RIL	Rilotumumab
RMP	Risk Management Plan
rPFS	Radiographic Progression Free Survival
SAE	Serious Adverse Event
SD	Standard Deviation
SDis	Stable Disease
SE	Standard Error

SLR	Systematic Literature Review
SMC	Scottish Medicines Consortium
SPC	Summary of Product Characteristics
SRE	Skeletal-Related Event
STA	Single Technology Assessment
SOC	Standard Of Care
TEAE	Treatment-Emergent Adverse Events
TTD	Time to Treatment Discontinuation
TTO	Time Trade-Off
VAS	Visual Analogue Scale
WTP	Willingness to Pay
ZOL	Zoledronic Acid

Definitions

Term	Definition
CRPC	Castration resistant prostate cancer is defined by the 2011 EAU Guideline on prostate cancer as having: • Castrate serum levels of testosterone (testosterone <50 ng/dl or <1.7 nmol/l). • Three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir. • Antiandrogen withdrawal for at least 4 week for flutamide and for at least 6 week for bicalutamide. • PSA progression, despite consecutive hormonal manipulations. • Progression of osseous lesions: progression or appearance of two or more lesions on bone scan or soft tissue lesions using Response Evaluation Criteria in Solid Tumours (RECIST) and with nodes >2 cm in diameter. The definition above is in agreement to that used in the AFFIRM study which is: • Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features. • Ongoing ADT with a GnRH analogue or orchiectomy (i.e., surgical or medical castration). • For patients who have not had an orchiectomy, there must be a plan to maintain effective GnRH-analogue therapy for the duration of the trial. • Serum testosterone level < 1.7 nmol/L (50 ng/dL) at the Screening visit. • Progressive disease by PSA or imaging after docetaxel-based chemotherapy in the setting of medical or surgical castration. Disease progression for study entry was defined as PSA progression, Soft tissue disease progression according to RECIST or Bone disease progression defined by two or more new lesions on bone scan.
mCRPC	Metastatic castration resistant prostate cancer is defined as CRPC with known metastases.
mPFS	Modified PFS is defined as the time to radiographic progression, first SRE or death due to any cause, which ever occurred first.
OS	Time from randomisation to death of any cause. OS data included in this submission correspond to two different data cut-off analyses: • Interim analysis (IA): Predefined analysis at the date of the 520th death (80% of the 650 targeted numbers of events for final analysis), i.e., 25 September 2011. This is the cut-off date for all analyses presented in this submission, except where specified otherwise.

	• Database lock: Database lock took place on 16 December 2011; a total of 576 deaths had occurred by then. A final analysis of OS and incidence of AEs was conducted at database lock when the data was unblinded. The analyses for these two parameters are also presented in this submission.
Pain palliation	In AFFIRM, pain palliation is defined as: • A ≥30% reduction in average pain score at Week 13 compared to baseline with a ≤30% increase in analgesic use • A ≥2 point reduction in the worst pain item (BPI-SF question #3) score at Week 13.
Pain progression	Pain progression is defined as an increase above baseline in the FACT-P pain assessment, which had to be confirmed by a second consecutive assessment 3 or more weeks later.
PSA response	PSA response is defined as ≥50% and ≥90% reductions in PSA from baseline to the lowest post-baseline PSA result.
PSA progression	PSA progression was defined according to the consensus guidelines of the PCWG2 as: • ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir, with confirmation by a second consecutive value obtained ≥ 3 weeks later. • For patients with no PSA decline at Week 13, PSA progression was defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above baseline was documented, which was confirmed by a second consecutive value 3 or more weeks later.
QoL response	QoL response is defined as having a 10-point improvement in global FACT-P score, as compared with baseline, on two consecutive measurements obtained at least three weeks apart.
Radiographic response	Radiographic response was assessed according to the RECIST version 1.1 for soft tissue disease.
rPFS	Time from randomisation date to radiological progression according to RECIST version 1.1 for soft tissue disease and to PCWG2 criteria for bone progression
SRE	The definition of a skeletal-related event can vary across studies. In AFFIRM, a skeletal related event (SRE) is defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. The health economic model definition of SREs differs slightly from the definition in the AFFIRM protocol as change of antineoplastic therapy to treat bone pain was not considered a SRE in the model.
TTD	Time from first dose to treatment discontinuation.

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: XTANDI™

Approved name: Enzalutamide.

Therapeutic class: The World Health Organisation International Working Group for Drug Statistics Methodology has not yet assigned enzalutamide a therapeutic class.

1.2 What is the principal mechanism of action of the technology?

Enzalutamide, formerly known as MDV3100[1], is a novel oral androgen receptor (AR) signalling inhibitor indicated for the treatment of adult men with metastatic castration-resistant prostate cancer (mCRPC) whose disease has progressed on or after docetaxel therapy (1).

Prostate cancer (PC) which is not suitable for interventions of curative intent is usually initially androgen sensitive and can respond dramatically and beneficially to androgen deprivation therapy (ADT), whether by surgical castration or inhibition of androgen production using luteinising hormone releasing hormone (LHRH) agonists or antagonists (7).

Over time however, the majority of patients develop resistance to primary androgen deprivation, and their disease becomes “castration-resistant” (8). Increasing evidence has shown that despite low or even undetectable levels of androgen, AR signalling remains active and continues to drive disease in castration-resistant prostate cancer (CRPC) (9). Stimulation of PC cell growth via the AR requires nuclear localisation and DNA binding (10).

Enzalutamide is an AR signalling inhibitor specifically selected for activity in models of mCRPC (11). Unlike other AR inhibitors such as bicalutamide (12), enzalutamide blocks the AR signalling pathway at three different levels (13) (Figure 1):

1. Competitively inhibits binding of androgens to ARs in the interior of prostate cells (cytosol)
2. Inhibits the nuclear translocation of receptors
3. Inhibits the association of the AR with DNA even when AR is over-expressed and in PC cells resistant to anti-androgens.

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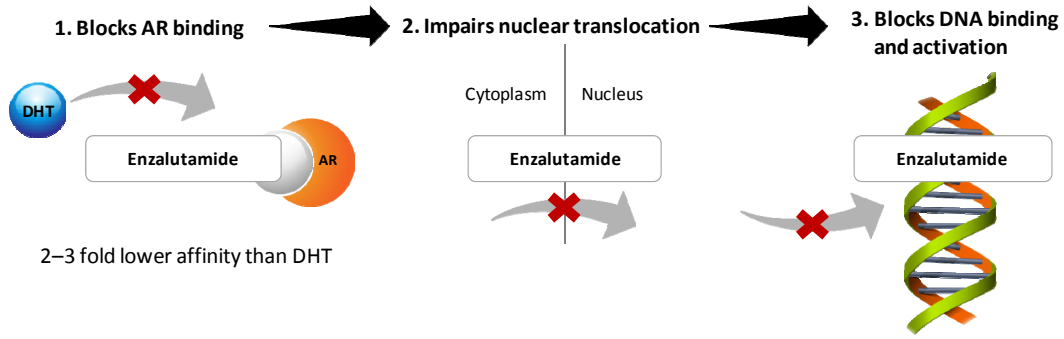
[1] MDV3100 was used to identify enzalutamide in phase 1 and 2 trials. Throughout the remainder of this submission the name enzalutamide will be used in all cases.

Thus, enzalutamide acts as a pure AR antagonist in contrast to other AR inhibitors which do not inhibit nuclear translocation or DNA binding and thus in some situations can act as partial agonists (12).

Figure 1: Signalling steps inhibited by enzalutamide (11) (14)



Abbreviation: AR: androgen receptor; DHT: dihydrotestosterone.

The ultimate consequence of the action of enzalutamide on AR signalling is:

- Reduced expression of AR-dependent genes
- Decreased growth of PC cells
- Induction of cancer cell death
- Tumour regression.

The mechanism of action of enzalutamide is different from the current standard of care (SOC) – abiraterone. Abiraterone is a selective inhibitor of androgen biosynthesis which irreversibly blocks cytochrome P17 (an enzyme involved in the production of testosterone), thereby stopping androgen synthesis in the adrenal glands, testes and the prostatic tumour (2). This mechanism of action is associated with side effects which require management via administration of concomitant steroids.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

On the 21st June 2013, XTANDI was approved by the European Medicines Agency (EMA) for the treatment of adult men with metastatic castrate-resistant prostate cancer (mCRPC) whose disease has progressed on or after docetaxel therapy.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions

attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

The European Public Assessment Report (EPAR) for enzalutamide is not yet published, however the CHMP assessment report made the following conclusions (6):

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

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

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

Identified risks, potential risks and missing information are adequately reflected and addressed in a risk management plan (RMP).

The marketing authorisation holder is required to perform pharmacovigilance activities and interventions detailed in the agreed RMP.

The associated pharmacovigilance plans will include the following safety concerns:

- 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.

A post-authorisation open-label study addressing the safety and tolerability of enzalutamide in patients previously enrolled in AFFIRM will be conducted. The data collected in this study will be limited to safety assessments, survival status, and new treatments for PC. Assessments of safety will include adverse events (AEs), clinical laboratory tests, physical examinations, electrocardiograms (ECGs), and vital signs. This study will allow additional insights into the risk mitigation recommendations in mCRPC.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Enzalutamide is indicated for the treatment of adult men with mCRPC whose disease has progressed on or after docetaxel therapy (1).

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

There are no ongoing studies involving enzalutamide that will provide additional comparative evidence in the next 12 months for the indication under review in this submission.

An open-label non-controlled phase II study in patients with mCRPC whose disease has progressed on or after docetaxel is currently ongoing, exclusively in Japan. No results are yet available and they are not expected to be in the next 12 months.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Enzalutamide is expected to have been launched in the UK within one week of receiving maketing authorisation (21st June 2013) .

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Enzalutamide has regulatory approval in the US (Food and Drug Administration [FDA]) approval date granted on 29th August 2012) for the treatment of patients with mCRPC who have previously received docetaxel.

Enzalutamide has regulatory approval in Canada. The market authorisation date (Notice of Compliance) was granted on 29th May 2013 for the treatment of patients with mCRPC in the setting of medical or surgical castration who have received docetaxel therapy.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Astellas will submit enzalutamide (in a post-chemotherapy setting) to the Scottish Medicines Consortium (SMC) on 1st July 2013.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 3: Unit costs of technology being appraised

Pharmaceutical formulation	Enzalutamide
Acquisition cost (excluding VAT)	Four cardboard wallets, each containing 28 soft capsules in PVC/PCTFE/aluminium blister (28 capsules per wallet; 4 wallets per carton). Price of 112 capsules: £ 2,734.67 [redacted]
Method of administration	A single oral daily dose.
Doses	160 mg (four x 40 mg capsules)
Dosing frequency	Daily until disease progression following clinical assessment. Time of dosing is independent of food administration.
Average length of a course of treatment	In AFFIRM, mean and median exposure to enzalutamide was 8.5 and 8.3 months (15), respectively. Duration on treatment in clinical practice is expected to be similar to that observed in AFFIRM, the study used for approval of enzalutamide in its label indication.
Average cost of a course of treatment	Treatment cost: • Assuming mean exposure of 8.5 months: £ 25,269 [redacted], with a daily cost of £97.67 [redacted]
Anticipated average interval between courses of treatments	Enzalutamide is administered daily until disease progression. There is no clear evidence that treatment beyond progression is associated with additional benefits. However, the definition of disease progression may differ across clinical practice (radiographic progression, PSA progression, etc) therefore, the estimated treatment duration is based on the total exposure time to enzalutamide in AFFIRM.
Anticipated number of repeat courses of treatments	There is no evidence to support repeat treatment with enzalutamide after clinical disease progression.
Dose adjustments	If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to ≤ Grade 2, then resumed at the same or a reduced dose (120 mg or 80 mg) if warranted (1). No dose adjustments are necessary for: • Patients with mild hepatic impairment. Caution is advised in patients with moderate hepatic impairment. Enzalutamide is not recommended in patients with severe hepatic impairment. • Patients with renal impairment: No dose adjustment is necessary for patients with mild or moderate renal impairment. Caution is advised in patients with severe renal impairment or end-stage renal disease). • Elderly patients The concomitant use of strong CYP2C8 inhibitors should be avoided. • If patients must be co administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily. • If co administration of the strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

Abbreviations: rPFS: radiographic progression-free survival; PAS: patient access scheme; PSA: prostate specific antigen.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No specific test is required to assess the eligibility of patients. Enzalutamide is an oral treatment self-administered by the patient. No special facilities are needed for enzalutamide administration (1).

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Enzalutamide requires no specified monitoring such as liver function tests (LFT) or cardiovascular monitoring (1). This can be considered a major advantage over the current SOC, abiraterone, for which LFT need to be performed every two weeks for the first three months of treatment, as well as monthly monitoring of blood pressure, serum potassium and fluid retention (2) all of which may be associated with an increase in the number of clinic visits and blood tests required. This may add to the burden of disease particularly if the patient needs to be taken by National Health Service (NHS) transport services (estimated to be 10% of patients by clinical experts) or a relative, to have their blood investigations completed (4).

In circumstances where enzalutamide is co-administered with an anticoagulant metabolised by CYP2C9, such as warfarin or acenocoumarol, additional international normalised ratio (INR) monitoring should be conducted (1).

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Like all other treatments in this patient population, enzalutamide is likely to be administered with LHRH agonists.

Enzalutamide is generally well tolerated and unlike alternative treatment options approved for mCRPC (abiraterone (2), cabazitaxel (16) and docetaxel (17)), enzalutamide does not need to be administered with concomitant corticosteroids, but can be at the discretion of the clinician.

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Metastatic CRPC is an advanced stage PC, when the disease shows signs of progression despite castrate levels of testosterone. Patients with castrate resistant disease in whom cancer cells have metastasised from the prostate to other parts of the body, most notably the bones, have mCRPC and it is the presence of metastatic disease which is often associated with symptoms.

In the early stages, PC is localised to the prostate and driven by androgens. At this stage, the disease may be cured with surgery or radiotherapy, or depending on the risk/benefit conservative management may be adopted (watchful waiting/active surveillance) (7). Patients who have inoperable locally advanced or metastatic disease at diagnosis or who have inoperable recurrent disease are treated with ADT as the disease is usually 'hormone sensitive' at this stage.

As the disease progresses, the tumour ceases to respond to androgen deprivation and becomes castration-resistant. CRPC tumours are not sensitive to ADT but may respond to therapy with anti-androgens (or anti-androgen withdrawal), inhibitors of androgen production, and estrogenic agents that further inhibit luteinising hormone (LH) (18). At the point of diagnosis of castrate resistance, most patients (84%) will also have metastatic disease (19). Of the patients with no metastases present at diagnosis of CRPC, 33% can expect to develop them within 2 years (19).

The prevailing mechanism underlying CRPC involves AR signalling being activated despite castrate levels of androgens. The ongoing production of androgens by the adrenals and PC cells themselves are thought to be key mechanisms of ongoing AR signalling along with AR gene amplification and over expression (12).

Most patients receive two or more hormonal manipulations and are then offered chemotherapy as the disease continues to progress (20). A randomised trial in mCRPC comparing docetaxel administered every three weeks vs. docetaxel weekly, vs. mitoxantrone showed a significant survival benefit for docetaxel every three weeks, but this response is not durable (21). Once patients progress on or following docetaxel, they may go on to receive post-docetaxel therapy for castrate resistant disease. Because many of these resistant tumours continue to overexpress ARs, second generation anti-androgens such as enzalutamide that are both more potent and pure antagonists represent a treatment breakthrough for patients who have failed docetaxel treatment. It is in these patients where enzalutamide has demonstrated significant benefit.

Currently, abiraterone is the only treatment recommended by NICE for mCRPC in a post-chemotherapy setting.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

Data from the Kantar Health CancerMPact report on CRPC suggest that in 2013 the prevalence of mCRPC in England and Wales will be 12,029, with an annual incidence (defined as patients with non-metastatic CRPC) of 3,433 (22). Of men with mCRPC around 33% will receive docetaxel chemotherapy (23). It is estimated that 75% of these patients may be candidates for further treatment with enzalutamide based on 1 year survival data following docetaxel (21) giving a potential patient population of 2,977.

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

No life-expectancy data has been published for patients with mCRPC in England and Wales. The median survival of patients with mCRPC in international clinical studies has been reviewed by Kirby et al (19) in a systematic literature review (SLR). The authors included five clinical studies where patients with mCRPC did not receive any additional line of treatment (four) or were treated with docetaxel (one). Median OS was estimated at 14 months (ranging between 9 and 30 months) (19). OS is prolonged when patients who progress on docetaxel move to the next line of treatment. Median OS defined as time from randomisation to death of any cause (24) was 15.8 months with abiraterone in the COU-AA-301 study (25).

Experts have reported no reason to assume that the survival estimates in England and Wales will differ from the OS estimates in the COU-AA-301 study (26). The patient population in COU-AA-301 was relevant to the UK population, with a large number of UK patients (COU-AA-301: n=178/1195, 14.8%).

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

A Single Technology Assessment (STA) for docetaxel in mCRPC was published in 2006 (27), and the guidance from this technology appraisal was subsequently incorporated into the PC guidelines on diagnosis and treatment published by NICE in 2008 CG58 (28). This clinical guideline covers treatment throughout the whole spectrum of PC management; from diagnosis and screening through to palliative care, including management of mCRPC. The guideline recommends docetaxel, within its licensed indications, as a treatment option for men with mCRPC only if their Karnofsky performance-status is ≥60%. It also recommends that treatment should be stopped after 10 courses of docetaxel treatment, with repeated cycles (i.e., docetaxel

rechallenge) not recommended. Concomitant use of corticosteroids (i.e., dexamethasone 0.5 mg daily) is also recommended for the treatment of mCRPC (28). The use of mitoxantrone is not discussed in the NICE CG58 guidelines.

NICE are currently in the process of updating the CG58 clinical guidelines on PC, with a revised version of these guidelines expected to be published in January 2014.

Following the publication of the 2008 clinical guideline; two other Technology Appraisals for the treatment of mCRPC in the post-chemotherapy setting were published by NICE: cabazitaxel (29) and abiraterone (5).

- Cabazitaxel (Jevtana®) was not recommended by NICE in May 2012. Therefore, cabazitaxel is only available for use through the cancer drugs fund (CDF).
- NICE recommended abiraterone for treatment of mCRPC in the post-chemotherapy setting for patients whose disease has progressed on or after one docetaxel-containing chemotherapy regimen. This recommendation is not reflected in NICE CG58 guidelines.

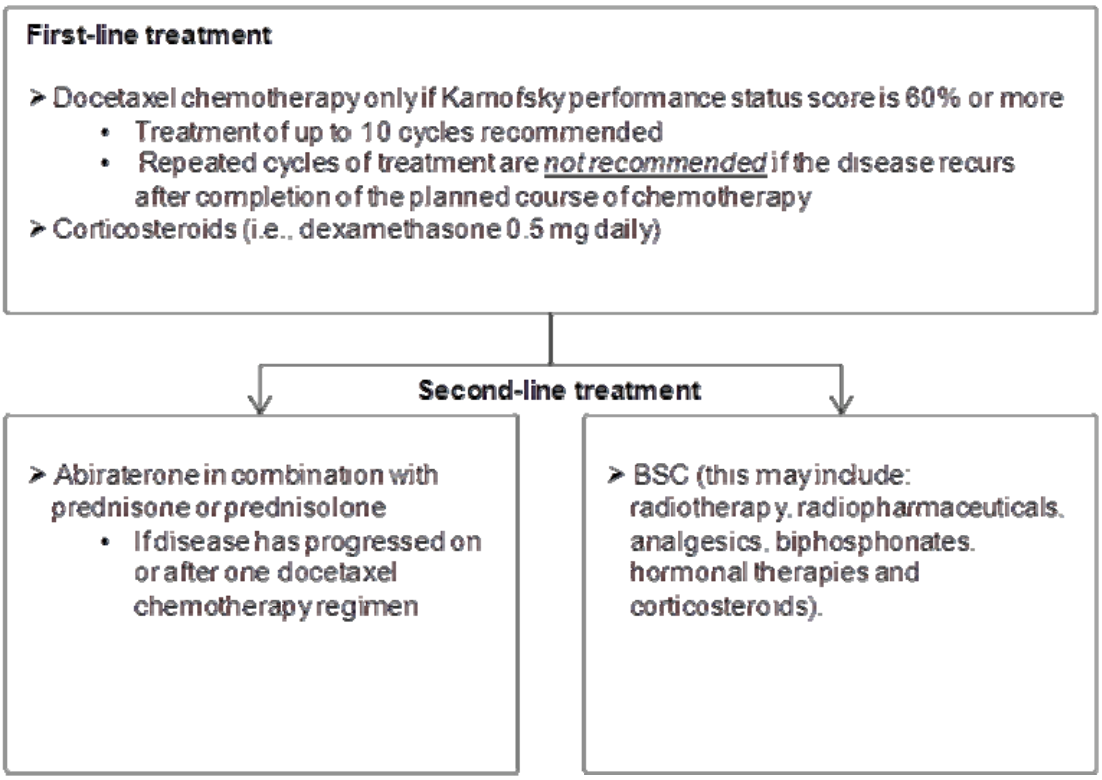
There is currently one STA ongoing for sipuleucel-T (30), a therapeutic vaccine, for the treatment of mCRPC. This technology appraisal is expected to be published in February 2014.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

The treatment pathway presented in Figure 2 has been constructed based on several NICE guidance documents and validated by expert opinion, and represents a more current pathway for mCRPC than that proposed in CG58.

As discussed in section 2.4, since the publication of CG58 abiraterone has been recommended for use in the post docetaxel chemotherapy setting.

Figure 2: Treatment algorithm of mCRPC in UK clinical practice



Note: The current treatment algorithm is applicable to NHS England and Wales only. It should also be noted that following a negative NICE recommendation cabazitaxel is only funded through the cancer drug fund on a case by case basis.
Source: NICE CG58 Prostate Cancer (28); TA225 cabazitaxel (29); TA259 abiraterone (5); Ad Board 2013(4).
Abbreviation: BSC: best supportive care; mCRPC: metastatic castrate-resistant prostate cancer.

Enzalutamide is anticipated to be used instead of abiraterone having demonstrated a small benefit in OS, and statistically significant benefits in rPFS, PSA response rate and QoL. Enzalutamide may offer financial and administrative benefits by requiring less routine product specific monitoring for liver toxicity, hypokalaemia, fluid overload and blood pressure, therefore avoiding associated hospital visits and clinician contact (3) (31).

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Clinical experts have described how the SOC has changed following the marketing authorisation of abiraterone in a post-chemotherapy setting (4). Prior to this licence physicians had a very limited choice of therapies and were typically restricted to best supportive care (BSC) – comprising: radiopharmaceuticals, analgesics, bisphosphonates, hormonal therapies and corticosteroids. Radiotherapy is also considered as BSC however, in AFFIRM when radiotherapy was given this was reported as a SRE event.

Some physicians used mitoxantrone (although unlicensed in mCRPC) prior to the license of any alternative; however no clinical evidence is available to support any survival benefit in mCRPC patients (4).

While abiraterone is an innovative addition to the limited treatment options that have been available to mCRPC patients, the use of abiraterone is still associated with several clinical considerations which highlight the need for further treatment options.

Firstly, not all patients respond to abiraterone as indicated by the high proportion of patients (approximately 30%) who showed PSA progression within three months in COU-AA-301 study (24). An alternative therapeutic option is needed for these patients who do not respond to abiraterone treatment.

Secondly, abiraterone has been associated with hepatotoxicity requiring regular monitoring of the liver function (2). This is not required for patients on enzalutamide (1), and as such less monitoring and associated hospital visits are anticipated for patients treated with enzalutamide. Similarly, abiraterone patients also require fluid retention, hypertension and hypokalaemia to be monitored.

Thirdly, abiraterone must be taken without food, to avoid increasing systemic exposure (2). Enzalutamide can be taken with or without food allowing patients flexibility and simplifying treatment.

Lastly, abiraterone must be administered with steroids to reduce the effects of mineralocorticoid excess inherent from its mechanism of action (2). Enzalutamide can be administered with or without steroids, allowing patients and clinicians the option of avoiding the steroid-related side-effects if clinically appropriate.

Cabazitaxel is also a licensed comparator, but following a non-recommendation by NICE, is only available in England via the CDF. Clinical experts report that use of cabazitaxel is declining given the availability of abiraterone via NHS commissioning (4).

Abiraterone was recently licensed for use in a pre-chemotherapy setting, i.e., the treatment of mCRPC in adult men who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated (32). This indication is not within the scope of the current decision problem and is therefore not considered relevant to this submission.

2.7 Please identify the main comparator(s) and justify their selection.

The comparators in the post-docetaxel setting considered in this submission are: abiraterone and BSC. Mitoxantrone is not licensed for use in mCRPC and is not included in the NICE 2008 CG (28). Mitoxantrone is not considered a relevant comparator to the decision problem and will not be discussed hereafter. Despite being included in the scope, mitoxantrone has a very low market share leading both clinical experts and NICE to recommend removing it from the submission.

The most relevant comparator is abiraterone (Zytiga®, Janssen-Cilag Ltd) administered with prednisone or prednisolone. In England and Wales oral abiraterone is the treatment of choice for mCRPC that has progressed on or after docetaxel therapy, but its administration is restricted to those patients who have received only one docetaxel containing chemotherapy regimen (5) (7). In patients who have received two previous docetaxel containing chemotherapy regimens, the only comparator is BSC which includes radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, hormonal therapies, and corticosteroids.

At present, patients in the post-docetaxel setting in the NHS who are not eligible for abiraterone are likely to be treated with BSC.

Cabazitaxel is only funded in England through the CDF following a negative NICE recommendation. Given that it is currently not recommended by NICE, cabazitaxel is not considered in this submission as a comparator for enzalutamide in the post-docetaxel setting, and is not included in the final scope.

The evidence of clinical efficacy of enzalutamide in the label indication comes primarily from a randomised, double-blind placebo-controlled phase III study (AFFIRM) (3). The comparator arm in this study was placebo plus BSC. At the time of developing the protocol for this study no treatment other than BSC was approved for patients with mCRPC in the post-docetaxel setting.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

In AFFIRM enzalutamide had an acceptable safety profile. The overall incidences of AEs with enzalutamide were comparable to that with placebo. “Very common” all grade adverse drug reactions were hot flushes and headaches, and “common” adverse drug reactions were neutropenia, visual hallucinations, anxiety, cognitive disorder, memory impairment, hypertension, dry skin, pruritus, fractures (includes all fractures with the exception of pathological fractures), and falls (15). Adverse events were generally manageable with symptomatic treatment and basic medical interventions (e.g antihypertensive medication) and were generally mild, and resulted in infrequent dose reductions, dose interruptions, or discontinuations.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

As enzalutamide is administered orally at the patient’s home there are no anticipated costs due to location of care, staff or administration. Monitoring will be conducted as per good clinical practice, but there are no routine monitoring requirements (1). Unlike the SOC abiraterone, regular monitoring for liver toxicity, hypokalaemia and fluid retention is not needed for patients on enzalutamide, and may represent a resource saving (33) (34).

2.10 Does the technology require additional infrastructure to be put in place?

It is not anticipated that additional infrastructure will be required. Enzalutamide is an oral treatment which can be taken at home. Further, enzalutamide is likely to improve convenience over the current SOC by allowing prescription with or without steroids, administration with or without food and no additional monitoring of liver toxicity, hypokalaemia and fluid retention (1), all of which may lead to reduced physician contact and use of NHS resources as compared to abiraterone.

3 Equality

3.1 *Identification of equality issues*

3.1.1 Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

Astellas are not aware of any issues relating to equality or equalities in NICE guidance or protocols of the treatment of mCRPC.

3.1.2 How has the analysis addressed these issues?

Not applicable.

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Enzalutamide is anticipated to be the treatment of choice in patients with mCRPC whose disease has progressed on or after docetaxel therapy.

Enzalutamide is the first and only AR antagonist that blocks the AR signalling pathway at three distinct levels:

- Competitively inhibits binding of androgens to AR in the cytosol.
- Inhibits the nuclear translocation of androgen receptors.
- Inhibits the association of the AR with DNA.

In the AFFIRM study, its mechanism of action was translated into a significantly longer OS and progression free survival (PFS) than BSC with comparable safety profile and tolerability (3).

The mechanism of action of enzalutamide is clearly distinct to that of abiraterone, an androgen biosynthesis inhibitor that inhibits the enzyme cytochrome P450 17 (CYP17) (2). Abiraterone thus inhibits synthesis of androgens but does not have any subsequent effect on the AR signalling pathway.

Unlike abiraterone, enzalutamide can be administered without steroids. The safety profile of enzalutamide does not need concomitant administration of steroids and therefore, their side effects can be avoided. Further, enzalutamide can be administered with or without food which renders its administration simpler than that of abiraterone in which absorption is modified by food intake (1). Experts have reported that this is a significant benefit and is a frequently reported source of concern/ enquiry for patients currently taking abiraterone, in particular for those patients who have concomitant medications to consider (4).

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

All health benefits were included in the quality-adjusted life year (QALY) calculation.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Not applicable.

5 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Men with mCRPC whose disease has progressed on or after docetaxel	As per the final scope	
Intervention	Enzalutamide	Enzalutamide once daily 160 mg (four x 40 mg) capsules	
Comparator(s)	Abiraterone in combination with prednisone or prednisolone Mitoxantrone alone or in combination with prednisolone BSC (this may include radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies, and corticosteroids).	As per the final scope, with the exception of not considering mitoxantrone as a comparator (section 2.7) Radiotherapy is considered as BSC but in AFFIRM its administration was reported as a SRE	Mitoxantrone is not licensed for mCRPC nor is it listed in NICE clinical guidelines as a treatment option for mCRPC, hence it was agreed with NICE during the "Section A meeting" that mitoxantrone would not be considered a relevant comparator in the current decision problem.
Outcomes	The outcome measures to be considered include: overall survival progression-free survival response rate prostate-specific antigen (PSA) response adverse effects of treatment Health-related quality of life (HRQoL).	As per the final scope	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The model developed is in line with the final scope. The current model is a Markov model with three health states: • Stable disease • Progressive disease • Dead The time horizon is 10 years; this time horizon is assumed to be sufficient to capture the remaining lifetime of mCRPC patients. The base case compares enzalutamide + BSC with the two available treatment alternatives: • Abiraterone (+ prednisolone + BSC) • BSC alone	
Subgroups to be considered	None	None	
Special considerations, including issues related to equity or	None	End-of-Life (EOL) criteria: to compare enzalutamide against BSC (section 7.10.4).	

equality			

Section B – Clinical and cost effectiveness

6 Clinical evidence

6.1 *Identification of studies*

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

A SLR (31) was conducted to identify clinical evidence regarding the efficacy and safety of both enzalutamide and comparator drugs as outlined in the scope, and to inform an indirect treatment comparison (ITC). The scope of the SLR included both randomised and non-randomised trials. The results for the studies with the comparator drugs are presented in section 6.7.

The databases searched for the SLR are detailed in Table 4 and supplemented by manual searching of the bibliographies of relevant articles and with unpublished data from the manufacturer. Using Boolean operators, the searches combined terms (including MeSH headings as appropriate) for mCRPC, pharmacological intervention(s) of interest, and clinical trial design. The search strategy is provided in section 10.2.

Table 4: Databases searched for clinical review

Topic	Inclusion criteria
Clinical efficacy and safety	PubMed/MEDLINE, Cochrane Library, EMBASE, clinical trial.gov, ClinLife; Endract; Trip, WHO ICTRP, Medline (R) In-Process, Conference proceedings (ASCO, ASCO-GU, ESMO, AUA, EUA, ECCO)
QoL	PubMed/MEDLINE, Cochrane Library[1], EMBASE, ProQolid, CEA registry, Medline (R) In-Process, Conference proceedings (ASCO, ASCO-GU, ESMO, AUA, EUA, ECCO, ISPOR; ISOQOL).

Source: SLR Report 2013 (31)
[1]Cochrane Library including Database of Abstracts of Reviews of Effects (DARE) and National Health Service Economic Evaluation Database (NHS EED)
Abbreviations: ASCO: American society of clinical oncology; ASCO-GU: American society of clinical oncology genitourinary cancers symposium; AUA: American urological association; EAU: European association of urology; ESMO: European society for medical oncology; ECCO: European cancer organisation; ISOQOL: International society for quality of life research; ISPOR: International society for Pharmacoeconomics and outcomes research; QoL: quality of life.

In agreement with NICE requirements, none of the searches were restricted by language and all searches were limited by date of publication: last 20 years for publications and the year 2012 for conference abstracts listed above. Full details of the searched articles can be found in appendix 2, section 10.2.

6.2 *Study selection*

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

The inclusion and exclusion criteria in the SLR can be found in Table 5.

Publications with a level of evidence of 1, 2, or 3 (according to the centre of evidence based medicine (CEBM) guidance (35)) assessing enzalutamide or any of the other interventions or comparators in patients with mCRPC who have progressed while being treated with docetaxel or afterwards were considered for review. Only those studies with two or more treatment groups were reviewed; single arm studies were excluded. When the results of a study had been published at several data cut-offs, only the final data for each relevant endpoint were reviewed herein. For example, if final OS data for a given study were published in Author 2000 and PFS in Author 1998, both articles were reviewed. However, if interim OS or PFS data were provided in Author 1996, this article was not reviewed.

Table 5: Eligibility criteria use in search strategy

	Clinical effectiveness
Inclusion criteria	**Population:** mCRPC that has progressed on or after docetaxel treatment. **Interventions**: enzalutamide, abiraterone (plus prednisone or prednisolone), mitoxantrone (plus prednisone or prednisolone). **Outcomes**: OS, PFS, ORR, PSA response, time to first SRE, TTD, AEs. **Study design:** randomised or non-randomised studies with two or more arms. **Language restrictions:** none.
Exclusion criteria	**Population:** patients not in the post-chemotherapy setting. **Interventions:** studies that did not include at least one of the interventions of interest. **Outcomes:** studies that did not assess at least one of the outcomes of interest. **Study design:** case studies. **Language restrictions:** none.

Source: SLR report 2013 (31)
Abbreviations: AE: adverse events; mCRPC: metastatic castrate-resistant prostate cancer; OS: overall survival; ORR: objective response rate; PFS: progression-free survival SRE: skeletal-related events; TTD: time to treatment discontinuation.

6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

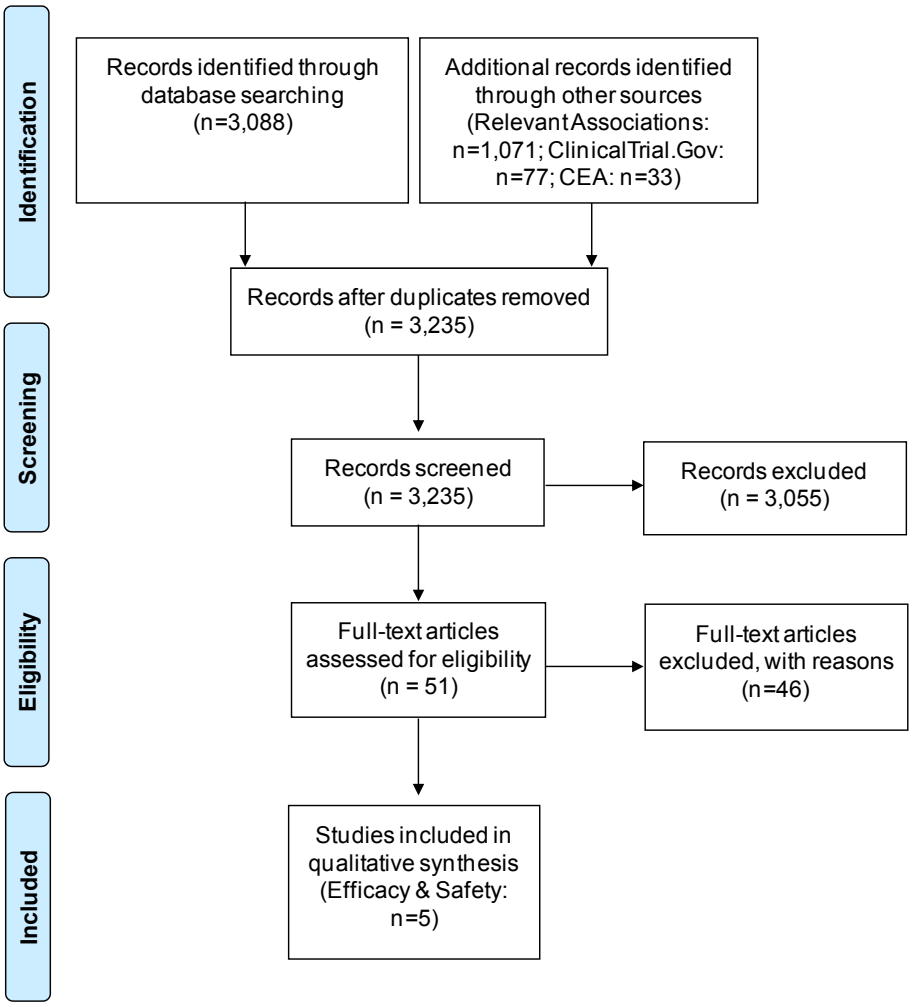
The SLR was conducted on January 2, 2013 and covered the period between 01 January 1993 and 01 January 2013.

Citations were first screened based on the title and abstract supplied with each citation. Those that did not match the eligibility criteria were excluded. Full-text copies of all references that could potentially meet the eligibility criteria were included at this stage.

The flow diagram below shows the records identified in each database as well as the number of records included and excluded from the SLR (Figure 3).

The eligibility criteria were then applied to the full-text citations. At each stage two independent reviewers screened the abstracts/full text articles; any discrepancies were reconciled between both reviewers.

Figure 3: PRISMA flow diagram with the efficacy and safety studies of enzalutamide identified through the predefined search strategy



Source: SLR Report 2013 (31)

6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

AFFIRM is the only study that compares enzalutamide to other treatment therapies in post-chemotherapy mCRPC (section 2.7). In this study patients in both treatment arms received BSC in addition to the study treatment. Therefore, the placebo arm can be considered the equivalent to BSC.

Data from the AFFIRM study comparing enzalutamide with placebo detailed in this submission are drawn from both published and unpublished sources:

- Published articles: Scher 2012a (3), De Bono 2012 (36); Published posters: Scher 2012b (13).
- Unpublished: AFFIRM clinical study report (CSR) (15) and the patient reported outcome (PRO) report (37).

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group.

One study has been conducted with enzalutamide in the post-docetaxel setting. This study is a phase III placebo-controlled study comparing enzalutamide plus BSC versus placebo plus BSC. The design of this study is summarised in Table 6.

Table 6: List of relevant randomised clinical trials selected for the NICE submission

Study (design)	Intervention	Comparator	Population	Previous chemo-therapy	References
AFFIRM (Phase III, DB, prospective, multinational, PLA-controlled trial)	ENZA (n=800): • ENZA 160 mg PO OD Use of glucocorticoids was allowed but not required	PLA (n=399) • PLA PO OD Use of glucocorticoids was allowed but not required	ENZA: Median age (range): 69 (41, 92) Race: White 745 (93.1%) ECOG 0/1/2: 37.3%/54.0%/8.8% Median PSA (range), ng/mL: 107.7 (0.2, 11794.1) PLA: Median age (range): 69 (49, 89) Race: White: 366 (91.7%) ECOG 0/1/2: 39.1%/52.9%/8.0% Median PSA (range), ng/mL: 128.3 (0.0−19000.0)	100% prior DTX ENZA • 1 course: 72.4% • 2 courses: 24.5% • ≥2 courses: 3.1% PLA • 1 course: 74.2% • 2 courses: 23.8% • ≥2 courses: 2.0%	Scher 2012a (3) De Bono 2012 (36) Scher 2012b (13) AFFIRM CSR (April 24, 2012) (15) PRO 2012 (37)

Abbreviations: ENZA: enzalutamide; DB: double-blind; DTX: docetaxel; ECOG: eastern cooperative oncology group; OD: once daily; PLA: placebo; PO: per os (oral); PRO: patient reported outcomes.

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

In the AFFIRM trial we assumed the placebo arm to represent BSC, the only treatment available when the trial was designed.

No head-to-head randomised controlled trial (RCT) comparing enzalutamide with abiraterone has been conducted. This was confirmed in the SLR.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

No identified studies were excluded from further discussion.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

No relevant non-RCTs were identified during the SLR.

6.3 *Summary of methodology of relevant RCTs*

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

The tolerability, pharmacokinetic (PK), and antitumor activity of enzalutamide were studied in a phase I multi-centre, open-label, dose-escalation study of enzalutamide in 140 patients with mCRPC (S-31000-1-01) (38). Patients were treated with

enzalutamide at doses of 30-600 mg/day until disease progression or intolerable side effects developed. The most commonly reported AE was fatigue, which appeared to be dose-dependent and generally resolved after dose reduction. No deaths due to AEs were reported. The median time to PSA progression was 316 days (38).

Based on the encouraging antitumor activity and safety profile seen in the S-3100-1-01 study, the AFFIRM phase III study was initiated with the intent of serving as an adequate and well-controlled study to demonstrate the efficacy and safety of enzalutamide in patients with mCRPC.

The clinical and QoL outcomes of AFFIRM have been published in the *New England Journal of Medicine* (3) and presented at European Society for Medicine Oncology (ESMO) 2012 (39) and American Society of Clinical Oncology - Genitourinary (ASCO-GU) 2012 (13). All analyses used data as of the interim analyses (IA) date of 25, 2011, i.e., the date at which the 520th death occurred. The analyses presented in this report were based on these data. The only exception is for final OS for which the date of the database lock and data unblinding was also used (December 2011) (15) (40).

The primary objective of AFFIRM was to determine the efficacy and safety of oral enzalutamide (160 mg/day) compared to placebo when administered to subjects with progressive mCRPC previously treated with docetaxel-based chemotherapy. Subjects could have received up to two prior chemotherapy regimens with at least one regimen containing docetaxel. Re-treatment with docetaxel was not considered a second regimen. However, adding another agent (such as bevacizumab) to docetaxel was considered a second regimen.

AFFIRM data have been analysed at two different data cut-offs:

- Interim analysis (IA): Predefined analysis at the 520th death (80% of the 650 targeted numbers of events for final analysis), i.e., 25 September 2011. This is the cut-off date for all analyses presented in this submission, except where specified otherwise.

- Database lock: The date of the 576th death was 16 December 2011. A final analysis of OS and all AEs was conducted at database lock when the data was unblinded. The analyses for these two parameters are also presented in this submission.

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

The methodology used in AFFIRM is provided in Table 7.

Table 7: Summary of methodology of the AFFIRM study

Trial title	AFFIRM: A multinational phase III, randomised, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 in patients with progressive castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy.
Location	The study was conducted at 156 sites in 15 countries (Argentina, Australia, Austria, Belgium, Canada, Chile, France, Germany, Italy, the Netherlands, Poland, South Africa, Spain, United Kingdom [12 sites] and the United States).
Design	AFFIRM was an international, randomised, double-blind, placebo-controlled, global multicentre Phase III study of enzalutamide in patients with mCRPC who had previously been treated with one or two chemotherapy regimens, at least one of which containing docetaxel.
Duration of study	24 months at IA of September 25, 2011*.
Method of randomisation	The study was centrally randomised by IVRS using a permuted block method. Randomisation was stratified by baseline ECOG performance status score (0-1 or 2) and mean BPI-SF Question #3 score averaged over the 7 days prior to randomisation ("On a scale of 0 to 10, please rate your pain at its worst in the last 24 hours," stratified by < 4 vs. ≥ 4). Patients were randomised in a 2:1 ratio, to receive oral enzalutamide (160 mg orally once daily as four 40-mg capsules) or matched placebo capsules. In addition to enzalutamide and placebo, all patients received BSC.
Method of blinding (care provider, patient and outcome assessor)	The control for this blinded study was placebo capsules that appeared identical to the enzalutamide capsules. All patients, Investigators, site personnel, and the Sponsor's staff involved in the conduct of the study were blinded to treatment assignment. The Sponsor, sites, and patients remained blinded to study drug until after database lock on 16 December 2011. An independent Data Monitoring Committee monitored and reviewed safety data on an ongoing basis.
Intervention(s) (n =) and comparator(s) (n =)	Intention-to-treat (ITT): N=1,199. • ENZA: n=800. • PLA: n=399.
Primary outcomes	OS: from randomisation to death from any cause. Available OS: IA (September 25, 2011) and database lock (December 16, 2011).
Secondary outcomes	• Time to PSA progression. • Radiographic progression-free survival (as defined by RECIST 1.1). • Time to first skeletal-related event. • FACT-P response rate. • Rate of pain palliation at Week 13.
Exploratory outcomes	• Prostate specific antigen response rate (50% or 90% decrease in PSA • Best overall radiographic response. • EQ-5D. • ECOG performance status. • Pain progression rate. • Time to pain progression. • Change from baseline in pain severity and pain interference. • Change from baseline in QoL scores. • Time to QoL deterioration.
Post-hoc outcomes	• Modified PFS • Time to treatment discontinuation. • Impact of corticosteroid use.
Duration of follow-up	Median duration of follow up was 14.4 months at IA and 15.0 months at database lock.

Source: AFFIRM Clinical Study Report (15)
Abbreviations: BPI: brief pain inventory; ECOG: eastern cooperative oncology group; ENZA: enzalutamide; FACT-P: functional assessment of cancer therapy-prostate; IA: Interim Analysis; IVRS: interactive voice and web response services; mPFS: modified progression-free survival; PLA: placebo; RECIST: response evaluation criteria in solid tumours; SRE: skeletal-related events.
Note: *IA took place on 25 September 2011; data lock was December 2012. The analyses presented in this report, unless otherwise specified were based on the IA dataset.

The following assessments of PC status were collected during the course of the study: survival, PSA, soft tissue disease on computed tomography (CT) scan or on

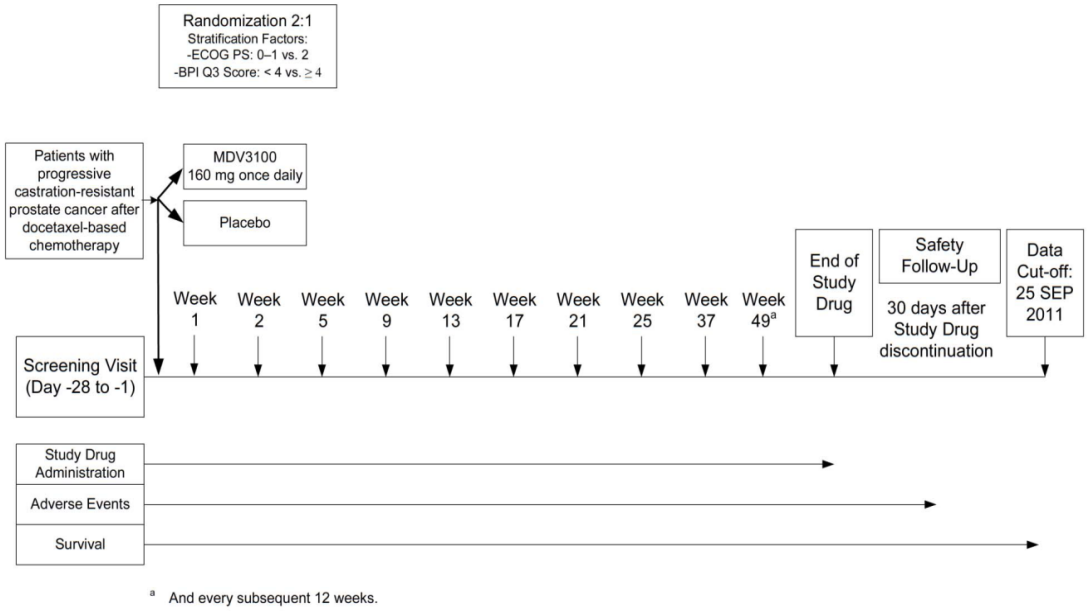
magnetic resonance imaging (MRI), bone disease on radionuclide bone scans, SREs which were assessed at all study visits, Brief Pain Inventory – Short Form (BPI-SF) Question #3 score administered at Week 13 only, analgesics use, Functional Assessment of Cancer Therapy – Prostate (FACT-P) which was administered at baseline and then at every regular study visit beginning at Week 13, the European Quality of Life-Domain Scale (EQ-5D) questionnaires (at select centres in Europe only) administered at screening, Week 13, and Week 25 visits, and at visits every subsequent 12 weeks , and circulating tumour cells (at select centres) (Figure 4).

Throughout the study, safety and tolerability were assessed by recording of AEs, monitoring of vital signs and physical examinations, safety laboratory evaluations, and 12-lead ECGs. Central laboratories were used for evaluation of safety laboratory assessments and ECGs.

Patients had a Safety Follow-Up visit 30 days after their last dose of study drug or prior to the initiation of another systemic antineoplastic therapy, whichever occurred first. AE and serious AEs were collected for 30 days after the patient's last dose of study drug or prior to the initiation of another systemic antineoplastic therapy, whichever occurred first. After treatment discontinuation, patients were followed for radiographic progression, occurrence of SRE, and death. Additional treatments for PC were also collected.

Based on the IA results (September 2011), on 02 November 2011 the Data Monitoring Committee recommended that the AFFIRM study be halted and that patients in the control group be crossed over to enzalutamide. The Sponsor, sites, and patients remained blinded to study drug until after database lock on 16 December 2011.

Figure 4: Study design and timings of assessments



Source: AFFIRM Clinical Study Protocol 2012 (41)
Abbreviations: BPI Q3: brief pain inventory – question #3; ECOG: eastern cooperative oncology group; PS: performance status.

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any difference between the trials.

Study selection criteria are listed in Table 8. Briefly, patients were eligible for enrolment if they had a histologically or cytologically confirmed diagnosis of PC, castrate levels of testosterone (<50 ng per deciliter [1.7 nmol per litre]), previous treatment with docetaxel and progressive disease defined according to Prostate Cancer Clinical Trials Working Group (PCWG2) criteria, including three increasing values for PSA or radiographically confirmed progression with or without a rise in PSA level.

Table 8: Eligibility criteria of the AFFIRM RCT

Inclusion criteria	Exclusion criteria
• Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features • Ongoing ADT with a GnRH analogue or orchiectomy (i.e., surgical or medical castration) • For patients who have not had an orchiectomy, there must be a plan to maintain effective GnRH-analogue therapy for the duration of the trial • Serum testosterone level < 1.7 nmol/L (50 ng/dL) at the Screening visit • Patients receiving bisphosphonate therapy must have been on stable doses for at least four weeks • Progressive disease by PSA or imaging after docetaxel-based chemotherapy in the setting of medical or surgical castration. Disease progression for study entry was defined as PSA progression, Soft tissue disease progression according to RECIST or Bone disease progression defined by two or more new lesions on bone scan. • ≤2 prior chemotherapy regimens with ≥1 regimen containing docetaxel • ECOG performance status of 0–2; • Estimated life expectancy of ≥6 months • Able to swallow the study drug and comply with study requirements • Willing and able to give informed consent.	• Severe concurrent disease, infection, or co-morbidity that would make the patient inappropriate for enrolment • Metastases in the brain or active epidural disease (patients with treated epidural disease are allowed) • Absolute neutrophil count < 1,500/μL, platelet count < 100,000/μL, and haemoglobin < 5.6 mmol/L (9 g/dL) at the Screening visit • Total bilirubin, alanine aminotransferase or aspartate aminotransferase >2 times the upper limit of normal at screening • Creatinine > 177 μmol/L (2 mg/dL) at screening; • Albumin < 30 g/L (3.0 g/dL) at screening • History of another malignancy within the previous 5 years other than curatively treated non-melanomatous skin cancer • Treatment with AR antagonists, 5-α reductase inhibitors estrogens, chemotherapy, therapeutic immunizations for prostate cancer, herbal products that may decrease PSA levels or systemic corticosteroids ≥ the equivalent to 10 mg of prednisone/prednisolone per day, ketoconazole, an investigational agent or Major surgery within four weeks of enrolment or plans to initiate treatment with any of these treatments during the study • Radiation therapy within 3 weeks (if single fraction of radiotherapy within 2 weeks) and radionuclide therapy within 8 weeks of enrolment (Day 1 visit) • Planned palliative procedures for alleviation of bone pain such as radiation therapy or surgery • Structurally unstable bone lesions suggesting impending fracture • History of seizure, including any febrile seizure, loss of consciousness, or transient ischemic attack within 12 months of enrolment (Day 1 visit), or any condition that may pre-dispose to seizure (e.g., prior stroke, brain arteriovenous malformation, head trauma with loss of consciousness requiring hospitalization) • Clinically significant cardiovascular disease • Have used or plan to use from 30 days prior to enrolment medications known to lower the seizure threshold or prolong the QT interval • Participation in a previous clinical trial of an investigational agent that blocks androgen synthesis or AR unless the patient had a PSA rise compared to his baseline level within the first 12 weeks of treatment with the investigational agent • Participation in a previous clinical trial of enzalutamide • Gastrointestinal disorder affecting absorption.

Source: AFFIRM Clinical Study Report (15)
Abbreviations: ADT: androgen deprivation therapy; AR: androgen receptor; ECG: electrocardiogram; ECOG: eastern cooperative oncology group; GnRH: gonadotropin releasing hormone; MUGA: multi-gated acquisition scan; NYHA: New York heart association; PSA: prostate-specific antigen; QTcF: QT interval by the fridericia correction formula; RECIST: response evaluation criteria in solid tumours.

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Both treatment arms were well balanced in terms of demographics, baseline disease characteristics and medical history (Table 9).

The majority of patients in both arms had an Eastern Cooperative Oncology Group (ECOG) of 0 (enzalutamide: 37.3%; placebo: 39.1%) or 1 (enzalutamide: 54.0%; placebo: 52.9%), had received a single prior chemotherapy regimen (enzalutamide: 72.4%; placebo: 74.2%) and had both bone and soft tissue disease at time of screening (enzalutamide: 63.1%; placebo: 60.4%).

Table 9: Demographics and baseline characteristics of patients in AFFIRM

	Enzalutamide(N = 800)	Placebo (N = 399)
Age (years)		
Median	69	69
Range	41-92	49-89
Race		
White	745 (93.1%)	366 (91.7%)
Black or African American	27 (3.4%)	20 (5.0%)
Asian	5 (0.6%)	8 (2.0%)
Indian/Alaskan	1 (0.1%)	1 (0.3%)
Other	21 (2.6%)	4 (1.0%)
Baseline ECOG performance		
0	298 (37.3%)	156 (39.1%)
1	432 (54.0%)	211 (52.9%)
2	70 (8.8%)	32 (8.0%)
PSA (ng/ml)		
Median	107.7	128.7
Range	0.2-11,794	0-19,000
No of previous chemotherapy treatment		
1	579 (72.4%)	296 (74.2%)
2	196 (24.5%)	95 (23.8%)
≥3	25 (3.1%)	8 (2.0%)
Previous chemotherapy treatment		
Docetaxel	800 (100.0%)	399 (100.0%)
Cabazitaxel	3 (0.4%)	0 (0.0%)
Anthracycline	77 (9.6%)	40 (10.0%)
Previous cancer therapy		
Surgery	429/797 (53.8%)	193/398 (48.4%)
Radiotherapy	570/797 (71.5%)	285/398 (71.6%)
Hormonal	796/797 (99.8%)	396/398 (99.4%)
Time (months) from Initial Diagnosis of Prostate Cancer to Randomisation		
Mean (SD)	86.1 (54.83)	81.9 (50.89)
Median	70.9	71.6
Gleason Score at Diagnosis		
2–4	10 (1.4%)	8 (2.2%)
5–7	349 (48.1%)	167 (45.5%)
8–10	366 (50.4%)	193 (52.4%)
Missing	74	31
Disease Localisation at Screening		

	Enzalutamide(N = 800)	Placebo (N = 399)
Bone only	225 (28.1%)	123 (30.8%)
Soft tissue only	62 (7.8%)	34 (8.5%)
Both bone and soft tissue	505 (63.1%)	241 (60.4%)
None	8 (1.0%)	1 (0.3%)
Type of Disease Progression at Study Entry		
PSA progression only	326 (41.0%)	164 (41.2%)
Radiographic progression	470 (59.0%)	234 (58.8%)
Bone only	205 (25.6%)	117 (29.3%)
Soft tissue only	127 (15.9%)	59 (14.8%)
Both bone and soft tissue	138 (17.3%)	58 (14.5%)
No evidence of bone or soft tissue disease	0 (0.0%)	0 (0.0%)
Missing	4	1
Measurable Soft Tissue Disease at Screening		
Yes	446 (55.8%)	208 (52.1%)
No	354 (44.3%)	191 (47.9%)
Distribution of Disease at Screening		
Bone	730 (92.2%)	364 (91.5%)
Lymph node	442 (55.8%)	219 (55.0%)
Visceral liver	92 (11.6%)	34 (8.5%)
Visceral lung	122 (15.4%)	59 (14.8%)
Other soft tissue	147 (18.6%)	70 (17.6%)
Missing	8	1
Number of Bone Metastases at Screening		
0	70 (8.8%)	35 (8.8%)
1	28 (3.5%)	21 (5.3%)
2–4	112 (14.0%)	45 (11.3%)
5–9	121 (15.1%)	68 (17.0%)
10–20	167 (20.9%)	79 (19.8%)
> 20	302 (37.8%)	151 (37.8%)

Source: AFFIRM Clinical Study Report (15)
Abbreviations: ECOG: eastern cooperative oncology group; PSA: prostate specific antigen; SD: standard deviation.

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQoL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice).

6.3.5.1 Primary endpoint

The primary endpoint was OS, which was defined as the time from randomisation to death from any cause in the intention to treat (ITT) population (defined as all randomised patients).

OS is considered the preferred primary endpoint; with favourable effects considered the most persuasive outcome of a clinical trial from both a clinical and methodological perspective (EMA) (42).

6.3.5.2 Secondary endpoints

The key secondary endpoints assessed in AFFIRM were:

- Time to PSA progression
- Radiographic PFS (rPFS)
- Time to first SRE
- FACT-P response rate
- Rate of pain palliation at Week 13

Time to PSA progression

PSA progression was defined according to the consensus guidelines of the PCWG2 (43) (44) as:

- ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir, with confirmation by a second consecutive value obtained ≥ 3 weeks later.
- For patients with no PSA decline at Week 13, the PSA progression date was defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the baseline was documented, which was confirmed by a second consecutive value 3 or more weeks later.

All serum PSA levels were measured by the same central laboratory. Time to PSA progression was also assessed. For this analysis, time of PSA progression was always determined by the initially noted time of progression.

Radiographic PFS

The criteria for assessing disease progression and confirmation are summarised in Table 10. Both soft tissue and bone progression at Week 13 required confirmation at a later date. rPFS included both radiographic progression and death from any cause.

Radiographic progression was defined by:

- Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 for soft tissue disease (45)
- PCWG2 criteria for bone disease (43) (44).

Unless warranted sooner, disease progression was first assessed at Week 13 and if deemed present then confirmed at least 6 weeks later. Disease progression was assessed again at Week 25 and then every 12 weeks until death. The assessment of radiographic disease progression was made by the Investigator using the results of CT or MRI and bone scans.

Table 10: Criteria for determining and confirming disease progression

Evidence of progression	Confirmation (6 weeks later)
Bone disease Appearance of ≥2 new bone lesions on bone scan	New lesions at the first scheduled reassessment at Week 13 must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should show additional new lesions compared to the Week 13 scan.
Soft tissue disease As defined by RECIST v1.1 on CT/MRI	Progression at the first scheduled reassessment at Week 13 must be confirmed by a second scan performed 6 or more weeks later. Confirmatory Scans should show progressively worsening disease compared to the Week 13 scan.

Source: AFFIRM Clinical Study Report (15)
Abbreviations: CT: computed tomography; MRI: magnetic resonance imaging; RECIST: response evaluation criteria in solid tumours.

Time to first skeletal-related event

A SRE was defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain.

An alteration of analgesic medication for bone pain was not considered a SRE. Patients were assessed for SREs at all study visits, long-term follow-up visits, safety follow-up visits, and survival follow-up telephone calls.

FACT-P response rate

The FACT-P questionnaire is a 39-item questionnaire consisting of 5 domains; “physical well-being,” “social/family well-being,” “emotional well-being,” “functional well-being,” and “additional concerns” (consisting of items relating to PC and its treatment). This questionnaire has been validated in patients with PC (46). Each item can be answered on a scale of 0–4. The sum of the score on the first 4 domains is the Functional Assessment of Cancer Therapy – General (FACT-G) score. The sum of scores on all 5 domains constitutes the FACT-P. The higher the score, the better a person’s quality of life (QoL) is (46) (47).

Patients were defined as having a positive QoL response if they had a 10-point improvement in their global FACT-P score, compared with baseline, on 2 consecutive measurements obtained at least 3 weeks apart. QoL, as measured by FACT-P, was assessed at baseline and then at every regular study visit beginning at Week 13.

Rate of pain palliation at Week 13

Only patients who had a stable and sufficient pain burden at study entry were included in the analysis of pain palliation. Pain burden was measured by Question #3 of the BPI–SF ("On a scale of 0 to 10, please rate your pain at its worst in the last 24 hours") averaged over the 7 days prior to randomisation. The BPI-SF was administered at screening and Week 13 visits.

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

6.3.5.3 Exploratory endpoints

The AFFIRM study also included the following exploratory endpoints which were pre-specified in the statistical analysis plan(48):

- PSA response rate
  - 50% decrease
  - 90% decrease
- Best overall radiographic response
- EQ-5D
- ECOG performance status
- Pain progression status
- Time to pain progression

In addition, several QoL-related endpoints were defined in the PRO statistical analysis plan (48) developed prior to the database lock:

- Change from baseline in pain severity and pain interference
- Change from baseline in QoL scores
- Time to first QoL deterioration.

PSA response rate

Confirmed and unconfirmed PSA responses, defined as ≥ 50% and ≥ 90% reductions in PSA from baseline to lowest post-baseline PSA result as determined by the central laboratory were calculated by treatment arm for patients with PSA values at the baseline assessment and at least 1 post-baseline assessment. A consecutive assessment that was conducted at least 3 weeks later was required to confirm PSA response. Exact binomial 95% confidence intervals (CIs) (Clopper-Pearson; 2-sided) were provided for the response rates. The response rates between each treatment arm were compared using a stratified Cochran-Mantel-Haenszel mean score test at the 2-sided 0.05 significance. Baseline ECOG performance status and the mean BPI-SF score (Question #3) were used as stratification factors.

Best overall radiographic response

To be eligible for the analysis of the best radiographic response, patients had to have measurable disease at screening and at least 1 target lesion. The best overall radiographic response was assessed using RECIST v1.1 as described in Table 11.

The best overall radiographic response was first assessed at Week 13, again at Week 25, and then every 12 weeks until death. The same imaging data used to determine time to radiographic progression were used to determine the best radiographic response. The assessment of best overall radiographic response was made both by the Investigator and also from the derived response assessments using tumour measurements entered by the sites. The Investigator assessment was considered the primary assessment of best radiographic response.

Table 11: Time point response: patients with target (± non-target) disease

Overall response	Target lesions	Non-target lesions	New lesions
Complete response	Complete response	Complete response	No
Partial response	Complete response	Non complete response Non-progressive disease	No
	Complete response	Not evaluated	No
	Partial response	Non-progressive disease or not at all evaluated	No
Stable disease	Stable disease	Non-progressive disease or not at all evaluated	No
In evaluable	Not all evaluated	Non-progressive disease	No
Progressive disease	Progressive disease	Any	Yes or No
	Any	Progressive disease	Yes or No
	Any	Any	Yes

EQ-5D

The EQ-5D is a standardised instrument for use as a measure of health outcome. Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each assessed on 3-point categorical scales ranging from “no problem” to “severe problem.” The EQ-5D was administered following an amendment to the protocol (April 2010) at all sites in France, Germany, Italy, Spain and the UK at the Screening, Week 13, and Week 25 visits, and at visits every subsequent 12 weeks (37).

ECOG performance status

ECOG performance status was assessed at every regularly scheduled study visit, unscheduled study visits, and the Safety Follow-Up visit. The ECOG performance status was assessed by the Investigator or Study Coordinator upon taking a history from and conducting a physical exam on the patient.

Pain progression status

Pain progression was defined as any increase in the average pain score at Week 13 compared to the baseline average pain score. To be included in the analysis of pain progression, patients had to have valid responses to Question #3 of the BPI-SF on at least 4 of the 7 days prior to randomisation, and during the 7 days preceding the Week 13 visit.

For analysis of time to pain progression, pain progression was defined as an increase above baseline in the FACT-P pain assessment, which had to be confirmed by a second consecutive assessment 3 or more weeks later.

Changes from baseline in pain severity and pain interference

The BPI-SF allows subjects to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function. It is a self-

administered questionnaire designed to capture two dimensions of pain: severity and interference. The recall period is 24 hours.

For both scales, a lower score indicates lower pain and lower interference.

Change from baseline in QoL scores

Changes from baseline in QoL scores over 25 weeks of treatment were analysed using mixed models repeated measures (MMRM) controlling for baseline covariates. A sensitivity analysis was performed based on missing data patterns (pattern-mixture model), where dropouts are assumed to follow the placebo arm evolution.

Time to QoL deterioration

Time to first QoL deterioration was assessed as a composite endpoint of death, or a decrease of ≥ 10 points on the FACT-P total score and summarised using Kaplan-Meier methods and a stratified log-rank test (2-sided, α=0.05) was used to compare the two treatment arms. Patients were stratified according to the ECOG performance-status score and the baseline means pain score (as measured by the BPI-SF Question #3).

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken).

6.3.6.1 Hypothesis objective

The primary hypothesis was to test whether enzalutamide can prolong survival in patients whose PC is resistant to primary ADT and who had previously received docetaxel chemotherapy for this disease. At the time of the initiation of the study, docetaxel was the only product with a demonstrated survival advantage in CRPC patients.

6.3.6.2 Statistical analysis

Sample size, power calculation

The study was designed to have a power of 90% to detect a hazard ratio (HR) of 0.76 for death in the enzalutamide arm as compared with the placebo arm, with a two-sided type I error rate of 0.05. It was planned to enrol approximately 1,170

patients, assuming a median survival of 15.7 months in the enzalutamide arm and 12.0 months in the placebo arm, an accrual period of approximately 12 months, and total study duration of approximately 30 months to observe the required 650 events.

A formal per-protocol (PP) interim analysis for OS was performed at 520 events. Based on the interim analysis results, in November 2011 the study Data Monitoring Committee recommended that the study be halted and that patients in the control arm be crossed over to enzalutamide. After discussions with the Steering Committee and the FDA, the number of death events required for the final analysis was reduced from 786 to 650.

The date of the 520th death (80% of the 650 targeted numbers of events for final analysis) was 25 September 2011. This is the cut-off date (IA) for all analyses presented in this submission, except where specified otherwise. Database lock and data unblinding took place on the 16 December 2011. At database lock there had been 576 events.

Data management, patient withdrawals

Survival data was captured regardless of whether a subject discontinued treatment, whereas, other endpoints were captured until treatment discontinuation as per time and event schedules.

For further information regarding patient disposition please refer to section 6.3.8**.**

A stratified log-rank test was used as the primary analysis to compare the enzalutamide and placebo arms, with a 2-sided test at the 0.05 level of significance. Patients were stratified according to baseline ECOG performance-status score and baseline mean pain score (as measured by the BPI-SF score); the OS results are presented as Kaplan–Meier curves.

Supportive analyses of OS were performed using an unstratified log-rank test and Cox proportional hazards models. Subgroup analyses were conducted to determine whether treatment effects were consistent across patient subgroups. A multivariate analysis was also performed.

Analysis of the secondary endpoints was conducted in a rank-prioritised order — the time to PSA progression, rPFS, and the time to the first SRE — with the significance of the previous endpoint gating further testing. These endpoints were tested by means of the stratified log-rank test in a protected hierarchical manner, each at the two-sided significance level of 0.05.

For the rPFS, mPFS, time to first SRE, time to PSA progression, time to pain progression, time to QoL deterioration and TTD analyses, patients who did not reach the endpoint were censored at their last assessment.

Several pain-related endpoints were assessed. The proportion of patients with pain palliation was analysed using a two-sided Cochran Mantel-Haenszel mean score test at the 0.05 level of significance. Baseline ECOG performance status and the mean BPI-SF score (Question #3) were used as stratification factors. In addition, as prespecified in the statistical analysis plan(48), an analysis was conducted looking at the Changes from baseline to Week 13 in Pain Severity and Pain Interference scores was analysed using an analysis of covariance (ANCOVA).

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post- hoc.

OS was examined in several patient subgroups that had been pre-specified in the study protocol on the basis of being accepted prognostic factors for PC, demographic features of interest, or represent different regional practice patterns.

- ECOG performance status at study entry (0 or 1 vs. 2)
- Average pain score based on Question #3 from the BPI-SF at study entry (< 4 vs. ≥ 4)
- Age (< 65 vs. ≥ 65)
- Geographic region (North America vs. Europe vs. rest of the world)
- Gleason Score at diagnosis (≤ 7 vs. ≥ 8)
- Number of prior chemotherapy regimens (1 vs. ≥ 2)

- Type of progression at study entry (PSA progression only vs. radiographic progression with or without PSA progression)
- Visceral disease at study entry (yes vs. no)
- Baseline PSA value (≤ median vs. > median)
- Baseline lactate dehydrogenase value (≤ median vs. > median)
- Baseline haemoglobin value (≤ median vs. > median).

6.3.7.1 Post-hoc analyses

In addition to the endpoints listed above, a post-hoc analysis on a modified definition of PFS and on the time to treatment discontinuation (TTD) was conducted. Both analyses were done because these two endpoints were deemed relevant for the health economic model (section 7.3.1.2).

Modified PFS

Modified PFS (mPFS) was defined as the time to radiographic progression, first SRE or death due to any cause, which ever occurred first. It is a composite endpoint that has been derived for modelling purposes by combining the primary endpoint of AFFIRM (OS) and two secondary endpoints (rPFS and time to first SRE).

The mPFS definition was analysed because it is a broader definition and probably more accurate than radiographic PFS. This definition is aligned with the PFS definition applied to abiraterone in the COU-AA-301 study, the study that led to approval of abiraterone in its post-docetaxel indication.

The mPFS results observed in AFFIRM are provided in section 6.5.3.

Time to treatment discontinuation

The TTD endpoint was assessed for modelling purposes as this was considered a more accurate reflection of what happens to mCRPC patients in clinical practice, and has previously been accepted by NICE (4) (5). For further details please refer to section 7.3.1.2.

In AFFIRM, TTD was based on a combination of criteria as patients received their assigned therapy until disease progression was documented and confirmed (i.e., confirmed radiographic progression or the occurrence of a SRE) <u>and</u> the patient was scheduled to initiate another systemic antineoplastic therapy. The occurrence of an AE where continued administration of study drug was deemed not in the patient's best interest by the Investigator and/or the Sponsor also resulted in the removal of the patient from therapy.

Participant flow

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This

information should be presented as a CONSORT flow chart.

In AFFIRM, a total of 1,199 patients were recruited and randomised to enzalutamide (n=800) or placebo (n=399). All randomised patients (i.e., ITT set) received at least one dose of enzalutamide or placebo and constituted the safety population. The numbers of patients included in each of the analyses presented here are provided in Table 12.

Table 12: Analysis sets in AFFIRM

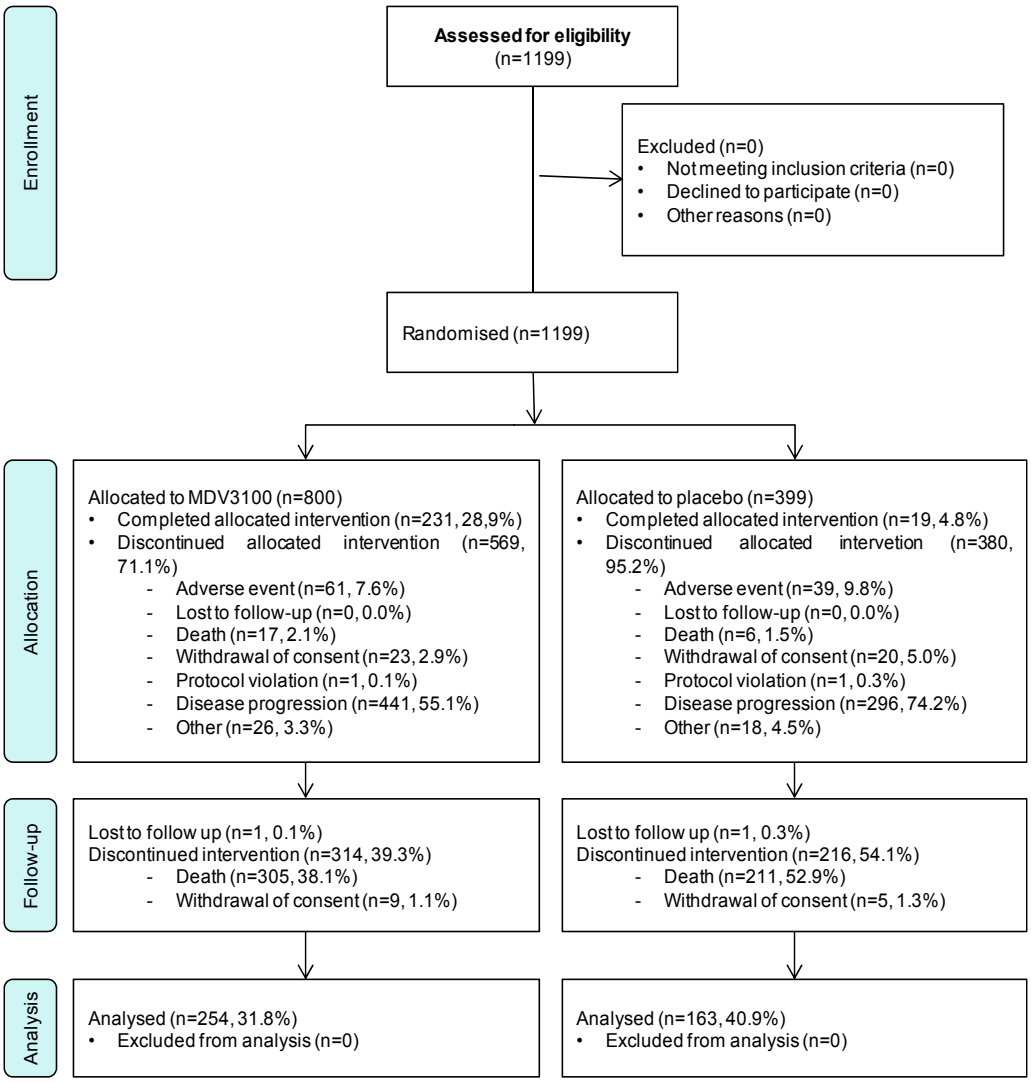
Analysis population	ENZA (N=800)	PLA (N=399)
Randomised (ITT Population)	800 (100%)	399 (100%)
Not treated with study drug	0 (0.0%)	0 (0.0%)
Evaluable for FACT-P	651 (81.4%)	257 (64.4%)
Evaluable for PSA Response	731 (91.4%)	330 (82.7%)
Evaluable for Pain Palliation	49 (6.1%)	15 (3.8%)
Evaluable for Best ORR	396 (49.5%)	167 (41.9%)
Evaluable for EQ-5D*	146 (18.3%)	68 (17.0%)
Evaluable for Pain Progression Rate	625 (78.1%)	259 (64.9%)
Safety Population	800 (100.0%)	399 (100%)

Source: AFFIRM Clinical Study Report (15)
Abbreviations: EQ-5D: European questionnaire 5 dimension scale; FACT-P: functional assessment of cancer therapy-prostate; ITT: intent-to-treat; PSA: prostate-specific antigen.
*The lower number of patients who completed at least one item of the EQ-5D is due to this questionnaire being administered only at sites in France, Germany, Italy, Spain, and the UK, but not in the other countries. Of these patients, 126 and 53 patients in the enzalutamide and placebo arms, respectively had evaluable data (i.e. with the 5 domain items correctly answered).

Overall, 231 (28.9%) patients on the enzalutamide arm and 19 (4.8%) patients on the placebo arm remained on the study drug as of the data cut-off date (Figure 5). AEs leading to discontinuation are lower in the enzalutamide treatment arm than in the placebo treatment arm (Table 12). The most commonly reported reason for study drug discontinuation in both arms was disease progression (enzalutamide: 55.1%; placebo: 74.2%). AEs were the reason of study drug discontinuation in 7.6% and 9.8% of patients in the enzalutamide and placebo arms, respectively.

As discussed in section 6.3.6 based on the interim analysis results, the study Data Monitoring Committee recommended that the AFFIRM study be halted earlier than anticipated and that patients in the control arm be crossed over to enzalutamide.

Figure 5: Patient disposition flow chart as of September 25 2011 (ITT)



Source: AFFIRM Clinical Study Report (15)
Note: *Ongoing treatment at data cut-off
Abbreviations: AE, adverse events; ENZA, enzalutamide; PLA, placebo.

6.4 *Critical appraisal of relevant RCTs*

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG.

AFFIRM is a randomised double-blind placebo-controlled study. All patients included in the study had the disease of interest, i.e., mCRPC that had progressed after or during docetaxel therapy.

The study included an independent data monitoring committee that monitored and reviewed safety data on an ongoing basis.

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format

A detailed quality assessment of AFFIRM is provided in appendix 3, section 10.3

6.4.3 If there is more than one RCT, tabulate a summary of responses applied to each of the critical appraisal criteria:

A summary is not applicable as there is only one relevant RCT.

The quality assessment of AFFIRM has been undertaken using the descriptive criteria recommended by NICE in their guidance to manufacturers on STA; please refer to appendix 5, section 10.5, Table 100.

6.5 *Results of the relevant RCTs*

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If

patients have been excluded from the analysis, the rationale for this should be given

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

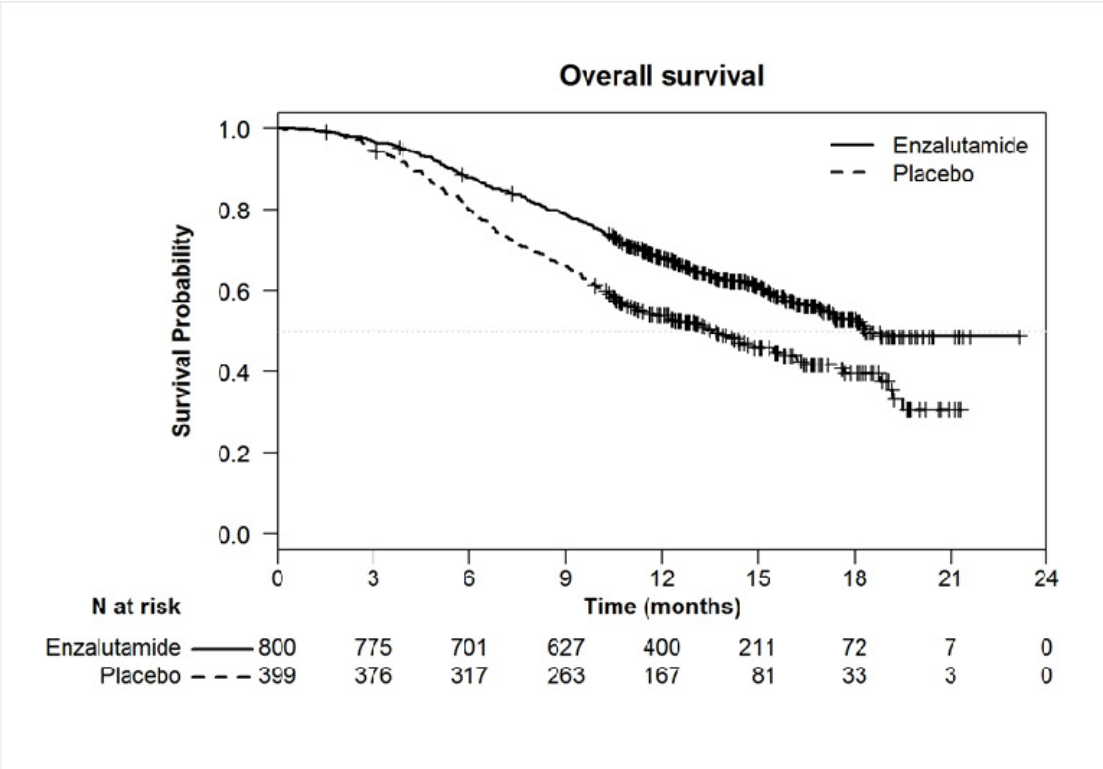
- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval (CI).
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of those RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

6.5.3.1 Results of the primary analysis of the primary outcome:

At the time of the IA (25 September 2011), 308 deaths had occurred among patients in the enzalutamide arm and 212 deaths had occurred among patients in the placebo arm (Figure 6). To note, not all deaths were reported as primary reason of study discontinuation. This accounts for the differences in the number of deaths reported in this section (308 and 212 for enzalutamide and placebo, respectively) and the numbers of deaths reported as primary cause of study discontinuation in Figure 5 (305 and 211 for enzalutamide and placebo, respectively).

In the protocol pre-specified interim OS analysis (median follow-up of 14.4 months), enzalutamide was associated with a significantly longer median OS (18.4 months; 95% CI: [17.3; not reached]) than placebo (13.6 months; 95% CI: [11.3; 15.8]; p<0.0001) (3). Enzalutamide significantly reduced the risk of mortality by 36.9% compared to placebo (stratified HR: 0.631; 95% CI: [0.529, 0.752]; p<0.001).

Figure 6: Kaplan-Meier curve for OS (ITT)



Source: Clinical study report (15)
Abbreviation: CI: confidence interval; ITT: intention to treat; HR: hazard ration; OS: overall survival.

Superiority of enzalutamide over placebo was also observed at the time of database lock (December 2011) when 344 (43%) deaths had occurred among patients in the enzalutamide arm and 232 (58%) deaths in the placebo arm. With a median follow-up of 15 months, enzalutamide was associated with a significantly longer median OS (17.8 months, 95% CI [16.7-18.8]) than placebo (13.3 months, 95% CI [11.2-14.2]). Enzalutamide significantly reduced the risk of mortality by 38.0% compared to placebo (stratified HR: 0.618, CI [0.523-0.730]; p<0.001).

Post study Treatment

Enzalutamide significantly prolonged OS compared to placebo despite a higher proportion of patients in the placebo arm being switched to therapies which are likely to further prolong survival after discontinuation of the trial medication. The median OS is not adjusted for post-study treatment, therefore this is likely to underestimate the OS benefit of enzalutamide over placebo. Table 13 shows details of post-study treatments

Importantly, the economic model assumes no impact on patient survival by use of subsequent therapies following discontinuation of the trial medication. This is likely to underestimate the relative benefit of enzalutamide when compared to placebo.

The impact of post-study treatment on OS might be stronger in the placebo arm than in the enzalutamide arm as suggested by the results of Loriot (49). The authors conducted a retrospective post-hoc analysis of the cohort of AFFIRM patients recruited in their centres who switched to abiraterone after progression on enzalutamide (n=38) or placebo (n=16). Median OS and PFS for patients who moved from enzalutamide to abiraterone was 7.2 months (95% CI [5.0–NR]) and 2.7 months (95% CI [2.3–4.1]), respectively, versus 11.4 months (95% CI [7.3 – NR]) and 6.5 months (95% CI [3.7–19.4]) for patients who switched from placebo to abiraterone. The longer OS and PFS for those patients who had been initially treated with placebo should be taken with caution given the small number of patients assessed (54 patients of the 1,199 included in AFFIRM).

Table 13: Subsequent therapies to treated PC used in ≥10% of patients in any arm (ITT)

	ENZA (N=800)	PLA (N=399)
Number of patients taking ≥1 subsequent therapy to treat PC	336 (42.0%)	245 (61.4%)
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%)
Endocrine Therapy	179 (22.4%)	108 (27.1%)
Abiraterone acetate	167 (20.9%)	97 (24.3%)

Source: AFFIRM Clinical Study Report (15)
Abbreviations: ENZA: enzalutamide; ITT: intention to treat; PC: prostate cancer; PLA: placebo.

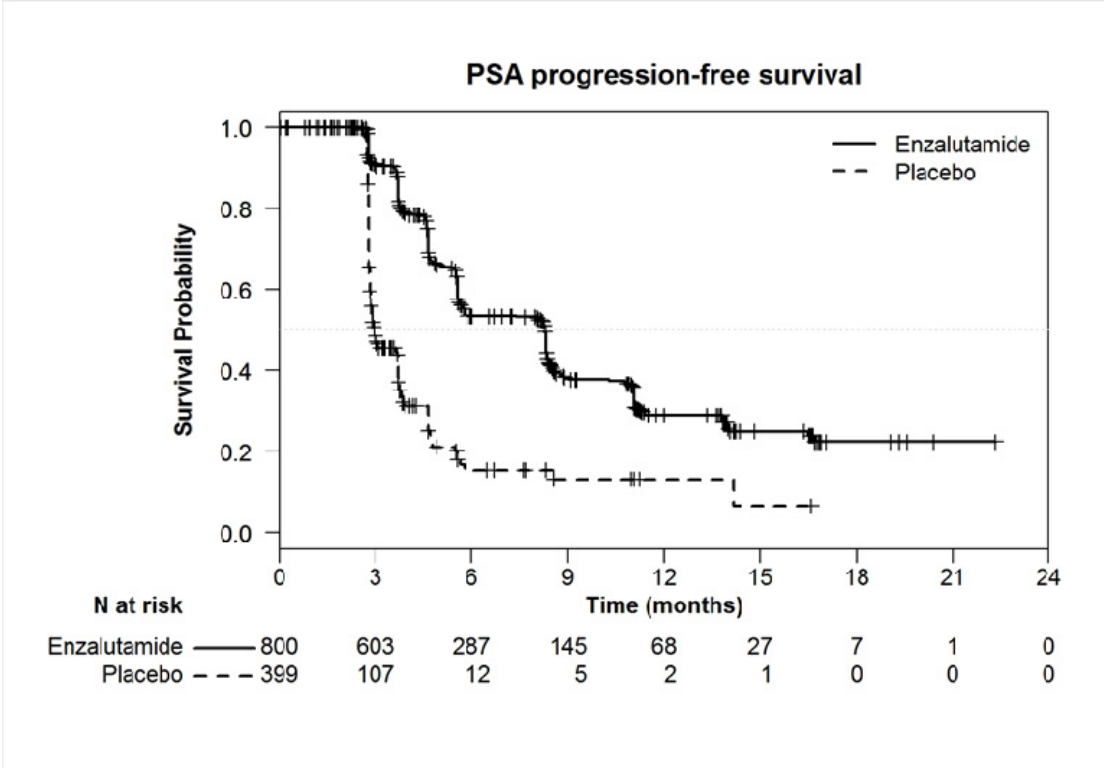
OS for different subgroups has been calculated and that the results are presented in section 6.5.3.3.

6.5.3.2 Results of secondary outcomes:

Time to PSA progression

In AFFIRM 400 patients in the enzalutamide arm and 190 patients in the placebo arm experienced PSA progression during the study. Median time to PSA progression was significantly longer for enzalutamide (8.3 months, 95% CI [5.3; 8.3]) than with placebo (3.0 months, 95% CI [2.9; 3.7]). Enzalutamide delayed time to PSA progression by 75% over placebo (HR: 0.248, 95% CI [0.204; 0.303], p<0.001) (Figure 7).

Figure 7: Time to PSA progression (ITT)



Source: Clinical study report **(15)**
Abbreviations: ITT: intention to treat; PSA: prostate specific antigen.

Radiographic progression-free survival

Median follow-up time for rPFS was 13.6 months for both treatment arms and for all the performed analyses. Enzalutamide was associated with significantly longer median rPFS (8.3 months; 95% CI: [8.2; 9.4]) than placebo (2.9 months; 95% CI: [2.8; 3.4]) (Table 14). Enzalutamide decreased the risk of disease progression by 60% (HR: 0.40, 95% CI [0.35; 0.47]; p<0.001) (3).

Sensitivity analyses of rPFS using derived soft tissue progression assessments based upon RECIST v1.1 criteria and modified censoring assumptions confirmed the primary analysis of median rPFS.

Table 14: Median rPFS (ITT)

	ENZA (N = 800)	PLA (N = 399)
Status of rPFS Survival Follow up		
Events	524 (65.5%)	337 (84.5%)
Radiographic progression	399 (49.9%)	246 (61.7%)
Death without documented radiographic progression	125 (15.6%)	91 (22.8%)
Censored	276 (34.5%)	62 (15.5%)
Duration of rPFS (months)		
Median (95% CI)	8.3 (8.2, 9.4)	2.9 (2.8, 3.4)
25% - 75% percentile	3.1 – 14.7	2.7 – 6.1
Stratified Analysis		
Hazard ratio (95% CI)	0.404 (0.350, 0.466)	
P-value (log-rank)	<0.0001	

Source: Scher 2012a (3).

Abbreviations: ENZA: enzalutamide; ITT: intention to treat; PLA: placebo; rPFS: radiographic progression free survival.

Time to first skeletal-related event

In AFFIRM, 35.9% (n=287/800) patients in the enzalutamide arm and 40.3% (n=161/399) patients in the placebo arm experienced SREs during the study (Table 15). The most commonly reported SRE was radiation to bone (enzalutamide: n=176/287, 61.3%; placebo: n=101/161, 62.7%) followed by spinal cord compression (enzalutamide: n=66/187, 23.0%; placebo: n=29/161, 18.0%).

Median time to first SRE with enzalutamide (16.7 months, 95% CI [14.4; 19.1]) was significantly longer than with placebo (13.3 months, 95% CI [9.9; not reached]). Enzalutamide delayed time to first SRE by 31.2% (HR: 0.688 [0.566; 0.835]; p<0.0001).

A sensitivity analysis was conducted that excluded a change of an antineoplastic therapy required to treat bone pain secondary to bone metastases. The results of this sensitivity analysis were consistent with the primary analysis resulting in a stratified HR of 0.744 (95% CI: 0.609, 0.911).

Table 15: Median time to first SRE (ITT)

	ENZA (n = 800)	**PLA (n = 399)**
Patients with SREs during the study n (%)*	287 (35.9)	161 (40.3)
Radiation to bone*	176 (22.0%)	101 (25.3%)
Surgery to bone *	6 (<1.0%)	1 (0.3%)
Pathologic bone fracture*	31 (3.9%)	16 (4.0%)
Spinal cord compression *	66 (8.3%)	29 (7.3%)
Change of antineoplastic therapy to treat bone pain*	20 (2.5%)	16 (4.0%)
Censored observations*	513 (64.1%)	238 (59.6%)
Time to first SRE (months)		
Median (95% CI)	16.7 (14.4, 19.1)	13.3 (9.9, not reached)
Stratified Analysis		
Hazard ration (95% CI)	0.688 (0.566; 0.835)	
P-value (log-rank)	<0.0001	

Source: Clinical Study Report (15)
Abbreviation: CI: confidence intervals; ENZA: enzalutamide; ITT: intention to treat; PLA: placebo; SRE: skeletal-related events.
*The percentages have been calculated over the total number of patients in each arm. The proportion of SREs that were radiation to bone, surgery to bone, pathologic bone fracture, spinal cord compression and change of antineoplastic therapy to treat bone pain were 61.3%, 2.1%, 10.8%, 23.0%, and 7.0% respectively in the enzalutamide arm and 62.7%, 0.6%, 9.9%, 18.0%, and 9.9%, respectively in the placebo arm.

FACT-P related outcomes

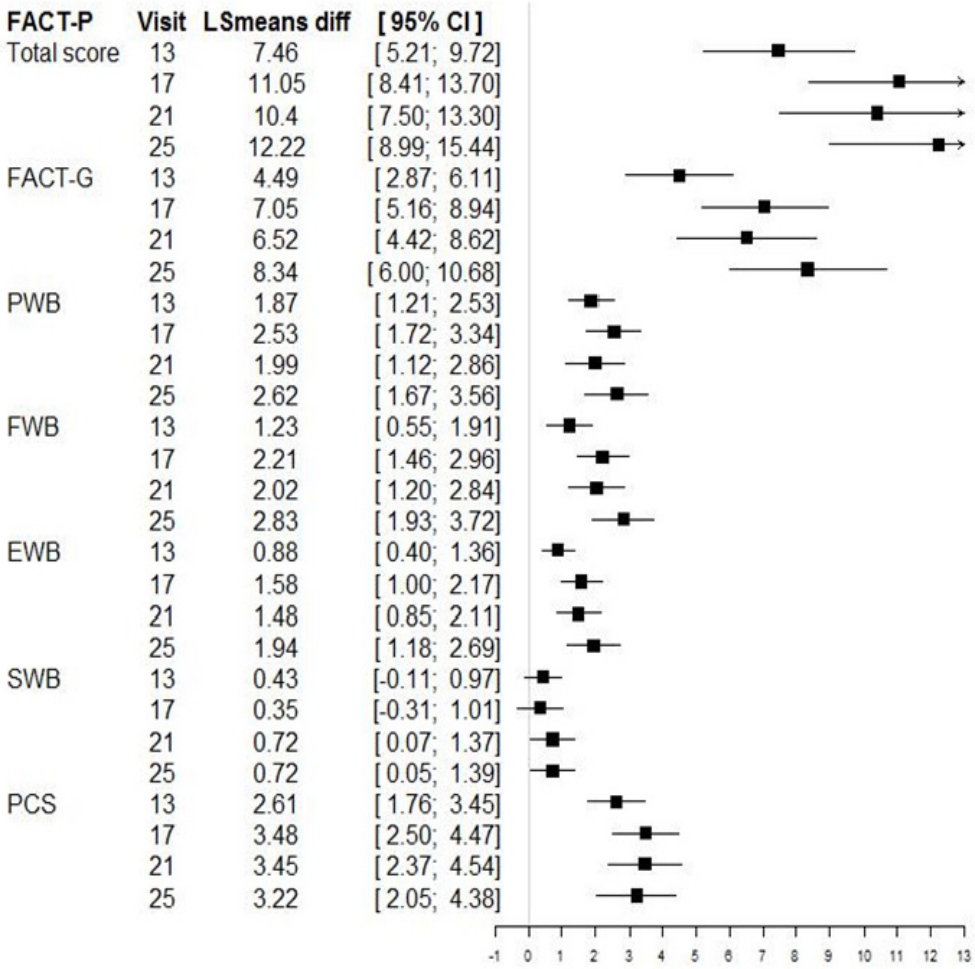
Both secondary and exploratory FACT-P outcomes are presented below.

FACT-P was administered at baseline and at every regular study visit from Week 13 onwards. Completion rates for FACT-P for patients remaining in the study at each assessment timepoint were high, ranging between 94.7% and 96.2% for measurements corresponding to the first 25 weeks and between 66.7% and 100% for the remaining measurements. However, there was a significant dropout rate in both arms, falling below 40% after Week 49. The dropout rate was much higher in the placebo arm mostly due to a higher rate of progressive disease.

A QoL response was defined as an increase in 10 or more units in the FACT-P total score at any time during the study. Enzalutamide was associated with a significantly higher proportion of patients with a positive QoL response than placebo (n=275/652, 42.2% vs. n=36/248, 14.5%; p=0.0018).

A MMRM was used to compare differences between treatment arms. Enzalutamide led to significantly better QoL than placebo in FACT-P total score and all sub-domains (physical, functional and emotional wellbeing and prostate cancer scale) at all time points except for social wellbeing which did not change (Figure 8).

Figure 8: FACT-P total score and domain scores: LS means difference between changes from baseline with enzalutamide and with placebo (ITT FACT-P)



Source: PRO report 2012 **(37) (47)**

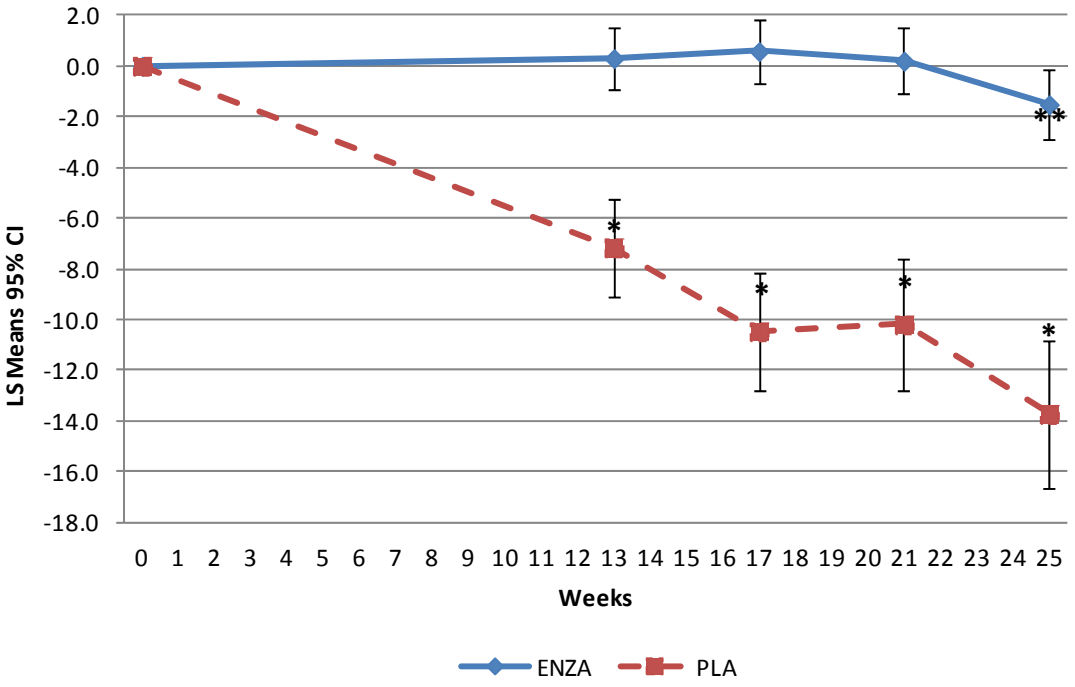
Note: Visit corresponds to weeks

Abbreviations: CI: confidence intervals; EWB: emotional well-being; FBW: functional well-being; FACT-G: functional assessment of cancer therapy – general; FACT-P: functional assessment of cancer therapy – prostate; ITT: intention-to-treat; LS: least square; PCS: prostate cancer-specific; SWB: social well-being.

While QoL was maintained whilst patients remained on enzalutamide treatment at a level comparable to baseline at all timepoints, a clinically meaningful deterioration (>6 points) (50) was observed as early as Week 13 for the placebo arm (Figure 9).

The results of the MMRM analysis were confirmed by the pattern-mixture model results.

Figure 9: Adjusted mean change from baseline in FACT-P total score (ITT FACT-P)



Source: PRO report 2012(37) (47)
Abbreviations: CI: confidence interval; ENZA: enzalutamide; FACT-P: functional assessment of cancer therapy – prostate; ITT: intention-to-treat; LS: least square: PLA: placebo.

Time to first QoL deterioration was assessed, where deterioration was defined as the composite endpoint of death or a decrease of ≥ 10 points in FACT-P total score, whichever occurred first. Enzalutamide significantly delayed time to first deterioration of QoL by 5.3 months compared with placebo (9.0 months; 95% CI [8.31; 11.10] vs. 3.71 months 95% CI [3.02; 4.624]; log-rank test p-value <0.001). The HR was 0.45 (95%CI: [0.37-0.55]; p<0.001).

Rate of pain palliation at Week 13

Pain palliation defined as a ≥2 point reduction in the worst pain item (BPI-SF question #3) score at Week 13 was available for 68.1% (n=545/800) and 58.1% (n=232/399) of patients in the enzalutamide and placebo arms, respectively. Significantly more patients on enzalutamide than on placebo experienced a ≥2 point reduction in the worst pain item (n=141/565, 25% vs. n=33/232, 14.2%; p<0.001).

Pain palliation was also defined as ≥30% reduction in average pain score at Week 13 without a ≥30% increase in analgesic use. However, only 6.1% and 3.8% of patients in the enzalutamide and placebo arms, respectively, could be assessed using this definition. Among these patients, significantly more patients experienced ≥30%

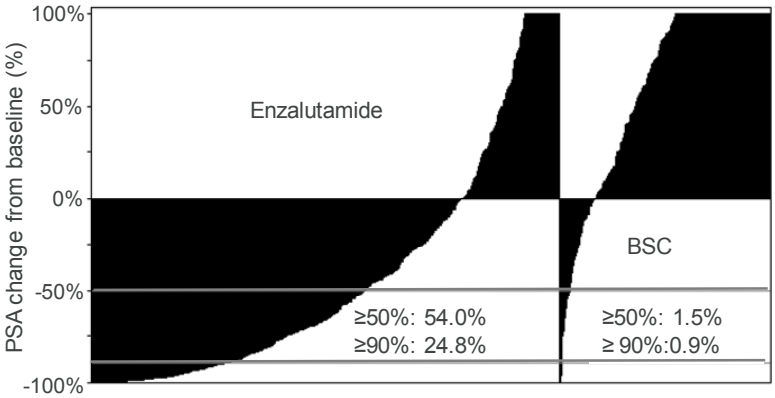
reduction in average pain score in BPI at Week 13 with enzalutamide (44.9%) than with placebo (6.7%; p=0.0079). The reason for such a low proportion of assessable patients was due to unusable analgesic dose information recorded in the pain diary making it impossible to strictly evaluate many patients for stable analgesic use over time.

6.5.3.3 Results of the exploratory outcomes:

PSA response rate

Enzalutamide led to a greater PSA response defined as ≥50% decrease confirmed 3 or 4 weeks later than placebo (54.0% vs. 1.5%; p<0.0001). The proportion of patients with a confirmed ≥90% PSA decrease was also significantly higher in the enzalutamide arm (24.8%) than in the placebo (0.9%; p<0.0001). The majority of patients treated with enzalutamide showed substantial decreases in PSA levels, as compared with a small minority of patients treated with placebo who had decreases in PSA levels (Figure 10).

Figure 10: Waterfall plot of PSA response



Source: Clinical study report (15)
Abbreviations: ≥50%: ≥50% decline in PSA levels; ≥90%: ≥90% decline in PSA levels.
To simplify data presentation for this analysis, the maximal PSA increase was set at 100%, although PSA could be more than double.

Best overall radiographic response

The objective response rate (ORR) defined as proportion of patients with complete or partial response as best tumour response was statistically significantly higher with enzalutamide (28.7%) than with placebo (3.8%, p<0.0001).

Similarly, enzalutamide was associated with more patients with stable disease and fewer patients with progressive disease (Table 16).

Table 16: Best overall radiographic response (ITT)

Best Overall Radiographic Response for the Study	ENZA	PLA
Number of patients with measurable disease at baseline, (N)	446	208
With at least 1 post baseline assessment, n (%)	398 (89.2)	169 (81.3)
With no post base line assessment, n (%)	48 (10.8)	39 (18.8)
Best overall response for the study, n (%)		
Complete response, n (%)	17 (3.8)	2 (1.0)
Partial response, n (%)	112 (25.1)	6 (2.9)
Stable disease, n (%)	175 (39.2)	61 (29.3)
Progressive disease, n (%)	90 (20.2)	98 (47.1)
In evaluable, n (%)	2 (0.4)	0 (0.0)
Analysis		
Objective responses (complete / partial response), n (%)	129 (28.9)	8 (3.8)
95% CI	24.8; 33.4	1.7; 7.4
Difference in objective response rate (95% CI) between the 2 groups	25.08%	
P-value (Cochran-Mantel-Haenszel mean score test)	<0.0001	

Source: AFFIRM (3).
Abbreviations: CI: confidence intervals; ENZA: enzalutamide; ITT: intention to treat; PLA: placebo.

EQ-5D

Administration of the EQ-5D questionnaire was instituted at all sites in France, Germany, Italy, Spain, and UK, but not in the other countries; this accounts for the limited number of patients with EQ-5D data in the AFFIRM study (enzalutamide: n=126/800; placebo: n=53/399 at baseline). The number of subjects with evaluable forms (i.e., with the 5 domain items correctly answered) throughout the study decreased more rapidly in the placebo arm (Table 17).

Table 17: Proportion of patients with EQ-5D post-baseline data

EQ-5D	ENZA N (%)	PLA N (%)
Number of subjects in ITT EQ-5D	126	53
Week 13	119 (94.4)	52 (98.1)
Week 25	85 (67.5)	16 (30.2)
Week 37	67 (53.2)	6 (11.3)
Week 49	25 (19.8)	2 (3.8)
Week 61	2 (1.6)	0 (0.0)

Source: AFFIRM patient-reported outcome report (37)
Abbreviations: ENZA: enzalutamide; PLA: placebo.

At baseline, the majority of patients in both arms scored level 1 for the Mobility, Self-Care, Usual Activities and Anxiety/Depression domains, and level 2 for Pain/Discomfort. Only 1.9%-7.5% of patients in the placebo arm and 0%-4.8% of patients in the enzalutamide arm scored level 3 for any of the domains. The baseline mean utility index and visual analogue scale (VAS) score were slightly lower for placebo ([redacted]) than for enzalutamide ([redacted]).

A MMRM was used to compare differences between treatment arms. The treatment effect on the EQ-5D utility index favoured enzalutamide both at Week 13 (LS Mean: [redacted], 95% CI [redacted]) and Week 25 (LS Mean: [redacted], 95% CI [redacted]), but did not reach statistical significance (Week 13: p=[redacted]; Week 25: p=[redacted]). [redacted]

The results of the MMRM analysis were confirmed by the pattern-mixture model results: no clinically or statistically significant differences were observed for the change from baseline between arms. As a result of the limited number of patients with EQ-5D collected, the FACT-P was mapped to the EQ-5D using an internal mapping algorithm (51) (section 7.4.4).

Pain progression

The proportion of patients with pain progression on Brief Pain Inventory-Short Form (BPI-SF) was significantly lower with enzalutamide (n=;) than with placebo (n=; ; p=). Enzalutamide significantly reduced by the proportion of patients who experience pain progression compared to placebo. Patients were assessed for pain progression if they had valid pain score entries in a pain diary for a minimum of 4 out of 7 days during the baseline run-in period and during the 7 days preceding the Week 13 visit.

Changes in pain severity and pain interference

Changes in pain severity were assessed with the BPI-SF. The severity of pain increased with placebo (mean change: ; p<) while enzalutamide significantly reduced the pain severity between baseline and Week 13 (mean change: ; p=). The between treatment difference was significant (p<) (Table 18).

Similarly, enzalutamide was associated with a decrease in the level of interference of pain whereas interference increased for patients on placebo. The between treatment difference was statistically significant and favoured enzalutamide (p<).

Table 18: Changes in pain severity and interference between baseline and Week 13

	ENZA	PLA	P-value
Change in pain severity			
Change in pain interference			

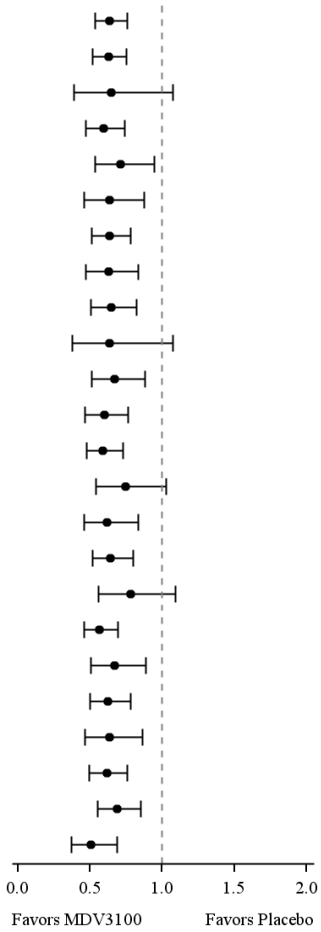
Source: PRO report 2012 (37)
Abbreviations: ENZA: enzalutamide; PLA: placebo.

Results of the OS subgroup analyses

Median OS in all patient subgroups favoured enzalutamide over placebo including more difficult-to-treat patient subsets such as patients over 65 years old, patients with 2 or more prior chemotherapy regimens, patients with radiographic progression at screening or patients with an ECOG ≥2. Treatment benefit of enzalutamide over placebo in these patient subgroups was consistently >3 months (4.5, 3.6, 4.3 and 3.3 months, respectively) (Figure 11).

Figure 11: Subgroup analyses of OS

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



Note: *IA

6.5.3.4 Results of the post-hoc outcomes:

Modified progression-free survival

Median mPFS was [redacted] months (95% CI [[redacted]]) for enzalutamide vs. [redacted] months (95% CI [[redacted]]) for placebo (Figure 12). The HR for mPFS favoured enzalutamide significantly (HR: [redacted], 95% CI: [[redacted]]; p <[redacted]).

Figure 12: Kaplan-Meier curves for modified PFS (ITT)

[redacted]

Source: Data on file
Abbreviations: ENZA: enzalutamide; ITT: intention-to-treat; mPFS: modified progression-free survival; PLA: placebo.

Time to treatment discontinuation

Median time on study drug was [redacted] and [redacted] months for enzalutamide and placebo arms, respectively. These median times are comparable to median rPFS in the study (8.3 months; 95% CI: [8.2; 9.4] for enzalutamide and 2.9 months; 95% CI: [2.8; 3.4] for placebo).

Overall, a higher proportion of patients remained on treatment for 12 or more months in the enzalutamide arm ([redacted]) than in the placebo ([redacted]) (HR: [redacted], 95% CI [[redacted]]; P <[redacted], Figure 13).

Figure 13: Kaplan-Meier curves for time to treatment discontinuation (ITT)

Source: Data on file.
Abbreviations: ENZA: enzalutamide; ITT: intention-to-treat; PLA: placebo

6.5.3.1 Conclusions

- AFFIRM was a randomised double-blind placebo-controlled study comparing enzalutamide to placebo in men with mCRPC whose disease had progressed on or after docetaxel therapy. In both arms, patients also received BSC in addition to the study treatment.

- All primary and secondary endpoints were reached. Enzalutamide has a significantly greater proportion of patients versus placebo, experiencing improvements in both life expectancy and quality of life (QoL), whilst being well tolerated.

- AFFIRM showed that enzalutamide leads to significantly longer OS and rPFS than placebo in men with mCRPC in the post-docetaxel setting.

- Enzalutamide was also associated with significantly improved mPFS (defined as the time to radiographic progression, first SRE or death due to any cause) than placebo.

- Superior treatment effect of enzalutamide over placebo was also observed in the radiographic tumour response, PSA response, pain palliation and HRQoL.

- The favourable effect of enzalutamide over placebo on OS was observed in all the patient subgroups pre-specified in the study protocol.

- Treatment with enzalutamide was associated with a significant improvement of FACT-P QoL scores and all sub-domains (physical, functional and emotional wellbeing and prostate cancer scale). Differences in favour of enzalutamide were also observed for the EQ-5D utility index and the BPI pain scores (Pain severity and Pain Interference).

6.6 *Meta-Analysis*

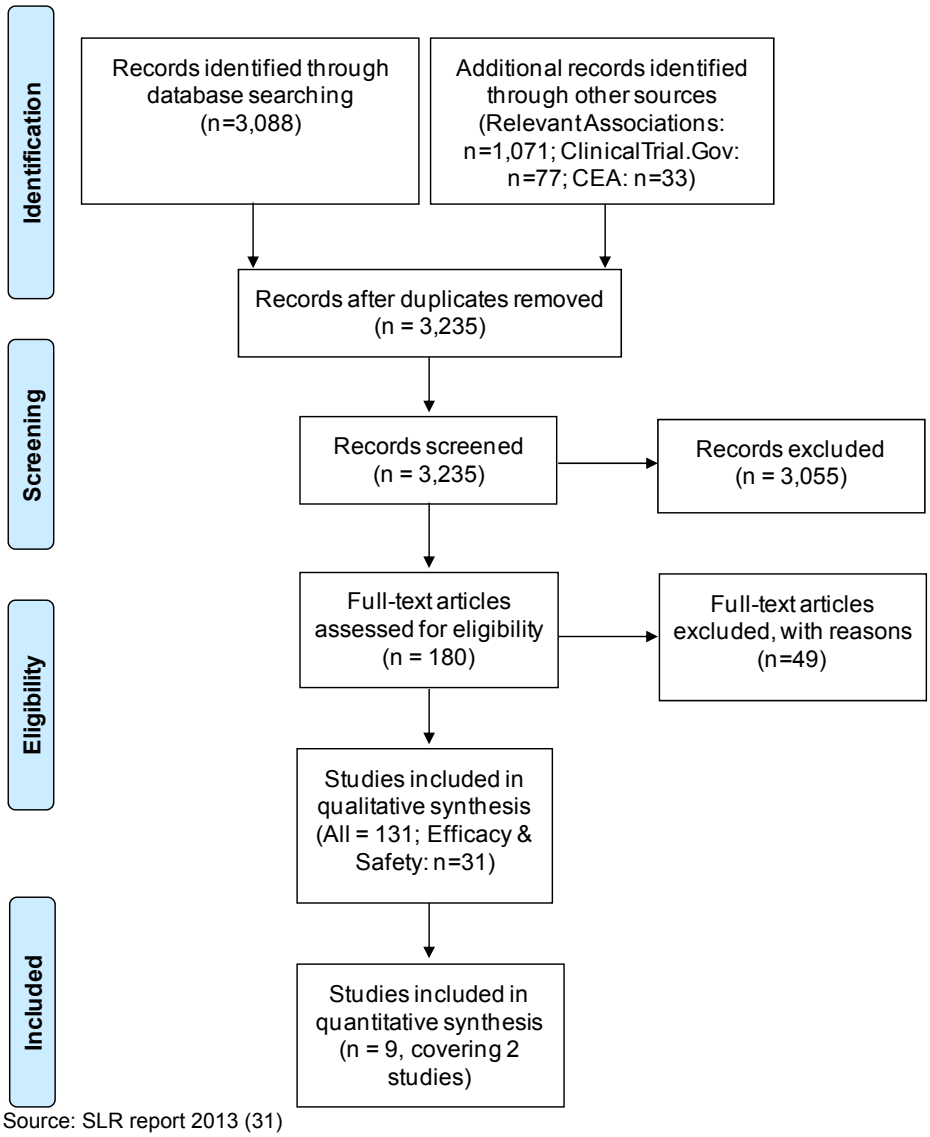
No meta-analysis could be performed because only one study was identified per pairs of treatment comparisons.

6.7 *Indirect and mixed treatment comparison*

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

Please see section 6.1 for the methods used to identify RCT evidence for enzalutamide and abiraterone in the treatment of patients with mCRPC that has progressed on or after docetaxel treatment (Figure 14).

Figure 14: PRISMA flow diagram with the efficacy and safety studies of enzalutamide and abiraterone for the ITC identified through the predefined search strategy



Source: SLR report 2013 (31)

6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Details of the inclusion and exclusion criteria employed for the SLR are presented in Table 5.

Following assessment and exclusion of studies based on title, abstract and full text, 23 clinical study-related references representing 11 RCTs in the post-chemo setting

were identified (Table 19). The network of RCT evidence identified by the SLR is described in Figure 15.

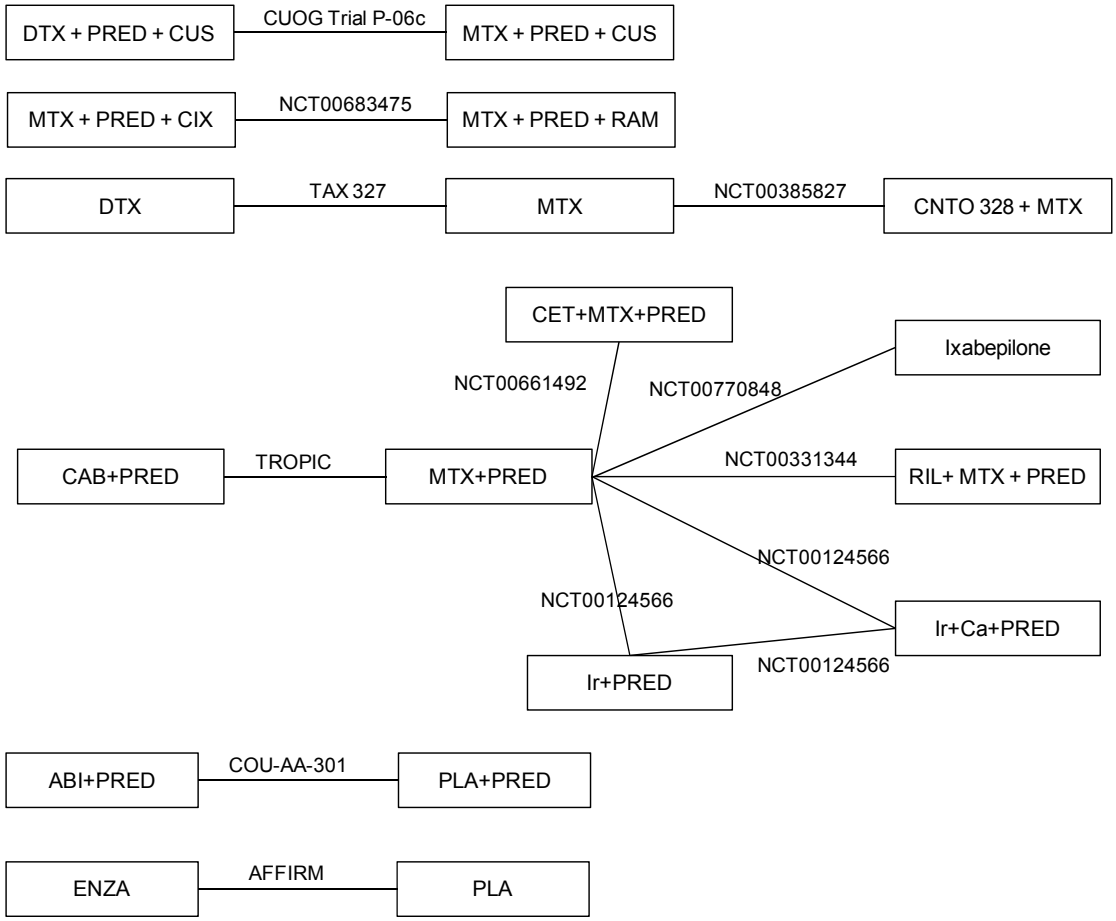
Table 19: List of RCTs identified by the systematic literature review

	Study (design)	Intervention	Comparator	References
Studies included in the ITC	AFFIRM (RCT, phase III, DB, PLA-controlled)	ENZA (n=800): • ENZA 160 mg PO OD Use of corticoids was allowed but not required	PLA (n=399) • PLA PO OD Use of corticoids was allowed but not required	Scher 2012a (3) De Bono 2012 (36) Scher 2012b(13) AFFIRM CSR (April 24, 2012) (15) PRO 2012 (37)
	COU-AA-301 (RCT, phase III, DB, PLA-controlled)	ABI+PRED (n=797) • ABI: 1g (4x250 mg tablets) PO OD • PRED: 5mg PO BID	PLA+PRED (n=398): • PLA: 4 tablets PO OD • PRED: 5mg PO BID	De Bono 2011(24) Fizazi2012(25) Goodman 2012 (52) Scher 2011(26) Efstathiou 2012 (53)
Studies not included in the ITC	NCT00124566 (RCT, phase II)	Ir+PRED: • Ir: 0.45 mg/kg, day 1 & 8 q3wk • PRED: 10mg OD	Ir+Ca+PRED: • Ir: 0.4 mg/kg day 1 & 15 • Ca: 2000 mg/m2 day 1-15 q4w • PRED: 10 mg OD MTZ+PRED: • MTZ 12 mg/m2 q3wK • PRED 10 mg OD	Hart 2006 (54) Berger 2007 (55)
	NCT00331344 (RCT, phase II, OL)	Ixabepilone (n=41) • 35 mg/m2 IV over 3 hour's q21 days. Cross-over was allowed	MTZ +PRED (n=41) • MTZ 14 mg/m2 IV q21 days • PRED 5 mg oral BID	Rosenberg 2007 (56)
	CUOG Trial P-06c (RCT, phase II, OL)	DTX + PRED + CUS (N=20) • DTX: 5mg, IV for 60min, on day 1 of each 21-day cycle • PRED: 5mg, oral, OD • CUS: 640mg, IV, 3x over 9-days, followed by x1wk administration	MTZ + PRED + CUS (N=22) • MTZ: 12mg, IV for 30min, on day 1 of each 21-day cycle • PRED: 5mg, oral, OD • CUS: 640mg, IV, 3x over 9-days, followed by x1wk administration	Saad 2011 (57)
	TROPIC (RCT. phase III, OL)	CAB+PRED (n=378) • CAB 25 mg/m2, IV over 1 h q3 wks (Day 1 of 21 cycle) • PRED 10 mg PO OD	MTZ+PRED (n=377) • MTZ 12 mg/m2, IV over 15–30 min q3wks (Day 1 of 21 cycle) • PRED 10 mg PO OD	De Bono 2010a(58) Oudard 2011 (59) Sartor 2011 (60)

	Study (design)	Intervention	Comparator	References
	TAX 327 (RCT, cross-over phase III)	Three arms: • DTX (x3 wk) to MTZ: n=89/232 • DTX (x1wk) to MTZ: n=76/232 • MTZ to DTX: n=67/232		Berthold 2008 (61)
	NCT00661492	CET + MTZ +PRED	MTZ + PRED	Fleming 2010 (62) Fleming 2012 (63)
	NCT00770848 (RCT, phase Ib/II, DB)	RIL15 mg/kg + MTZ +PRED	RIL 7.5 mg/kg + MTZ +PRED PLA + MTZ	Ryan 2012 (64)
	NCT00683475 (RCT, phase II)	MTZ 12 mg/m2 IV every 3 wks + PRED 5 mg PO BID for up to 12 cycles + CIX 6 mg/kg (n=66)	MTZ 12 mg/m2 IV every 3 wks + PRED 5 mg PO BID for up to 12 cycles + RAM 6 mg/kg IV q w (n=66)	Hussain 2012 (65)
	NCT00385827 (non randomised, phase II)	CNTO 328+ MTZ	MTZ	De Bono 2010b (66)

Source: SLR Report 2013 (31)
Abbreviations: ABI: abiraterone; BID: twice daily; Ca: capecitabine; CAB: cabazitaxel; CET: cetuximab; CIX: cixutumumab; CUS: custirsen; DB: double-blind; DTX: docetaxel; ENZA: enzalutamide; Ir: irofulven; ITC: indirect treatment comparison; MTZ: mitoxantrone; OD: once daily; OL: open-label; PLA: placebo; PO: per os (oral); PRED: prednisone; RAM: ramucirumab; RCT: randomised clinical trial; RIL: rilotumumab.

Figure 15: Network diagram of RCTs identified by the systematic literature review



Abbreviations: ABI: abiraterone; Ca: capecitabine; CAB: cabazitaxel; CET: cetuximab; CIX: cixutumumab; CUS: custirsen; DTX: docetaxel; ENZA: enzalutamide; Ir: Irofulven; MTZ: mitoxantrone; PLA: placebo; PRED: prednisone; RCT: randomised clinical trial; RIL: rilotumumab.

Consideration of identified studies for inclusion in the indirect comparison

Of the 11 studies listed in Table 19, two studies were identified that would allow an ITC of enzalutamide to abiraterone: AFFIRM and COU-AA-301. To be able to perform the ITC the comparator arms in both studies were considered similar. However, the treatment received in both comparator arms differed in:

- Proportion of patients exposed to prednisone: 100% in the placebo arm of COU-AA-301 vs. 45.6% in the placebo arm of AFFIRM.
- Reason for the need of corticosteroids: to avoid toxicity in COU-AA-301 and supportive treatment in AFFIRM.

The placebo arm in COU-AA-301 (100% of patients on prednisone) was assumed to have the same treatment outcomes as the placebo arm in AFFIRM.

Study methodology

A summary of the methodology of the two studies (AFFIRM and COU-AA-301) included in the indirect comparison is provided in Table 20. The study design of AFFIRM and COU-AA-301 studies were comparable. Both studies were randomised, double-blinded, placebo-controlled phase III trials and the primary endpoint of both studies was OS.

Table 20: Comparative summary of methodology of RCTs included in the indirect comparison

	AFFIRM	**COU-AA-301**
Location	156 sites in 15 countries (Argentina, Australia, Austria, Belgium, Canada, Chile, France, Germany, Italy, the Netherlands, Poland, South Africa, Spain, United Kingdom (12 sites and 132 patients) and the United States).	147 sites in 13 countries (Australia, Austria, Belgium, Canada, France, Germany, Hungary, Ireland, Italy, Netherlands, Spain, United Kingdom and the United States).
Design	Phase III, multinational, randomised, DB, PLA-controlled study.	Phase III, multinational, randomised, DB, PLA-controlled study.
Duration of study	Sep 2009 - Nov 2010.	May 2008 - Jul 2009.
Method of randomisation	Eligible subjects were randomised (2:1) using a centrally administered, randomised, permuted block method and were stratified by baseline ECOG performance status score (0-1 or 2) and mean BPI-SF Question #3 score averaged over the 7 days prior to randomisation ("On a scale of 0 to 10, please rate your pain at its worst in the last 24 hours" stratified by < 4 vs. ≥ 4).	Eligible subjects were randomised (2:1) using a centralised Interactive Web Response System (IWRS) and were stratified by baseline ECOG performance status score (0-1 or 2), presence or absence of pain, 1 versus 2 prior chemotherapy regimens, and documented type of prostate cancer progression at entry [PSA progression only versus radiographic progression in bone or soft tissue with or without PSA progression]).
Method of blinding (care provider, patient and outcome assessor)	Double blind: Patients and Investigators were blinded to the study drug. Placebo matched the enzalutamide tablets in size, colour and shape.	Double blind: Patients and Investigators were blinded to the study drug. Placebo matched the abiraterone acetate tablets in size, colour and shape. All subjects, family members, study personnel, and members of the Independent Data Monitoring Committee (IDMC) were to remain blinded to treatment assignment until completion of the study.
Intervention(s) (n =) and comparator(s) (n =)	ENZA: N=800. PLA: N=399.	ABI+PRED: N=797. PLA+PRED N=398.
Primary outcomes	OS: from randomisation to death from any cause.	OS (25): time from randomisation to death from any cause.
Secondary outcomes	• rPFS • Time to PSA response • Time to first SRE • PSA response • FACT-P • Pain palliation.	• rPFS • Time to PSA response • Time to first SRE • PSA response • ORR • FACT-P • Pain palliation

	AFFIRM	COU-AA-301
		• Pain progression.
Exploratory outcomes	• ORR • EQ-5D • ECOG • Pain progression • Time to pain progression • Change from baseline in QoL scores • Time to QoL deterioration • Portion of patients having a QoL response on FACT-P total score.	
Post hoc analysis	• mPFS • Time to treatment discontinuation • Impact on corticosteroids.	• mPFS • Time to treatment discontinuation.
Duration of follow-up	14.4 months (IA), 15 months (DB lock)	20.2 months (DB lock)
Publications	Scher 2012 (3); Clinical study report (15)	Fizazi et al 2012 (25); Logothetis et a (67)l; NICE submission 2012 (5)

Abbreviations: ABI: abiraterone; DB: double-blind; ECOG: Eastern cooperative oncology group; ENZA : enzalutamide; FACT-P: functional assessment of cancer therapy-prostate ; NICE; national institute of health and care excellence; ORR: objective response rate; PLA: placebo; PFS: progression-free survival; PRED: prednisone; PSA: prostate specific antigen; QOL: quality of life; RECIST: response evaluation criteria In solid tumours; SRE: skeletal related events; MO: months; BPI-SF: brief pain inventory short form.

The outcomes considered in the ITC were OS, rPFS, modified PFS, time to first SRE, time to treatment discontinuation, all grade and grade 3+ AEs and tolerability (Table 21).

Table 21: Endpoints assessed and data sources for the indirect treatment comparison

	References used for enzalutamide	References used for abiraterone
OS	Data on file	Fizazi et al (25)
rPFS	Scher et al (3)	Fizazi et al (25)
Modified PFS	Data on file	NICE submission (5)
Time to first SRE	Scher et al (3)	Logothetis et al (67)
ORR	Scher et al (3)	Fizazi et al (25)
PSA response	Scher et al (3)	Fizazi et al (25)
AEs	Clinical Study report (15)	Fizazi et al (25)
Tolerability	Scher et al (3)	Fizazi et al (25)
Time to treatment discontinuation	Data on file	NICE submission (5)

Abbreviations: AEs: adverse events; mPFS: modified progression-free survival; ORR: objective response rate; OS: overall survival; PSA: progression free survival; rPFS: radiographic progression-free survival; SRE: skeletal-related events.

The key efficacy study endpoint definitions assessed in AFFIRM and COU-AA-301 are summarised in Table 22.

The definitions of OS, rPFS, PSA response and time to treatment discontinuation were the same in both studies, but the definitions of SREs and mPFS differed slightly.

Table 22: Key efficacy endpoints assessed in AFFIRM and COU-AA-301

	AFFIRM	COU-AA-301
Primary endpoint		
OS	Time from randomisation to death of any cause.	Same as in AFFIRM.
Secondary endpoints		
rPFS	Time from randomisation date to radiological progression according to RECIST version 1.1 for soft tissue disease and to PCWG2 criteria for bone progression.	Same as in AFFIRM.
Time to first SRE	Time from randomisation to the first documented SRE defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. An alteration of analgesic medication for bone pain was not considered a SRE.	Time from randomisation to the first documented SRE defined as radiation therapy or surgery to bone, pathologic bone fracture, or spinal cord compression.
PSA response	≥50% decrease confirmed 3 or 4 weeks later.	Same as in AFFIRM.
Exploratory		
ORR	Proportion of patients with a complete or partial radiographic response as best response according to RECIST 1.1.	Same as in AFFIRM.
Post-hoc		
Modified PFS	mPFS is defined as the time to radiographic progression, first SRE or death due to any cause, which ever occurred first. It is a composite endpoint that has been driven for modelling purposes by combining the primary endpoint of AFFIRM (OS) and two secondary endpoints (rPFS and time to first SRE).	mPFS based on meeting one of the criteria for discontinuation of study treatment which involved time to death or first observation of any one of the following: 1. PSA progression 2. Radiographic progression 3. Pain progression, SRE, increase in glucocorticoid use, or initiation of a new systemic anti-cancer therapy.
Time to treatment discontinuation	Time from first dose to treatment discontinuation.	Same as in AFFIRM.

Source: Scher 2012 (3); Scher 2011 (26); Fizazi 2011 (25)
Abbreviations: ORR: objective response rate; OS: overall survival; PCWG: prostate cancer working group; PFS: progression-free survival; RECIST: response evaluation criteria in solid tumours; rPFS: radiographic progression-free survival; SRE: skeletal-related events.

In addition, the ITC also assessed tolerability and incidence of all grades and grade 3+ AEs (Table 23).

Table 23: Key safety endpoints assessed in AFFIRM and COU-AA-301

	AFFIRM	COU-AA-301
Safety endpoint		
All grades AEs	Proportion of patients with those AEs more commonly reported in the enzalutamide arm than in the placebo or AEs that were clinically significant have been reported in Scher et al (3). The CSR provides information on those AEs with a ≥2% absolute difference in event frequency between treatment groups for all grades and at a ≥1% frequency in either arm for grade 3+ (15).	The authors do not clarify whether the data they provide relates only to the most commonly reported AEs or all AEs.
Grade 3+ AEs	Proportion of patients with those AEs more commonly reported in the enzalutamide arm than in the placebo or AEs that were clinically significant have been reported in Scher et al (3). The CSR provides information on those AEs with a ≥1% frequency in either arm for grade 3+ (15).	The authors do not clarify whether the data they provide relates only to the most commonly reported grade 3+ AEs or all grade 3+ AEs.
Tolerability	Study drug discontinuation due to AEs.	Same as in AFFIRM.

Source: Scher 2012 (3); Fizazi 2011 (25)
Abbreviations: AEs: adverse events; CSR: clinical study report.

In both studies the active treatment (enzalutamide and abiraterone) was associated with significantly better efficacy than the control arm.

Study participants

The study population of AFFIRM and COU-AA-301 studies were comparable. Similar selection criteria were applied and both studies included men with mCRPC whose disease had progressed on or after up to two chemotherapy regimens of which one had to be docetaxel-based.

Both studies were comparable in terms of demographic and baseline characteristics (Table 24). Median age was 69 years in both studies; the percentage of patients with ≥ 75 years was similar in both studies (AFFIRM: 25%; COU-AA-301: 28%). The proportion of patients with bone metastases and time since diagnosis was also comparable between the trials. Both studies comprised mainly patients with ECOG 0-1. The proportion of patients with ECOG 2 was 10%-11% in COU-AA-301 and 8.0%-8.8% in AFFIRM. In COU-AA-301, 30% and 31% in the abiraterone and in the prednisone monotherapy arms respectively had received two previous cytotoxic chemotherapy regimens; all other patients had received one regimen only. In AFFIRM 24.5% and 23.8% of patients in the enzalutamide and placebo arms respectively had received two regimens, and 3.1% and 2.0%, respectively three regimens. All other patients had received one regimen only.

Table 24: ITC – Baseline characteristics of AFFIRM and COU-AA-301 trials

	AFFIRM		COU-AA-301	
	ENZA (n=800)	**PLA (n=399)**	**ABI + PRED (n=797)**	**PLA + PRED (n=398)**
Age (years)				
Median (range)	69 (41, 92)	69 (49, 89)	69 (42, 95)	69 (39, 90)
≥75 years	199 (24.9%)	104 (26.1%)	220/797 (28%)	111/397 (28%)
Time since diagnosis (mo)*				
Mean ± SD	86.1 ± 54.83	81.9 ± 50.89	85.8 ± 53.6	82.5 ± 56.3
Race				
White	745 (93.1%)	366 (91.7%)	744 (93.3%)	369 (92.7%)
Black	27 (3.4%)	20 (5.0%)	28 (3.5%)	15 (3.8%)
Asian	5 (0.6%)	8 (2.0%)	11 (1.4%)	9 (2.3%
Indian/Alaskan	1 (0.1%)	1 (0.3%)	3 (0.4%)	0 (0%)
Other	21 (2.6%)	4 (1.0%)	11 (1.4%)	5 (1.3%)
ECOG				
0-1	730 (91.3%)	367 (92.0%)	715/797 (90%)	353/398 (89%)
2	70 (8.8%)	32 (8.0%)	82/797 (10%)	45/398 (11%)
PSA (ng/ml)				
Number of patients	788	399	788	393
Median	107.7	128.3	128.8	137.7
Range	(02; 1,1794.1)	(0; 1,9000.0)	(0.4; 9253)	(0.6; 10114)
Gleason score at initial diagnosis				
≤7	355/726 (49%)	175/368 (48%)	341/697 (49%)	161/350 (46%)
≥8	366/726 (50%)	193/368 (52%)	356/697 (51%)	189/350 (54%)
Number of previous cytotoxic chemotherapy regimens				
1	579 (72.4%)	296 (74.2%)	558/797 (70%)	275/398 (69%)
2	196 (24.5%)	95 (23.8%)	239/797 (30%)	123/398 (31%)
3	25 (3.1%)	8 (2.0%)	0	0
Disease location				
Bone	730 (92.2%)	364 (91.5%)	709/797 (89%)	357/397 (90%)
Node	92 (11.6%)	34 (8.5%)	361/797 (45%)	164/397 (41%)
Liver	442 (55.8%)	219 (55.0%)	90/797 (11%)	30/397 (8%)
Previous cancer therapy				
Surgery	531 (66.4%)	243 (60.9%)	429/797 (54%)	193/398 (49%)
Radiotherapy	571 (71.4%)	287 (71.9%)	570/797 (72%)	285/398 (72%)
Hormonal	800 (100%)	399 (100%)	796 (100%)	396 (100%)

Source: Scher 2012 (3); Scher 2011 (26); Fizazi 2011 (25)
Abbreviations: ABI: abiraterone; PLA: placebo; PRED: prednisone.
*Time since diagnosis for patients in the abiraterone study has been recalculated; original data is provided in days (abiraterone + prednisone: 2,611 ± 1,630; placebo plus prednisone: 2,510 ± 1,712 days).

Quality assessment

The quality assessment's of both the AFFIRM and COU-AA-301 studies can be found in appendix 3, section 10.3 and appendix 5, section 10.5, respectively.

The methods used to generate random allocation sequence and for concealment of allocation sequence were reported for both studies and were judged as adequate. Blinding status was clear for both studies and neither of the studies showed any evidence of selective reporting. Overall, neither of the two studies used in the ITC were identified as being at a high risk of bias, resulting in the validity of the results not been affected.

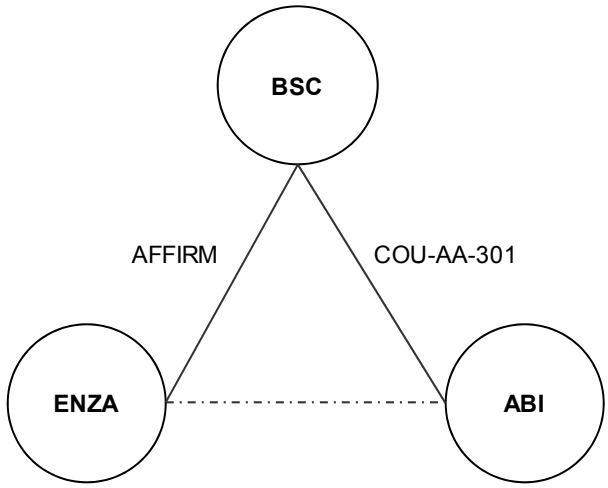
6.7.3 Provide a summary of the trials used to conduct the indirect comparison.

As indicated in section 6.7.2, the ITC was restricted to the comparison of enzalutamide vs. abiraterone in the post-chemotherapy setting. The studies included in the ITC are AFFIRM and COU-AA-301.

The evidence network used for the ITC is depicted in Figure 16.

The ITC of enzalutamide with abiraterone was mediated via one comparator namely BSC.

Figure 16: Evidence network used in the ITC



Notes: Dotted line shows indirect comparison.
Abbreviations: ABI=Abiraterone; BSC=Best supportive case; ENZA=Enzalutamide

6.7.4 For the selected trials, provide a summary of the data used in the analysis.

The ITC was performed for the following outcomes: OS, rPFS, mPFS, time to SRE, ORR, and PSA response. An ITC for TTD was not possible because data for TTD was marked as confidential in the COU-AA-301 trial. The ITC also included all grade and grade 3+ specific AEs; details of this analysis are provided in section 6.9.

The HR used for rPFS was based on assessments by the Independent Review Committee. The definition of rPFS was similar in the two studies, i.e., time from randomisation date to radiological progression according to RECIST version 1.1.

A summary of the data used in the analysis is provided in Table 25 and Table 26. All abiraterone-related data including OS correspond to the final analysis as reported in Fizazi 2012 (25), Logothetis et al (67) and the NICE submission (5).

The data cut-off used for the AFFIRM study is the IA analysis (September 25, 2011) for all outcome measures [Scher 2012a (3)] with the exception of OS, where the database lock was used (December 16 2011).

Table 25: Summary of OS, rPFS and time to first SRE data included in the ITC

Outcome	AFFIRM	COU-AA-301
OS	0.62 [0.52; 0.73]	0.74 [0.64; 0.86]
rPFS	0.40 [0.35; 0.47]	0.66 [0.58; 0.76]
Time to first SRE	0.69 [0.57; 0.84]	0.62 [0.48; 0.79]
mPFS	0.46 [0.40; 0.53]	0.63 [0.55; 0.72]
TTD	0.34 [0.30; 0.39]	Not reported

Source: SLR 2013 (31)
Abbreviations: ABI: abiraterone; ENZA: enzalutamide; PLA: placebo; HR: hazard ratio; OS: overall survival; rPFS: radiographic progression-free survival; SRE: skeletal-related events.
Note: The definition of PSA response was also similar in the two studies: a decrease in ≥50% from the pre-treatment baseline PSA value confirmed after 4 weeks or more.

Table 26: Summary of ORR and PSA response data included in the ITC

Outcome		AFFIRM		COU-AA-301	
		ENZA	PLA	ABI	PRED
ORR	% (n/N)	28.9% (129/446)	3.8% (8/208)	14.8% (118/797)	3.3% (13/398)
	OR [95% CI]	10.17 [4.87; 21.23]		5.15 [2.86; 9.25]	
PSA response	% (n/N)	54.0% (395/731)	1.5% (5/330)	29.5% (235/797)	5.5% (22/398)
	OR [95% CI]	76.41 [31.22; 187.04]		7.15 [4.53; 11.28]	

Source: SLR 2013 (31)
Abbreviations: ABI: abiraterone; ENZA: enzalutamide; HR: hazard ratio; OR: odds ratio; ORR: objective response rate; PLA: placebo; PRED: prednisone; PSA: prostate specific antigen.

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

The ITC was performed using the "adjusted" indirect comparison methodology described by Bucher (68). This model was developed with the odds ratios (OR) as the measure of treatment effect, and was specifically designed for the indirect comparison of B versus C when direct evidence of A versus B and A versus C was available. The method was further extended by Wells et al in 2009 (69) for other effect measures including relative risk, risk difference, hazard ratio, and mean difference. The method preserves the benefits of a randomisation and assumes consistency of treatment effect within the different subgroups; the subgroups being defined by the different comparisons being made. In this case, one subgroup was "enzalutamide vs. BSC" and the other subgroup was "abiraterone vs. BSC". The difference between the summary effects in the two subgroups provides an estimation of the comparison of "enzalutamide vs. abiraterone". Results were expressed as HRs with 95% CIs for the time to event outcomes and OR with 95% CIs for dichotomous outcomes.

6.7.6 Please present the results of the analysis.

The list of endpoints analysed in the ITC can be seen in Table 21 and the definitions of these endpoints can be found in Table 22.

The results of the ITC for OS, radiographic and modified PFS and time to first SRE are provided in Table 27. Enzalutamide was associated with a significantly higher likelihood of attaining radiographic (HR: [redacted], 95% CI [[redacted]]) and modified (HR:

[redacted], 95% CI [[redacted]]) PFS than abiraterone. In contrast, no significant differences were observed for OS or time to first SRE.

Table 27: Results of the indirect comparison for OS, rPFS, time to first SRE and mPFS

[redacted]

Source: SLR 2013 (31)
Note: An analysis of TTD was not possible because this data is not published for abiraterone
Abbreviations: ABI: abiraterone; ENZA: enzalutamide; HR: hazard ratio.

Although the ITC for OS did not show a significant difference between enzalutamide and abiraterone, it should be noted that the analysis did indicate a clear trend towards enzalutamide having longer OS than abiraterone, being on the boundary of significance (upper value of 95% CI is [redacted]). In addition, the ITC on OS should be interpreted with caution as it uses the OS HR for abiraterone as reported in the Fizazi 2012 publication (25). The paper states the following regarding the OS HR: "As the proportional hazards requirement was not met, the HR should be interpreted with caution".

As the HR was not proportional (i.e. not constant over time), comparing survival between two treatments on the basis of HR is unreliable. The reported Kaplan Meier graphs in Fizazi et al show that the curves converge in the final section, indicating a decreasing treatment benefit over time (25). The abiraterone OS HR may therefore overestimate abiraterone's OS benefit. For enzalutamide OS, the proportionality of hazards was met, indicating a constant treatment benefit over time.

The results of the ITC for ORR and PSA response are provided in Table 28. Enzalutamide is associated with a significantly higher likelihood to achieve a PSA response (defined as ≥50% decrease confirmed 3 or 4 weeks later) than abiraterone (OR: [redacted], 95% CI [[redacted]]). However, no significant differences were observed between enzalutamide and abiraterone for ORR (OR: [redacted], 95% CI [[redacted]]).

Table 28: Results of the indirect comparison for ORR and PSA response

Outcome	**Treatment comparison: ENZA vs. ABI**	
	OR	**95% CI**
ORR	[redacted]	[redacted]
PSA response	[redacted]	[redacted]

Source: SLR 2013 (31)
Abbreviations: ABI: abiraterone; ENZA: enzalutamide; HR: hazard ratio.
In bold: statistically significant outcomes.

6.7.6.1 *Conclusion*

The outcomes of the indirect comparison of enzalutamide versus abiraterone in patients with mCRPC whose disease has progressed on or after docetaxel treatment can be summarised as follows:

- Enzalutamide is associated with a significantly lower hazard ratio for radiographic progression than abiraterone (HR: [redacted]; 95% CI [[redacted]])
- Enzalutamide is associated with a significantly higher likelihood of achieving a PSA response than abiraterone (OR: [redacted], 95% CI [[redacted]])
- Enzalutamide is associated with a significantly lower hazard ratio for modified progression free survival. The HR for enzalutamide vs. abiraterone is [redacted] (95% CI [[redacted]]).

Although the ITC for OS did not show a significant difference between enzalutamide and abiraterone, it should be noted that the analysis did indicate a clear trend towards enzalutamide having longer OS than abiraterone, being on the boundary of significance (OS: HR: [redacted], 95% CI: [redacted]).

The treatment effect of enzalutamide on the following endpoints is not statistically different from that observed with abiraterone:

- Time to first SRE: HR: [redacted]; 95% CI [[redacted]].
- ORR: OR: [redacted], 95% CI [[redacted]].

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Because the data for each pairwise treatment comparison came from single studies no statistical assessment of heterogeneity was undertaken. We have however examined possible sources of heterogeneity which could arise from:

- Comparability of the control arm in both studies.
- Comparability of the patient population.
- Definition used for mPFS.

Abiraterone needs to be taken with steroids which is not the case for enzalutamide. Therefore a different percentage of patients in control arm of AFFIRM and the COU-AA-301 study received steroids (n=182/399, 45.6% vs. n=398/398, 100%). There is no evidence to suggest that steroids have an impact on PFS or OS. Experts noted that patients would have already received steroids and progressed on this treatment earlier on in the disease (4) and that the benefit of steroids is likely negligible in this patient population.

Until very recently no treatment options were available to patients after they had progressed on docetaxel therapy. In this respect abiraterone changed the treatment pathway for mCRPC patients. Considering the time at which the COU-AA-301 study started it could be thought that a more prevalent mCRPC patient group may have existed. However, this was not the case. When comparing baseline characteristics it seems there is no difference between the populations. Time since PC diagnosis was comparable in both studies (Table 24).

Finally the definition of mPFS differs between the two studies (Table 22). Several clinicians indicated that these differences were small (4) (70). In addition when looking at the individual components of mPFS, rPFS, time to first SRE and PSA progression) the ITC results show a consistent trend.

In addition, the internal validity and similarity of the two included studies was examined (section 6.7.3). As described, the baseline population characteristics of individuals in the studies were comparable in terms of demographics and disease status. We therefore concluded that the two trials were suitably similar to indicate that an adjusted indirect comparison of enzalutamide versus abiraterone was appropriate.

6.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

Not applicable as only one study was included in the ITC.

6.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

A network-meta-analysis could not be performed due to a lack of trials that linked between different treatments and therefore no testing of inconsistency was possible.

6.8 *Non-RCT evidence*

No relevant non-RCTs were identified during the SLR.

6.9 *Adverse Events*

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

The search strategy and methodology used to identify safety-related clinical studies for the ITC are the same as the strategy provided in section 6.1.1. A separate search was not conducted for AEs, but AEs were included as part of the search algorithm (appendix 2, section 10.2). No safety specific studies with enzalutamide were identified however, safety was a secondary endpoint in AFFIRM (3).

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

6.9.2.1 **Adverse Events in AFFIRM**

Safety was a secondary objective in AFFIRM. The overall incidence of AEs with enzalutamide was similar to those of placebo in this study. Further, incidence of all

grade and of grade 3+ was either comparable or lower in the enzalutamide arm than with placebo.

The source for all safety data reported in this chapter is the Summary of Clinical Safety (71) unless stated otherwise. Similarly, AFFIRM safety data presented here correspond to the September 2011 IA unless stated otherwise. For the database lock date the only safety data available were limited to the overall incidence of AEs (Table 32); no data on individual AEs has been calculated.

Treatment-emergent adverse events (TEAE)

The TEAE reporting period in AFFIRM was defined as all AEs with an onset date on or after the date of the first dose of study drug up to 30 days after the date of the last dose of study drug or initiation of subsequent systemic antineoplastic treatment, whichever came first. The median TEAE reporting period for patients in the enzalutamide treatment arm was 9.3 months as compared with 3.8 months in the placebo treatment arm. The total TEAE reporting period represented 605.37 patients-years in the enzalutamide treated arm and 166.73 patient-years in the placebo-treated arm.

Table 29: Summary of all grades AEs and grade ≥3 in AFFIRM

System organ Class	All Grade AEs reported in at least 5% of patients			Grade 3 ≥ AE in at least 1% of patients		
	ENZA	PLA	Relative risk (95% CI)	ENZA	PLA	Relative risk (95% CI)
Number of Patients Reporting ≥ 1 Adverse Event	785 (98.1%)	390 (97.7%)	1.00 [0.99; 1.02]	-	-	-
Number of Patients Reporting ≥ Grade 3 or Higher AE	-	-	-	362 (45.3%)	212 (53.1%)	0.85 [0.76; 0.96]
Blood and Lymphatic System Disorders	134 (16.8%)	84 (21.1%)	0.80 [0.62; 1.02]	72 (9.0%)	41 (10.3%)	0.88 [0.61; 1.26]
Anaemia	115 (14.4%)	76 (19.0%)	0.75 [0.58; 0.98]	62 (7.8%)	38 (9.5%)	0.81 [0.55; 1.20]
Thrombocytopenia	-	-	-	8 (1.0%)	3 (0.8%)	1.33 [0.35; 4.99]
Gastrointestinal Disorders	539 (67.4%)	279(69.9%)	0.96 [0.89; 1.04]	48 (6.0%)	32 (8.0%)	0.75 [0.49; 1.15]
Nausea	265 (33.1%)	167(41.9%)	0.79 [0.68; 0.92]	12 (1.5%)	13 (3.3%)	0.46 [0.21; 1.00]
Constipation	188 (23.5%)	110(27.6%)	0.85 [0.70; 1.04]	6 (0.8%)	5 (1.3%)	0.60 [0.18; 1.95]
Diarrhoea	**171 (21.4%)**	**70 (17.5%)**	1.22 [0.95; 1.57]	9 (1.1%)	1 (0.3%)	4.49 [0.57; 35.31]
Vomiting	130 (16.3%)	88 (22.1%)	0.74 [0.58; 0.94]	9 (1.1%)	10 (2.5%)	0.45 [0.18; 1.10]
Abdominal pain	41 (5.1%)	23 (5.8%)	0.89 [0.54; 1.46]	-	-	-
General Disorders and Administration Site Conditions	506 (63.3%)	231(57.9%)	1.09 [0.99; 1.21]	99 (12.4%)	49 (12.3%)	1.01 [0.73; 1.39]
Fatigue	**269 (33.6%)**	**116(29.1%)**	1.16 [0.96; 1.39]	50 (6.3%)	29 (7.3%)	0.86 [0.55; 1.34]
Oedema peripheral	**122 (15.3%)**	**53 (13.3%)**	1.15 [0.85; 1.55]	8 (1.0%)	3 (0.8%)	1.33 [0.35; 4.99]
Asthenia	140 (17.5%)	67 (16.8%)	1.04 [0.80; 1.36]	20 (2.5%)	10 (2.5%)	1.00 [0.47; 2.11]
Pyrexia	54 (6.8%)	28 (7.0%)	0.96 [0.62; 1.49]	-	-	-
General physical health deterioration	-	-	-	19 (2.4%)	8 (2.0%)	1.18 [0.52; 2.68]
Infections and Infestations	285 (35.6%)	117(29.3%)	1.21 [1.02; 1.45]	45 (5.6%)	20 (5.0%)	1.12 [0.67; 1.87]
Urinary tract infection	63 (7.9%)	28 (7.0%)	1.12 [0.73; 1.72]	10 (1.3%)	3 (0.8%)	1.66 [0.46; 6.01]
Pneumonia	-	-	-	14 (1.8%)	5 (1.3%)	1.40 [0.51; 3.85]
Investigations	148 (18.5%)	77 (19.3%)	0.96 [0.75; 1.23]	27 (3.4%)	19 (4.8%)	0.71 [0.40; 1.26]
Weight decreased	94 (11.8%)	41 (10.3%)	1.14 [0.81; 1.62]	7 (0.9%)	7 (1.8%)	0.50 [0.18; 1.41]
Metabolism and Nutrition Disorders	280 (35.0%)	155(38.8%)	0.90 [0.77; 1.05]	44 (5.5%)	24 (6.0%)	0.91 [0.56; 1.48]
Decreased appetite	225 (28.1%)	121(30.3%)	0.93 [0.77; 1.12]	**17 (2.1%)**	**4 (1.0%)**	2.12 [0.72; 6.26]
Dehydration	-	-	-	6 (0.8%)	6 (1.5%)	0.50 [0.16; 1.54]
Hyponatremia	-	-	-!	8 (1.0%)	6 (1.5%)	0.67 [0.23; 1.90]
Musculoskeletal and Connective Tissue Disorders	516 (64.5%)	259(64.9%)	0.99 [0.91; 1.09]	112 (14.0%)	59 (14.8%)	0.95 [0.71; 1.27]
Back pain	197 (24.6%)	96(24.1%)	1.02 [0.83; 1.27]	**40 (5.0%)**	**16 (4.0%)**	1.25 [0.71; 2.20]
Arthralgia	152 (19.0%)	69(17.3%)	1.10 [0.85; 1.42]	20 (2.5%)	7 (1.8%)	1.43 [0.61; 3.34]
Bone pain	101 (12.6%)	61(15.3%)	0.83 [0.62; 1.11]	18 (2.3%)	13 (3.3%)	0.69 [0.34; 1.40]
Pain in extremity	119 (14.9%)	65 (16.3%)	0.91 [0.69; 1.21]	14 (1.8%)	14 (3.5%)	0.50 [0.24; 1.04]

System organ Class	All Grade AEs reported in at least 5% of patients			Grade 3 ≥ AE in at least 1% of patients		
	ENZA	PLA	Relative risk (95% CI)	ENZA	PLA	Relative risk (95% CI)
Muscular weakness	**74 (9.3%)**	**27 (6.8%)**	1.37 [0.89; 2.09]	12 (1.5%)	7 (1.8%)	0.86 [0.34; 2.15]
Musculoskeletal pain	**116 (14.5%)**	**46 (11.5%)**	1.26 [0.91; 1.73]	9 (1.1%)	1 (0.3%)	4.49 [0.57; 35.31]
Musculoskeletal chest pain	62 (7.8%)	34 (8.5%)	0.91 [0.61; 1.36]	3 (0.4%)	5 (1.3%)	0.30 [0.07; 1.25]
Myalgia	50 (6.3%)	26 (6.5%)	0.96 [0.61; 1.52]	-	-	-
Pathological fracture	-	-	-	**12(1.5%)**	**2 (0.5%)**	2.99 [0.67; 13.31]
Nervous System Disorders	389 (48.6%)	149 (37.3%)	1.30 [1.13; 1.51]	-	-	-
Headache	**93 (11.6%)**	**22 (5.5%)**	2.11 [1.35; 3.30]	-	-	-
Dizziness	55 (6.9%)	22 (5.5%)	1.25 [0.77; 2.01]	-	-	-
Paresthesia	**52 (6.5%)**	**18 (4.5%)**	1.44 [0.85; 2.43]	-	-	-
Spinal cord compression	51 (6.4%)	18 (4.5%)	1.41 [0.84; 2.39]	**46 (5.8%)**	**15 (3.8%)**	1.53 [0.86; 2.71]
Nerve root compression	-	-	-	3 (0.4%)	4 (1.0%)	0.37 [0.08; 1.66]
Psychiatric Disorders	199 (24.9%)	77 (19.3%)	1.29 [1.02; 1.63]			-
Insomnia	**70 (8.8%)**	**24 (6.0%)**	1.45 [0.93; 2.28]			-
Anxiety	**51 (6.4%)**	**16 (4.0%)**	1.59 [0.92; 2.75]			-
Depression	44 (5.5%)	18 (4.5%)	1.22 [0.71; 2.08]			-
Renal and Urinary Disorders	185 (23.1%)	97 (24.3%)	0.95 [0.77; 1.18]	33 (4.1%)	20 (5.0%)	0.82 [0.48; 1.42]
Hematuria	**52 (6.5%)**	**18 (4.5%)**	1.44 [0.85; 2.43]	12 (1.5%)	4 (1.0%)	1.50 [0.49; 4.61]
Urinary retention	-	-	-	3 (0.4%)	5 (1.3%)	0.30 [0.07; 1.25]
Respiratory, Thoracic, and Mediastinal Disorders	210 (26.3%)	102(25.6%)	1.03 [0.84; 1.26]	25 (3.1%)	17 (4.3%)	0.73 [0.40; 1.34]
Dyspnoea	79 (9.9%)	39 (9.8%)	1.01 [0.70; 1.45]	5 (0.6%)	6 (1.5%)	0.42 [0.13; 1.35]
Cough	47 (5.9%)	25 (6.3%)	0.94 [0.59; 1.50]			-
Pulmonary embolism	-	-	-	6 (0.8%)	4 (1.0%)	0.75 [0.21; 2.64]
Vascular Disorders	249 (31.1%)	78 (19.5%)	1.59 [1.27; 1.99]	26 (3.3%)	11 (2.8%)	1.18 [0.59; 2.36]
Hot flush	**162 (20.3%)**	**41 (10.3%)**	1.97 [1.43; 2.72]	-	-	-
Hypertension	**49 (6.1%)**	**11 (2.8%)**	2.22 [1.17; 4.23]	16 (2.0%)	5 (1.3%)	1.60 [0.59; 4.33]
Neoplasms Benign, Malignant, and Unspecified (Incl Cysts and Polyps)	-	-	-	35 (4.4%)	21 (5.3%)	0.83 [0.49; 1.41]
Metastatic pain	-	-	-	**15 (1.9%)**	**3 (0.8%)**	2.49 [0.73; 8.56]
Cancer pain	-	-	-	10 (1.3%)	5 (1.3%)	1.00 [0.34; 2.90]
Metastases to bone	-	-	-	0 (0.0%)	4 (1.0%)	-

Source: Summary of Clinical Safety (71):
Note: In bold those AEs more common in the enzalutamide arm with ≥2% absolute increase in incidence from placebo; the remaining events are either comparable between groups or more common in the placebo arm.
Abbreviations: AEs: adverse events; ENZA: enzalutamide; PLA: placebo; mg: milligrams.

In line with longer rPFS with enzalutamide, in AFFIRM the mean and median time on study treatment was higher in the enzalutamide arm (8.5 and 8.3 months, respectively) than in the placebo arm (4.3 and 3.0 months, respectively). A similar proportion of patients had one or more dose interruptions in both arms (enzalutamide: n=97/800, 12.1%; placebo: n=61/399, 15.3%) during the study. Similarly, the proportion of patients needing a dose reduction was comparable (enzalutamide: n=18/800, 2.2%; placebo: n=11/399, 2.8%).

As expected for this patient population with advanced PC, nearly all enzalutamide-treated and placebo-treated patients experienced at least 1 AE in AFFIRM (Table 30). Despite the substantially longer exposure to the study treatment in the enzalutamide arm, the proportion of patients with AEs leading to discontinuation of study drug, dose reduction or to death, serious adverse events (SAEs), and Grade 3+ AEs were all numerically lower in the enzalutamide arm than in the placebo arm. If adjusted for duration of exposure, the difference in the incidence of these AEs would be even more favourable to enzalutamide as can be seen in section 7.3.1.3.

Table 30: Summary of AEs in the AFFIRM study

Number of patients with ≥1:	ENZA (N=800)	PLA (N=399)
AE	785 (98.1%)	390 (97.7%)
AE associated with study drug discontinuation	128 (16.0%)	73 (18.3%)
AE as primary reason for study drug discontinuation	61 (7.6%)	39 (9.8%)
AE leading to dose reduction of study drug	17 (2.1%)	11 (2.8%)
AE leading to temporary interruption of study drug dosing	102 (12.8%)	61 (15.3%)
AE leading to death	23 (2.9%)*	14 (3.5%)
Serious AE	268 (33.5%)	154 (38.6%)
Grade 3 or higher AE	362 (45.3%)	212 (53.1%)

Source: Clinical Study Report (15)
Note: Adverse events were included in this analysis if they occurred during the treatment-emergent adverse event reporting period defined as the date of the first dose of study drug up to 30 days after the last dose of study drug or the initiation of subsequent antineoplastic treatment, whichever occurred first.
*All AEs leading to death occurred in one patient each except general physical health deterioration (n=6, 0.8%), pneumonia (n=2, 0.3%) and sepsis (n=2, 0.3%) in the XTANDI group and general physical health deterioration (n=5, 1.3%) and hepatic encephalopathy (n=2, 0.5%) in the BSC group.
Abbreviations: AE: adverse events; ENZA: enzalutamide; PLA: placebo.

Regarding grade 3 or higher AEs, enzalutamide was associated with a lower incidence of these AEs and treatment with enzalutamide was also associated with a longer time to experiencing any Grade 3 or higher AE. Table 29 summarises Grade 3 or higher AEs that occurred in at least 1% of either treatment arm by system organ class. Grade 3 or higher AEs more commonly reported with enzalutamide with at least 1% absolute difference in incidence from placebo are:

- Decreased appetite (enzalutamide: n=17/800, 2.1%; placebo: n=4/399, 1.0%).
- Back pain (enzalutamide: n=40/800, 5.0%; placebo: n=16/399, 4.0%).
- Pathological fractures (enzalutamide: n=12/800, 1.5%; placebo: n=2/399, 0.5%).
- Metastatic pain (enzalutamide: n=15/800, 1.9%; placebo: n=3/399, 0.8%).
- Spinal cord compression (enzalutamide: n=46/800, 5.8%; placebo: n=15/399, 3.8%).

Treatment-related adverse reactions

Overall, 69.3% of patients on enzalutamide and 66.7% of patients on placebo experienced at least one AE that was assessed by the investigator as either possibly, probably or definitely related to study drug (Table 31). The study drug related AEs occurring at ≥1% frequency and with an incidence of at least 2% higher in the enzalutamide-treatment arm than that placebo treated arm were:

- Fatigue (enzalutamide: n=172/800, 21.5%; placebo: n=71/399, 17.8%).
- Hot flush (enzalutamide: n=120/800, 15.0%; placebo: n=32/399, 8.0%).
- Headache (enzalutamide: n=36/800, 4.5%; placebo: n=9/399, 2. 3%).

The adverse drug reactions in AFFIRM are listed in Table 31. The most common adverse reactions associated with enzalutamide treatment are hot flushes (enzalutamide: n=162/800, 20.3%; placebo: n=41/399, 10.3%) and headaches (enzalutamide: n=93/800, 11.6%; placebo: n=22/399, 5.5%).

Table 31: Summary of adverse reactions in AFFIRM

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

Source: Summary of Clinical Safety (71):
Note: * Includes all fractures with the exception of pathological fractures
Abbreviations: ENZA: enzalutamide; PLA: placebo.

Deaths, serious AEs and other significant AEs

Irrespective of the analysis date (data cut-off or database lock), a lower proportion of patients died due to any cause or to disease progression in the enzalutamide arm than in the placebo arm (Table 32). Adverse events leading to death occurred in 23 (2.9%) patients in the enzalutamide group and 14 (3.5%) patients in the placebo group. The causes of death are comparable between arms. The most frequently AE

reported as the cause of a fatality in both arms was general physical health deterioration (enzalutamide: n=6, 0.8%; placebo: n=5, 1.3%). This AE was likely due to disease progression. All other fatal AEs were reported in ≤2 patients in any arm.

Table 32: Deaths and causes of deaths in AFFIRM

	Interim Analysis		Database lock	
	ENZA (N = 800)	PLA (N= 399)	ENZA (n = 800)	PLA (n = 399)
Total number of deaths at or prior to data cut-off date	308(38.5%)	212(53.1%)	344(43.0%)	232(58.1%)
Cause of death				
Disease progression	274(34.3%)	192(48.1%)	303(37.9%)	207(51.9%)
Other	22 (2.8%)	13 (3.3%)	25 (3.1%)	16 (4.0%)
Unknown	12 (1.5%)	7 (1.8%)	16 (2.0%)	9 (2.3%)
Deaths occurring ≤30 days of the first dose of study drug	2 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
Deaths occurring ≤30 days of the last dose of study drug	64 (8.0%)	25 (6.3%)	64 (8.0%)	25 (6.3%)

Source: Summary of Clinical Safety (71):
Abbreviation: ENZA: enzalutamide; PLA: placebo.

TEAE leading to death occurred in 23 (2.9%) patients in the enzalutamide treatment arm and 14 (3.5%) patients in the placebo treatment arm. The cause of death was comparable between the two arms.

In the enzalutamide treatment arm, all AEs leading to death were identified in one single patient each, except for general physical health deterioration (n=6, 0.8%), pneumonia (n=2, 0.3%) and sepsis (n=2, 0.3%). In the placebo treatment arm, the exceptions were: general physical health deterioration (n=5, 1.3%) and hepatic encephalopathy (n=2, 0.5%).

Table 33: Study drug-related adverse events occurring at a ≥1% frequency in either enzalutamide or placebo terms by preferred term

	Grade 3/4/5 ENZA			All		
Adverse event	**ENZA (N=800)**	**PLA (N=399)**	**RR (95% CI)**	**ENZA (N=800)**	**PLA (N=399)**	**RR (95% CI)**
Patients reporting ≥1 study drug-related adverse event	93 (11.6%)	48 (12.0%)	0.97 [0.70; 1.34]	554 (69.3%)	266 (66.7%)	1.04 [0.96; 1.13]
Nausea	5 (0.6%)	6 (1.5%)	0.42 [0.13; 1.35]	161 (20.1%)	99 (24.8%)	0.81 [0.65; 1.01]
Fatigue	25 (3.1%)	12 (3.0%)	1.04 [0.53; 2.05]	172 (21.5%)	71 (17.8%)	1.21 [0.94; 1.55]
Hot flush	0 (0.0%)	0 (0.0%)	1.00 [0.02; 63.93]	120 (15.0%)	32 (8.0%)	1.87 [1.29; 2.71]
Anorexia	8 (1.0%)	1 (0.3%)	3.99 [0.50; 31.79]	88 (11.0%)	51 (12.8%)	0.86 [0.62; 1.19]
Asthenia	7 (0.9%)	3 (0.8%)	1.16 [0.30; 4.48]	80 (10.0%)	37 (9.3%)	1.08 [0.74; 1.56]
Diarrhoea	2 (0.3%)	1 (0.3%)	1.00 [0.09; 10.97]	71 (8.9%)	31 (7.8%)	1.14 [0.76; 1.71]
Vomiting	5 (0.6%)	6 (1.5%)	0.42 [0.13; 1.35]	55 (6.9%)	39 (9.8%)	0.70 [0.48; 1.04]
Constipation	1 (0.1%)	0 (0.0%)	2.50 [0.06; 103.05]	37 (4.6%)	20 (5.0%)	0.92 [0.54; 1.57]
Headache	1 (0.1%)	0 (0.0%)	2.50 [0.06; 103.05]	36 (4.5%	9 (2.3%)	2.00 [0.97; 4.10]
Anaemia	8 (1.0%)	6 (1.5%)	0.67 [0.23; 1.90]	22 (2.8%)	17 (4.3%)	0.65 [0.35; 1.20]
Oedema peripheral	0 (0.0%)	0 (0.0%)	1.00 [0.02; 63.93]	27 (3.4%)	10 (2.5%)	1.35 [0.66; 2.75]
Dysgeusia	0 (0.0%)	0 (0.0%)	1.00 [0.02; 63.93]	25 (3.1%)	10 (2.5%)	1.25 [0.60; 2.57]
Weight decreased	1 (0.1%)	0 (0.0%)	2.50 [0.06; 103.05]	22 (2.8%)	13 (3.3%)	0.84 [0.43; 1.66]
Dizziness	1 (0.1%)	0 (0.0%)	2.50 [0.06; 103.05]	27 (3.4%)	6 (1.5%)	2.24 [0.93; 5.39]
Myalgia	2 (0.3%)	3 (0.8%)	0.33 [0.06; 1.98]	17 (2.1%	10 (2.5%)	0.85 [0.39; 1.83]
Insomnia	0 (0.0%)	0 (0.0%)	1.00 [0.02; 63.93]	22 (2.8%)	4 (1.0%)	2.74 [0.95; 7.91]
Arthralgia	1 (0.1%)	1 (0.3%)	0.50 [0.03; 7.95]	18 (2.3%)	5 (1.3%)	1.80 [0.67; 4.80]
Decrease appetite	0 (0.0%)	0 (0.0%)	1.00 [0.02; 63.93]	14 (1.8%)	8 (2.0%)	0.87 [0.37; 2.06]
Back pain	2 (0.3%)	1 (0.3%)	1.00 [0.09; 10.97]	12 (1.5%)	9 (2.3%)	0.67 [0.28; 1.57]
Abdominal pain upper	0 (0.0%)	0 (0.0%)	1.00 [0.02; 63.93]	12 (1.5%)	8 (2.0%)	0.75 [0.31; 1.82]
Hypertension	5 (0.6%)	2 (0.5%)	1.25 [0.24; 6.40]	15 (1.9%)	3 (0.8%)	2.49 [0.73; 8.56]
Abdominal distension	0 (0.0%)	0 (0.0%)	1.00 [0.02; 63.93]	12 (1.5%)	5 (1.3%)	1.20 [0.42; 3.37]
Dyspnoea	0 (0.0%)	0 (0.0%)	1.00 [0.02; 63.93]	12 (1.5%)	5 (1.3%)	1.20 [0.42; 3.37]
Hyperhidrosis	0 (0.0%)	6 (1.5%)	0.05 [0.00; 0.65]	11 (1.4%)	0 (0.0%)	17.49 [0.56; 547.35]
Lethargy	0 (0.0%)	7 (1.8%)	0.05 [0.00; 0.65]	8 (1.0%)	0 (0.0%)	12.99 [0.41; 413.38]

Adverse event	Grade 3/4/5 ENZA			All		
	ENZA (N=800)	PLA (N=399)	RR (95% CI)	ENZA (N=800)	PLA (N=399)	RR (95% CI)
Muscular weakness	1 (0.1%)	6 (1.5%)	0.08 [0.01; 0.69]	10 (1.3%)	2 (0.5%)	2.49 [0.55; 11.33]
Rash	1 (0.1%)	6 (1.5%)	0.08 [0.01; 0.69]	10 (1.3%)	0 (0.0%)	15.99 [0.51; 502.68]
Abdominal pain	0 (0.0%)	5 (1.3%)	0.06 [0.00; 0.79]	9 (1.1%)	0 (0.0%)	14.49 [0.46; 458.03]
Dry skin	0 (0.0%)	0 (0.0%)	1.00 [0.02; 63.93]	14 (1.8%)	0 (0.0%)	21.98 [0.71; 681.39]
Cough	0 (0.0%)	3 (0.8%)	0.10 [0.01; 1.38]	10 (1.3%)	0 (0.0%)	15.99 [0.51; 502.68]
Flatulence	0 (0.0%)	4 (1.0%)	0.08 [0.01; 1.01]	9 (1.1%)	0 (0.0%)	14.49 [0.46; 458.03]
Muscle spasms	0 (0.0%)	6 (1.5%)	0.05 [0.00; 0.65]	7 (0.9%)	2 (0.5%)	1.75 [0.36; 8.36]
Pain in extremity	0 (0.0%)	5 (1.3%)	0.06 [0.00; 0.79]	7 (0.9%)	2 (0.5%)	1.75 [0.36; 8.36]
Night sweats	0 (0.0%)	3 (0.8%)	0.10 [0.01; 1.38]	9 (1.1%)	0 (0.0%)	14.49 [0.46; 458.03]
Paresthesia	0 (0.0%)	1 (0.3%)	0.25 [0.01; 4.71]	10 (1.3%)	0 (0.0%)	15.99 [0.51; 502.68]
Pruritus	0 (0.0%)	1 (0.3%)	0.25 [0.01; 4.71]	10 (1.3%)	0 (0.0%)	15.99 [0.51; 502.68]
Anxiety	1 (0.1%)	1 (0.3%)	0.50 [0.03; 7.95]	8 (1.0%)	0 (0.0%)	12.99 [0.41; 413.38]
Dehydration	0 (0.0%)	5 (1.3%)	0.06 [0.00; 0.79]	3 (0.4%)	1 (0.3%)	1.50 [0.16; 14.34]
Hypotension	0 (0.0%)	4 (1.0%)	0.08 [0.01; 1.01]	2 (0.3%)	1 (0.3%)	1.00 [0.09; 10.97]
Neck pain	0 (0.0%)	4 (1.0%)	0.08 [0.01; 1.01]	1 (0.1%)	0 (0.0%)	2.50 [0.06; 103.05]

Source: Summary of Clinical Safety (71)
Abbreviations: ENZA: enzalutamide; PLA: placebo; RR: relative risk.

Other serious AEs

Among AEs that led to permanent treatment discontinuation, the most commonly reported AEs were:

- Fatigue: enzalutamide: n=5, 0.6%; placebo: n=2, 0.5%.
- Dysphagia: enzalutamide: n=3, 0.4%; placebo: n=2, 0.5%.
- Vomiting: enzalutamide: n=3, 0.4%; placebo: n=2, 0.5%.
- Nausea: enzalutamide: n=3, 0.4%; placebo: n=1, 0.3%.
- Cerebrovascular accident: enzalutamide: n=3, 0.4%; placebo: n=1, 0.3%.

All other AEs leading to treatment discontinuation occurred in ≤2 patients except for seizure or convulsion. Although only two patients were listed as permanently discontinuing study drug for an event of seizure (convulsion), all five patients that were reported to have had a seizure by the September data IA date (collectively reported as convulsion, partial seizure, and status epilepticus) were permanently discontinued from study drug as per protocol. In one event of seizure, study drug had already been discontinued 26 days prior to the event.

Regarding important AEs, six merit special attention based on potential safety issues observed with other drugs with similar pharmacologic effects, potential safety issues identified from nonclinical toxicology studies; dose-limiting toxicities identified in the phase I dose-escalation study S-3100-1-01; and the safety results from AFFIRM. These AEs are seizures, spinal cord compression, hypertension, neuropsychiatric events (hallucinations) and falls.

Seizures

Seizure was first identified as a potential enzalutamide-associated toxicity in the phase I dose-escalation S-3100-1-01 study (38). In S-3100-1-01 involving 140 patients, no patients experienced seizures at or below daily doses of 240 mg, whereas 3 seizures were reported, 1 each at 360, 480, and 600 mg/day (72).

In AFFIRM a number of measures were taken to reduce the risk of seizure and to increase the vigilance of reporting of seizures. Patients with a history of seizure or conditions predisposing to seizure were excluded, as were patients taking medications known to lower the seizure threshold. These medications were also prohibited as concomitant medications during the study. Patients with diagnosed brain metastases were also excluded from the study (3). Enzalutamide and its metabolite M2 is thought to inhibit the Gamma-Aminobutyric Acid (GABA)-gated chloride channel which may explain the potential of enzalutamide to cause seizures in patients with predisposing factors (73) (74) (75).

In AFFIRM, seizures were required to be reported as SAEs, whether or not they resulted in hospitalisation or met other criteria for seriousness (3).

As of the IA (25 September 2011), 5 (n=5/800, 0.6%) patients were reported to have had AEs of seizure, with preferred terms of convulsion (2 events), partial seizure (2), and status epilepticus (1). All 5 (0.6%) patients had been randomised to the enzalutamide arm. No case of seizure was reported among placebo-treated patients. One additional SAE reported by the Investigator as syncope was identified by the study sponsor as having several features suggesting seizure as the most likely

diagnosis. In addition, one patient was reported to have had a seizure after the safety data cut-off date and before database lock.

Of the 5 patients with a seizure before September 2011, 4 had other predisposing factors that increased their risk of seizures:

- Patient ID 014-02 had a brain metastasis in the right temporal lobe with haemorrhage, vasogenic oedema, and mass effect.
- Patient ID 358-05 had cerebellar metastases and pachymeningitis carcinomatosis.
- Patient ID 300-21 had a partial convulsion immediately after 40 mg of lidocaine was inadvertently injected intravenously prior to planned administration of the anaesthetic into the pleura. He had also received propafenone.
- Patient ID 812-01 had a history of heavy alcohol use, had started haloperidol 7 days prior to his unwitnessed event, and was found to have atrophy on head CT.

Until April 2012, 10 patients (n=10/1,100, 0.9%) exposed to enzalutamide have been reported (either by the investigator or manufacturer) to have experienced a seizure at a dose of 150/160mg. Three of these patients had been recruited to other enzalutamide studies (studies 9785-CL-0007, 9785-CL-0321 and 9785-CL-0222) (71).

The XTANDI™ summary of product characteristics (SPC) states 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*"(1).

Spinal cord compression and pathological fractures

In AFFIRM spinal cord compression and pathological fractures were more commonly reported with enzalutamide than with placebo despite enzalutamide significantly increasing time to first SRE.

Sites were instructed to report all SREs, defined as spinal cord compression, pathologic bone fracture, radiation therapy or surgery to bone, or change of antineoplastic therapy to treat bone pain, on the SRE case report form (CRF). If the SRE resulted in hospitalization or met other criteria for a SAE, the event had to be reported as a SAE as well. Non-serious SREs were not required to be reported as AEs, although some were.

The reporting period was also different for SREs and AEs. AEs were reported if they started during the treatment-emergent period. SREs were reported at any time after the first dose of study drug, even if subsequent to the treatment-emergent period. Therefore, the most complete information about spinal cord compression and pathological fractures was reported on the SREs CRF. The data from the SRE CRF is provided in Table 34.

When adjusted for the exposure to study treatment, the event rate per 100 patient-years for spinal cord compression and pathological fracture is lower with enzalutamide (11.9 and 6.8, respectively) than with placebo (18.6 and 9.0, respectively) (Table 34). This suggests that it is unlikely that spinal cord compression

and pathological fracture are adverse drug reactions associated with enzalutamide therapy (71).

Table 34: Spinal cord compression and pathological fractures in AFFIRM

	ENZA (N=800)	PLA (N=399)
Spinal cord compression		
Patients with ≥ 1 SRE in the time to first SRE analysis	66 (8.3%)	29 (7.3%)
Patients with ≥1 SRE during the treatment-emergent reporting period	66 (8.3%)	29 (7.3%)
Event rate per 100 patient years of risk	11.9	18.6
Pathological fracture		
Patients with ≥ 1 SRE in the time to first SRE analysis	31 (3.9%)	16 (4.0%)
Patients with ≥1 SRE during the treatment-emergent reporting period	36 (4.5%)	15 (3.8%)
Event rate per 100 patient years of risk	6.8	9.0

Source: Summary of Clinical Safety (71):
Abbreviations: CRF: case report form; ENZA: enzalutamide; PLA: placebo; SRE: skeletal-related events.

Hypertension

Of the enzalutamide-treated patients, 2.0% had a Grade 3 AEs of hypertension as compared with 1.5% of patients in the placebo arm with a Grade 3 or above AE. One (0.1%) patient in the enzalutamide treatment arm discontinued study drug treatment due to an AE of hypertension.

Review of AEs such as renal failure, renal insufficiency, myocardial infarction, congestive heart failure, and stroke did not show any evidence that treatment with enzalutamide was associated with any common clinical sequelae of severe uncontrolled hypertension.

Neuropsychiatric events (hallucinations)

Neuropsychiatric AEs that may be attributed to enzalutamide include hallucinations and cognitive and memory impairment. The etiology of the hallucinations is unknown. While the use of concomitant medications such as opioids may cause hallucinations, the imbalance between groups suggests a relationship to enzalutamide.

Falls

Treatment with enzalutamide was associated with an increase in falls in this study (4.0% vs.1.3%). Only 1 enzalutamide-treated patient had a serious AE of fall; the other enzalutamide-treated patients reported non-serious events. No patients in the enzalutamide treatment arm or placebo arm discontinued study drug treatment due to a fall.

6.9.2.2 ***Adverse Events ITC***

The safety-related outcomes included in the ITC were: all grades AEs and grade 3+ AEs. The information on AEs provided in the different studies was limited. This accounts for missing data for several AEs.

In the ITC only AEs for which data are available for both the AFFIRM and COU-AA-301 studies are included. The AEs provided in the publications of these two studies are:

- For AFFIRM, Scher et al (3) report the proportion of patients with those AEs more commonly reported in the enzalutamide arm than in the placebo or AEs that were clinically significant. In addition, the CSR provides information on those AEs with a ≥2% absolute difference in event frequency between treatment arms for all grades and at least a ≥1% frequency in either arm for grade 3+ (3).
- For COU-AA-301, de Bono et al (24) and Fizazi et al (25) report all grades and grade 3+ AEs. The authors do not clarify whether the data they provide relates only to the most common AEs or all AEs. For the ITC, the AEs reported in the final analysis are included (i.e., those reported in Fizazi et al (25)).

All grade AEs

Data included in the ITC for all grades AEs

The incidence of all grades AEs included in the ITC is provided in Table 35. To note, no data is provided for dehydration, leucopenia, pulmonary embolism or seizure in COU-AA-301. Therefore, no ITC for these AEs could be conducted.

In AFFIRM, enzalutamide was associated with a significantly lower likelihood to be associated with anaemia (OR: 0.71 [0.52; 0.98]), nausea (OR: 0.69 [0.54; 0.88]), and vomiting (OR: 0.69 [0.51; 0.93]) while it had a higher likelihood of hypertension (OR: 2.30 [1.18; 4.48]) than placebo.

In COU-AA-301, abiraterone was associated with a significantly lower likelihood to be associated with bone pain (OR: 0.45 [0.34; 0.60]) and a higher likelihood of arthalgia (OR: 1.36 [1.03; 1.80]), diarrhoea (OR: 1.42 [1.02; 1.98]), hypokalemia (OR: 2.19 [1.49; 3.23]) and of oedema peripheral/fluid retention (OR: 1.57 [1.19; 2.07]) than prednisone alone.

Table 35: Summary of all grades AEs included in the ITC

	AFFIRM			COU-AA-301		
AE	**ENZA (%)**	**PLA (%)**	**OR [95% CI]**	**ABI (%)**	**PRED (%)**	**OR [95% CI]**
Abdominal pain	[redacted]	[redacted]	[redacted]	12.90%	11.93%	1.09 [0.76; 1.58]
Anaemia	[redacted]	[redacted]	[redacted]	25.03%	27.92%	0.86 [0.66; 1.13]
Arthralgia	[redacted]	[redacted]	[redacted]	30.21%	24.11%	1.36 [1.03; 1.80]
Asthenia	[redacted]	[redacted]	[redacted]	15.42%	13.71%	1.15 [0.81; 1.62]
Back pain	[redacted]	[redacted]	[redacted]	33.12%	35.79%	0.89 [0.69; 1.15]
Bone pain	[redacted]	[redacted]	[redacted]	15.93%	29.70%	0.45 [0.34; 0.60]
Dehydration	[redacted]	[redacted]	[redacted]	NA	NA	NA
Diarrhoea	[redacted]	[redacted]	[redacted]	19.72%	14.72%	1.42 [1.02; 1.98]
Dyspnoea	[redacted]	[redacted]	[redacted]	14.66%	12.44%	1.21[0.85; 1.73]
Fatigue	[redacted]	[redacted]	[redacted]	47.03%	44.16%	1.12 [0.88; 1.43]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	0.38%	0.00%	NA
Hypertension	[redacted]	[redacted]	[redacted]	11.13%	8.12%	1.42 [0.93; 2.16]
Hypokalaemia	[redacted]	[redacted]	[redacted]	18.08%	9.14%	2.19 [1.49; 3.23]
Leukopenia	[redacted]	[redacted]	[redacted]	NA	NA	NA
Nausea	[redacted]	[redacted]	[redacted]	32.62%	32.99%	0.98 [0.76; 1.27]
Neutropenia	[redacted]	[redacted]	[redacted]	1.01%	0.51%	2.00 [0.42; 9.48]
Oedema Peripheral/Fluid retention	[redacted]	[redacted]	[redacted]	33.00%	23.86%	1.57 [1.19; 2.07]
Pain	[redacted]	[redacted]	[redacted]	4.80%	5.33%	0.90 [0.52; 1.55]

AE	AFFIRM			COU-AA-301		
Pain in extremity	[redacted]	[redacted]	[redacted]	19.72%	20.81%	0.93 [0.69; 1.26]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	NA	NA	NA
Seizure	[redacted]	[redacted]	[redacted]	NA	NA	NA
Thrombocytopaenia	[redacted]	[redacted]	[redacted]	3.79%	3.81%	1.00 [0.53; 1.87]
Vomiting	[redacted]	[redacted]	[redacted]	24.15%	25.63%	0.92 [0.70; 1.22]

Source: Summary of Clinical Safety (71)
Abbreviations: AE: adverse events; ABI: abiraterone; ENZA: enzalutamide; NA: not available; PLA: placebo; PRED: prednisone.

ITC comparison for all grades AEs

The results of the indirect analyses of enzalutamide relative to abiraterone for specific AEs (all grades) are provided in Table 36.

The ITC shows that enzalutamide has a similar likelihood to be associated with all specific AEs (all grades) of interest to abiraterone except for:

- Bone pain: a [redacted]-fold higher likelihood for enzalutamide compared with abiraterone (OR: [redacted] [[redacted]]). In AFFIRM, enzalutamide was associated with significantly more patients with pain palliation than placebo, irrespective of pain palliation being defined as a reduction of ≥2 point (25% vs. 14.2%; p>0.001) or ≥30% (44.9% vs. 6.7%; p=0.0079) in the worst pain item (BPI-SF item 3) score. The proportion of patients with bone pain reported as an AE in AFFIRM was 13.9% and 17.0% in the enzalutamide and placebo treatment arms, respectively, In COU-AA-301 this incidence was 15.9% and 29.7% in the abiraterone and placebo treatment arms, respectively.

- Hypokalemia: a lower likelihood for enzalutamide compared with abiraterone (OR: [redacted] [[redacted]]).

Table 36: Results of indirect comparison of all grades specific AEs

AE	ENZA vs. ABI OR [95% CI]
Abdominal pain	[redacted]
Anaemia	[redacted]
Arthralgia	[redacted]
Asthenia	[redacted]
Back pain	[redacted]
Bone pain	[redacted]
Diarrhoea	[redacted]
Dyspnoea	[redacted]
Fatigue	[redacted]
Hypertension	[redacted]
Hypokalaemia	[redacted]
Nausea	[redacted]
Neutropenia	[redacted]
Oedema Peripheral/Fluid retention	[redacted]
Pain	[redacted]
Pain in extremity	[redacted]
Thrombocytopaenia	[redacted]
Vomiting	[redacted]

Source: SLR 2013 (31)
Abbreviations: AE: adverse events; ABI: abiraterone; ENZA: enzalutamide; NA: not available; OR: odds ratio; PLA: placebo; PRED: prednisone; SRE: skeletal-related event.
In bold: statistically significant outcomes.

Grade 3 or more AEs

Data included in the ITC for grade 3+ AEs

The incidence of grade 3+ AEs for those AEs considered of relevance for this SLR and used in the ITC is provided in Table 37.

While in AFFIRM, enzalutamide was not associated with a significantly higher or lower likelihood for any particular grade 3+ AE than placebo, in COU-AA-301, abiraterone was associated with a significantly higher likelihood of grade 3+ hypokalemia (OR: [redacted] [95% CI [redacted]]) than prednisone alone.

Table 37: Summary of grade 3 or more AEs included in the selected studies

	AFFIRM			COU-AA-301		
AE	ENZA (%)	PLA (%)	OR [95% CI]	ABI (%)	PRED (%)	OR [95% CI]
Abdominal pain	[redacted]	[redacted]	[redacted]	2.28%	2.03%	1.12 [0.48; 2.61]
Anaemia	[redacted]	[redacted]	[redacted]	7.84%	8.12%	0.96 [0.62; 1.50]
Arthralgia	[redacted]	[redacted]	[redacted]	5.06%	4.31%	1.18 [0.66; 2.11]
Asthenia	[redacted]	[redacted]	[redacted]	3.29%	2.03%	1.64 [0.74; 3.66]
Back pain	[redacted]	[redacted]	[redacted]	7.08%	10.15%	0.67 [0.44; 1.03]
Bone pain	[redacted]	[redacted]	[redacted]	6.45%	7.87%	0.81 [0.51; 1.28]
Dehydration	[redacted]	[redacted]	[redacted]	NA	NA	NA
Diarrhoea	[redacted]	[redacted]	[redacted]	1.14%	1.27%	0.90 [0.30; 2.69]
Dyspnoea	[redacted]	[redacted]	[redacted]	1.77%	2.28%	0.77 [0.33; 1.80]
Fatigue	[redacted]	[redacted]	[redacted]	9.10%	10.41%	0.86 [0.58; 1.29]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	0.38%	0.00%	3.50 [0.18; 67.97]*
Hypertension	[redacted]	[redacted]	[redacted]	1.26%	0.25%	5.03 [0.64; 39.45]
Hypokalaemia	[redacted]	[redacted]	[redacted]	4.42%	0.76%	6.03 [1.84; 19.74]
Leukopenia	[redacted]	[redacted]	[redacted]	NA	NA	NA
Nausea	[redacted]	[redacted]	[redacted]	2.15%	2.79%	0.76 [0.35; 1.65]
Neutropenia	[redacted]	[redacted]	[redacted]	0.13%	0.25%	0.50 [0.03; 7.97]
Oedema Peripheral/Fluid retention	[redacted]	[redacted]	[redacted]	2.53%	1.02%	2.53 [0.86; 7.45]
Pain	[redacted]	[redacted]	[redacted]	0.88%	2.03%	0.43 [0.16; 1.20]
Pain in extremity	[redacted]	[redacted]	[redacted]	3.03%	5.08%	0.59 [0.32; 1.07]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	NA	NA	NA
Seizure	[redacted]	[redacted]	[redacted]	NA	NA	NA
Thrombocytopaenia	[redacted]	[redacted]	[redacted]	1.39%	0.51%	2.76 [0.61; 12.53]
Vomiting	[redacted]	[redacted]	[redacted]	2.65%	3.05%	0.87 [0.42; 1.78]

Source: SLR 2013 (31)
Abbreviation: AEs: adverse events; CI: confidence intervals; ENZA: enzalutamide; NA: not available; OR: odds ratio; PLA: placebo. * a continuity correction was applied by adding 0.5 to the number of events and non-events in both arms.

ITC for grade 3+ AEs

The relative effect of enzalutamide compared with abiraterone on the incidence of the different grade 3+ AEs is provided in Table 38.

The ITC shows that the likelihood of enzalutamide to be associated with any of the grade 3+ AEs assessed is not statistically different from that of abiraterone.

Table 38: Results of indirect comparison of grade 3+ specific AEs

AE	ENZA vs. ABI OR [95% CI]
Abdominal pain	[redacted]
Anaemia	[redacted]
Arthralgia	[redacted]
Asthenia	[redacted]
Back pain	[redacted]
Bone pain	[redacted]
Diarrhoea	[redacted]
Dyspnoea	[redacted]
Fatigue	[redacted]
Febrile neutropenia	[redacted]
Hypertension	[redacted]
Hypokalaemia	[redacted]
Nausea	[redacted]
Neutropenia	[redacted]
Oedema Peripheral/Fluid retention	[redacted]
Pain	[redacted]
Pain in extremity	[redacted]
Thrombocytopaenia	[redacted]
Vomiting	[redacted]

Source: SLR 2013 (31)
Abbreviations: ABI: abiraterone; AE: adverse events; CI: confidence interval; ENZA: enzalutamide; OR: odds ratio.

SRE

The incidences of SREs were assessed in the ITC. No significant differences were observed between enzalutamide and abiraterone (OR: [redacted] [95% CI [redacted]]) (Table 39).

Table 39: Results of indirect comparison of SRE data

Comparison	OR [95% CI]
ENZA vs. ABI	[redacted] [[redacted]]

Source: SLR 2013 (31)
Abbreviations: ABI: abiraterone; ENZA: enzalutamide; OR: odds ratios.

Tolerability assessed as discontinuation due to AEs

Data included in the ITC for tolerability

The studies included for the ITC on tolerability were also AFFIRM and COU-AA-301.

In both studies, the proportion of patients who discontinued treatment due to an AE was higher with study intervention (enzalutamide and abiraterone) than the comparator (Table 40).

Table 40: Summary of tolerability data included in the ITC

	AFFIRM (Scher 2012a)		COU-AA-301 (Fizazi 2012)	
	ENZA	PLA	ABI + PRED	PLA + PRED
Tolerability response	7.6% (61/800)	9.8% (39/399)	13.3% (105/791)	18.0% (71/394)
OR [95% CI]	0.76 [0.50; 1.16]		0.70 [0.50; 0.97]	

Source: Scher 2012 (3); Fizazi 2012 (25)
Abbreviations: ABI: abiraterone; ENZA: enzalutamide; OR: odds ratio; PLA: placebo; PRED: prednisone.

ITC for tolerability

The rate of treatment discontinuation (tolerability) was also assessed in the ITC. No significant differences were observed (OR: [redacted], 95% CI [[redacted]]) (Table 41).

Table 41: Results of indirect comparison of tolerability data

Comparison	OR [95% CI]
ENZA vs. ABI	[redacted]

Source: SLR 2013 (31)
Abbreviations: ABI: abiraterone; ENZA: enzalutamide; OR: odds ratios.

Conclusion

Overall, the results of the ITC showed that enzalutamide has a similar safety profile as abiraterone. The only significantly reduced AE with enzalutamide was hypokalemia (OR:[redacted]). In contrast, a higher risk of bone pain was observed with enzalutamide than abiraterone (OR: [redacted]). However, in AFFIRM, enzalutamide was associated with significantly more patients with pain palliation than placebo, irrespective of pain palliation being defined as a reduction of ≥2 point (25% vs. 14.2%; p>0.001) or ≥30% (44.9% vs. 6.7%; p=0.0079) in the worst pain item (BPI-SF item 3) score. No other significant differences are observed between enzalutamide and abiraterone.

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

In AFFIRM the overall incidence of AEs with enzalutamide was comparable to those with placebo. The safety profile of enzalutamide 160 mg daily is considered acceptable and generally manageable with pharmacological treatment when needed (1). In AFFIRM toxicities were generally mild and resulted in infrequent dose reductions, dose interruptions, or discontinuations. Importantly, SAEs and grade 3+ AEs were more frequent in the placebo arm than with enzalutamide despite the longer exposure to treatment in the enzalutamide arm.

In AFFIRM, the most commonly reported treatment-related AEs observed with enzalutamide include nausea, fatigue, anorexia and hot flush.

Of all AEs reported with enzalutamide, seizures merit special attention based on potential safety issues observed with other drugs with similar pharmacologic effects, potential safety issues identified from nonclinical toxicology studies; dose-limiting toxicities identified in the phase I dose-escalation study S-3100-1-01; and the safety results from the CRPC2 study. Seizures occurred in 0.9% (n=7/800) of patients in the

enzalutamide arm in AFFIRM. However, seizures were generally self-limited and did not recur upon cessation of dosing.

Unlike other pharmacological options for post-docetaxel mCRPC (i.e., abiraterone, and cabazitaxel), enzalutamide does not need to be administered with corticosteroids to improve its tolerability. This reduces the treatment burden of these patients and any possible corticosteroid-related toxicity. Further, unlike other interventions used in the post-docetaxel setting, with enzalutamide hepatotoxicity and mineralocorticoid excess-related toxicity including hypokalemia and fluid retention do not require product specific monitoring. The safety profile of enzalutamide is clearly distinct from that typically induced by conventional cytotoxic agents (e.g., cabazitaxel) and other anti-androgens (e.g., abiraterone) (for further information please refer to section 6.10.2).

In conclusion, enzalutamide is a generally well-tolerated drug. The maintenance of QoL as assessed with FACT-P and EQ-5D with enzalutamide suggests that the majority of AEs reported with enzalutamide do not have any impact on the patient´s QoL. This is of particular relevance in the context of non-curative therapy for an end-stage disease.

6.10 *Interpretation of clinical evidence*

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Patients with mCRPC who have progressed on or after docetaxel-based chemotherapy have a limited life expectancy. Until recently, there were no other treatment options available for these patients other than BSC. The introduction of abiraterone and cabazitaxel has increased the number of therapeutic options substantially. These treatments have increased survival of patients by approximately 2.4-4.6 months.

Enzalutamide expands the current treatment arena; its significant efficacy with favourable safety profile renders this agent an alternative to the treatment options currently available for this indication (4).

The clinical benefit of enzalutamide has been demonstrated in the pivotal Phase III RCT, AFFIRM and confirmed in the ITC of enzalutamide vs. standard of care, abiraterone.

The AFFIRM study was a well-conducted pivotal RCT that adequately supports the efficacy of enzalutamide in patients with mCRPC previously treated with docetaxel-based chemotherapy. The main objective of the AFFIRM study was to demonstrate superiority in efficacy and safety of enzalutamide (160 mg/day) plus BSC as compared to placebo + BSC, the only comparator approved for the treatment of mCRPC post chemotherapy, when the trial was designed.

The pivotal trial (AFFIRM) demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint, OS, compared with BSC. Median OS was 18.4 months (95% confidence interval [CI], 17.3 to not yet reached) in the

enzalutamide group versus 13.6 months (95% CI, 11.3 to 15.8) in the placebo group (hazard ratio for death in the enzalutamide group, 0.63; 95% CI, 0.53 to 0.75; P<0.001). The treatment benefit of enzalutamide on OS (+4.5 months [December 2011] and +4.8 months [September 2011] months) is similar to that observed with abiraterone (+4.6 months) (25) in the same setting. The ITC between enzalutamide and abiraterone supports equal OS estimates (estimates HR: [redacted]; 95% CI [redacted]). However, it should be noted that the analysis did indicate a clear trend towards enzalutamide having longer OS than abiraterone, being on the boundary of significance.

The concordant results across the secondary and exploratory endpoints demonstrate the robustness of outcomes. The ITC indicate significantly better PSA decrease (OR: [redacted], 95% CI [redacted]) and median rPFS (HR: [redacted], 95% CI [redacted]) of enzalutamide over abiraterone.

The QoL assessments (based on the FACT-P instrument) showed statistically and clinically important differences between enzalutamide and BSC in FACT-P total score and all sub-domains (physical, functional and emotional wellbeing and prostate cancer scale) at all time points in patients who continued on therapy except for social wellbeing which did not change (47). Differences in favour of enzalutamide were also observed for the BPI pain scores (Pain severity and Pain Interference).

The clear treatment benefit of enzalutamide in the post-docetaxel setting is associated with a favourable safety profile. In AFFIRM the overall incidence of AEs was similar between enzalutamide and placebo. The proportion of patients with serious AEs, grade 3+ AEs or with AEs leading to death or to permanent discontinuation of the study drug were either comparable or numerically lower for the enzalutamide arm, despite the substantially longer exposure to enzalutamide (median duration of treatment of 8.3 vs. 3.0 months in the enzalutamide and placebo arms, respectively). While being associated with a favourable safety profile compared with placebo or current alternatives, enzalutamide has been shown to increase the risk of seizure in patients with predisposing factors. Caution should be used when prescribing enzalutamide to patients with a history of seizures or other predisposing factors In AFFIRM, 7 (n=7/800, 0.9%) patients in the enzalutamide 160 mg experienced a seizure. The current incidence of seizure in the overall enzalutamide clinical program is also 0.9%. Seizures were generally self-limited and did not recur upon cessation of dosing.

Further, unlike other currently available treatments for patients with mCRPC whose disease has progressed on or after docetaxel therapy, enzalutamide does not need to be administered with corticosteroids. Routine product specific liver function, potassium and fluid balance monitoring is also not required with enzalutamide.

In conclusion, the overall efficacy and safety results support a positive benefit/risk assessment of the use of enzalutamide at a daily dose of 160 mg in adult men with mCRPC whose disease has progressed on or after docetaxel therapy. Importantly, enzalutamide did not compromise patient's QoL (37). Instead, a significant greater proportion of patients showed improvement in QoL during the first 25 weeks when assessed using FACT-P with enzalutamide than with placebo (47). Better QoL with enzalutamide is partly due to its treatment benefit on PFS and its favourable safety profile.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

The strengths of enzalutamide in the post-chemotherapy setting are related to its clinical efficacy in the AFFIRM study, a high quality, robust and clinically relevant RCT conducted in patients with mCRPC who progressed on or after docetaxel chemotherapy. The effect of enzalutamide has been clearly demonstrated, leading to an increase in the life expectancy with a safety profile overall acceptable and generally manageable.

Enzalutamide is the first and only AR signalling inhibitor that inhibits three steps in the signalling pathway (section 1.2). Unlike other anti-androgens, enzalutamide has not been associated with hepatotoxicity requiring routine monitoring which is a well-known toxicity of this drug class and of abiraterone acetate (Brahm (76); Lin (77); de Bono (24)). Enzalutamide has a safety profile distinct from abiraterone as it is not associated with mineralocorticoid excess, including hypokalemia and fluid retention (Sonpavde (78)), it does not have a food effect and it is not associated with hepatic toxicity and therefore, does not require any regular monitoring of the liver function.

The majority of patients in the AFFIRM trial were Caucasian (n=1,111/1,199, 92.6%), with the UK being the third highest enrolling country (n=132, 11.0%) after the US (n=288, 24.0%) and France (n=273, 22.8%), making the study results particularly relevant to the UK population. However, as noted in the SPC (1), safety data in patients of non-White race in the AFFIRM trial is scarce and lacking for patients with severe cardiovascular, renal or hepatic disease, brain metastases or concomitant QT interval prolonging medication.

The comparator in the AFFIRM trial was BSC, the current SOC for these patients at the time of study design. AFFIRM did not include abiraterone as a comparator arm since it was not an approved therapy at the time this trial began. Relative efficacy of enzalutamide over abiraterone has been assessed by an ITC; however the reliability of an ITC is inferior to that of a head-to-head study.

Further, in the AFFIRM study the BPI was administered only at baseline and Week 13. This makes it difficult to draw any conclusions on the treatment effect of enzalutamide on pain as measured with BPI. Similarly, the EQ-5D was administered only in the European countries. This accounts for the lower number of patients completing EQ-5D. However, 126/800 enzalutamide patients and 53/399 placebo patients filled in at least one form. A mapping of FACT-P to EQ-5D was conducted as an alternative source to derive utilities for the entire AFFIRM population.

In summary, enzalutamide represents an efficacious, once-daily, well tolerated treatment with an acceptable safety profile demonstrating significant improvement in key outcomes, making it a treatment alternative for patients with mCRPC. Patients receiving enzalutamide should expect to maintain QoL whilst experiencing improvement in survival.

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in

clinical trials to the clinical benefits experienced by patients in practice.

The AFFIRM trial directly compares enzalutamide to placebo + BSC. Since BSC is no longer the only comparator of interest in the UK (as it was at the time of trial design), we conducted an ITC with abiraterone, currently the only NICE-approved comparator for the post-docetaxel setting.

Quality of life data was not as comprehensive as it could have been with an amendment to the study protocol introduced at a time that only allowed selected sites in Europe to administer the EQ-5D questionnaire. As a result, the QoL analysis was limited to secondary and exploratory endpoints. However, the FACT-P questionnaire (51), the most widely used QoL measure in PC, had a very high completion rate in the AFFIRM study (N=902/1,199, 75.7%) allowing QoL to be adequately measured within the trial (37) (47).

In conclusion, the clinical endpoints in AFFIRM are consistent to those specified in the decision problem and therefore can be considered applicable to UK clinical practice. For further information regarding the relevance of the endpoints assessed please refer to section 6.3.5.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

The use of enzalutamide in AFFIRM reflects its intended use in clinical practice. The efficacy, safety profile and tolerability expected for enzalutamide in clinical practice are the same as those observed in the clinical program of this AR inhibitor.

The manufacture does not anticipate that the study results observed in the AFFIRM trial will differ from the use of enzalutamide in UK clinical practice. A substantial proportion of patients in the AFFIRM trial were enrolled in the UK (n=132, 11.0%), suggesting that the clinical benefits and safety profile demonstrated within the trial are not likely to differ from those expected in UK clinical practice (4).

7 Cost Effectiveness

Key points

- This economic analysis evaluated the cost-effectiveness of enzalutamide compared with abiraterone and BSC for the treatment of adult men with mCRPC whose disease has progressed on or after docetaxel therapy.
- A Markov model was developed with three health states: stable disease, progressive disease and dead, which can be considered to be the standard economic modelling approach in oncology (79). AEs and SREs were included in the model.
- Key inputs for OS and progression free survival (PFS) were derived from the AFFIRM study of enzalutamide and the COU-AA-301 study of abiraterone. The control arms in both studies were considered comparable, as all patient characteristics were similar except for a difference in the requirement of steroids in the COU-AA-301 study.
- Treatment discontinuation in the trial was considered the best proxy for disease progression (and thus discontinuation) in clinical practice; Oncologists actively treating PC in the UK confirmed that the decision to discontinue treatment is not made on a single measure of progression alone (e.g. rPFS) (4) (80) and that patients in clinical practice would be discontinued according to the same criteria as in the trial, or even before all trial discontinuation criteria are met (4). Furthermore, this endpoint has previously been accepted by NICE (5).
- The AFFIRM placebo arm was selected as reference curve, and five different parametric models were fit to the OS and PFS data. The Weibull curve was selected by clinical experts due to the more realistic shape of the tail (4). Survival curves for enzalutamide and abiraterone were derived by applying a HR to the AFFIRM placebo Weibull curve.
- The base case incremental cost effectiveness ratio (ICER) for enzalutamide was £14,795 against abiraterone and £43,587 against BSC.
- Enzalutamide meets the criteria for appraisal of end of life medicines versus BSC.
- Extensive scenario analyses and deterministic and probabilistic sensitivity analysis showed that the model was robust, and that enzalutamide is a cost-effective treatment option. The PSA showed an 83% probability of enzalutamide being cost-effective against abiraterone at a willingness to pay (WTP) of £20,000 per QALY gained, and 98% at a WTP of £30,000 per QALY gained. Enzalutamide showed an 81% probability of being cost-effective against BSC at a WTP of £50,000 per QALY gained, a threshold previously used for the recommendation of abiraterone (5).
- Experts suggested that Astellas include a scenario analysis to review the cost effectiveness of enzalutamide and abiraterone assuming equal overall survival, time to treatment discontinuation and drug acquisition cost, while including the difference in monitoring costs and requirement for steroids. This scenario elicits a cost saving of £1,007 compared to abiraterone while resulting in the same number of QALYs.

7.1 *Published cost-effectiveness evaluations*

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

A SLR was conducted to retrieve relevant data from the published literature regarding the cost-effectiveness of enzalutamide and relevant comparators as outlined in the scope. The search strategy for relevant economic studies is detailed in appendix 10**,** section 10.10. The databases searched were PubMed/MEDLINE, Cochrane Library (including DARE and NHS EED databases), EMBASE, EconLit, HTA Watch (81), HEED, Medline (R) In-Process, Conference proceedings (ISPOR). This was supplemented by hand searching the bibliographies of relevant review articles, conference proceedings and trial databases and with unpublished data from the manufacturer.

In agreement with NICE requirements, none of the searches were restricted by language. The searches were limited to the last 20 years for publications, as this was assumed to include all relevant economic studies for enzalutamide or its comparators. The search was limited to the year 2012 for conference abstracts, as all relevant studies published as abstract before 2012 would have been published as a manuscript in the mean time.

Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

The systematic literature review identified six economic evaluations directly related to the decision problem. An additional 21 economic evaluations were associated with a health technology assessment (HTA) appraisal.

All relevant economic studies are presented in Table 42, and all HTAs are presented in Table 43. The economic evaluation of abiraterone in the UK is the study that is most relevant to the decision problem.

Table 42: Summary list of relevant cost-effectiveness evaluations in mCRPC

Study	Country(ies) where study was performed	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Chopra 2012 (82)	US	-CEA (decision-analytical model) -Payer perspective	That of COU-AA-301	ABI+PRED vs. PRED: +0.38 LY +0.30 QALY	ABI+PRED vs. PRED: $39,320 (US dollars, 2011)	ABI+PRED vs. PRED: $102,600/LY and $129,000/QALY. Main drivers: • Drug acquisition cost • Median OS • Health utility values.
Pereira 2012 (83)	Not reported	CEA Brazilian Private Health System perspective	Not reported	QALY • ABI: 0.7977 • CAB: 0.7329 LYG • ABI: 1.3559 • CAB: 1.2895	• ABI: R$79,974 • CAB: R$90,025 (Brazilian $)	ABI: dominant
Efstathiou 2012(84)	Greece	CEA (costs per incremental month) Greek health care perspective	Pts in COU-AA-301 and TROPIC	NA	<u>Total costs</u> • ABI: €25.847 • CAB: €26.648 <u>Drug acquisition costs</u> • ABI: €24,899 • CAB: €23,886 <u>Administration costs</u> • ABI: €844 • CAB: €2.292 <u>AE management costs</u> • ABI: €104 • CAB: €470 CAB • PFS: €19,034 • OS: €11,103	<u>Total costs per incremental month:</u> *ABI* • PFS: €12,924 • OS: €5,619
Persson 2012 (85)	Sweden	CEA Societal perspective	Not reported	ABI: 0.94 QALY CAB: 0.83QALY	Drug costs per 3-week-model-cycle were • ABI: $3,180 (€2,300)	ABI was dominant to CAB

Study	Country(ies) where study was performed	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
					• CAB: $6,730 (€4,860) Total health care cost per pt • ABI: $103,100 (€74,400) • CAB: $104,600 (€75,500) (US $ and EUR)	
Maran 2012 (86)	Not reported	CEA Italian RHS perspective	Not reported		CAB vs. MTZ • Costs: + €18,785	CAB vs. MTZ: • ICER: € 93,925/LYG
Wilson 2012 (87)	Not reported	CEA Societal perspective	Not reported			ICERs • MTZ vs. PLA: $110K/QALYS and $63K/LYS • ABI vs. MTZ: $76K/QALYS and $52K/LYS • CAB vs. ABI: $925K/QALYS and $378K/LYS

Source: SLR 2013 (31)
Abbreviations: ABI: abiraterone; AE: adverse event; BIA: budget impact analysis; CAB: cabazitaxel; CEA: cost effectiveness analysis; CUA: cost utility analysis; CIC: commercial in confidence; ICER: incremental cost effectiveness ratio; LY: life years; LYG: life years gained; MTZ: mitoxantrone; PRED: prednisone; QALY: quality-adjusted life years

Table 43: Relevant HTAs reporting economic outcomes in mCRPC

Agency, date	Country	Summary of model	Patient population	Costs	QALY/LYs	ICER
PBAC Nov 2011 (88)	Australia	CUA, Perspective not reported	COU-AA-301	NA	NA	Initial ICER ABI vs. BSC: $105,000 - $200,000 BSC: MTZ+PRED or PRED
PBAC Mar 2012 (89)						Revised price: ICER ABI vs. CAB: $45,000-$75,000/QALY
PBAC Jul 2012 (90)						No ICER was provided in the latest submission. Comparators were BSC and CAB
NCPE, May 2012 (91)	Ireland	CUA, Irish Health Service Executive	COU-AA-301	NA	NA	ICER ABI vs. MTZ: €144,485/QALY €108,737/LYG.

Agency, date	Country	Summary of model	Patient population	Costs	QALY/LYs	ICER
		perspective				All ICER values > 45,000EUR/QALY and >20,000/LYG. 0% probability of being cost-effective for all ICER's up to €132,000/QALY.
CVZ, Feb 2012 (92)	Netherlands	CUA, Health care perspective	COU-AA-301	Incremental costs: ABI vs. PRED: +€ 31,313 ABI vs. CAB: +€4,381	Incremental QALY: ABI vs. PRED: +0.3 QALY ABI vs. CAB: +0.07QALY	ICER ABI vs. PRED: 104,454 EUR/QALY ICER ABI vs. CAB: 61,171 EUR/QALY
TLV, May 2012 (93)	Sweden	CUA, perspective not reported	COU-AA-301	NA	Incremental QALY: ABI vs. PRED: +0.38 QALYs	ICER ABI vs. CAB: 1.135 million kronor/QALY
TLV Sep 2012 (94)			COU-AA-301	NA	Incremental QALY: ABI vs. PRED: +0.38 QALYs	ICER ABI vs. PRED: Manufacturer: SEK 1,160,000/QALY TLV estimated: SEK 1,300,000/QALY (use of 2 additional packages per patient)
AWMSG, Jan 2012 (95)	UK	CUA, NHS Wales. perspective	COU-AA-301	Drug acquisition costs (per three weeks) ABI: CIC PRED: £2 MTZ (12 mg/m^2, every three weeks): £100 to £200 CAB (25 mg/m2, every three weeks): £3,696 DOC (75mg/m2, every three weeks): £900	NA	ICER: CIC
NICE, Jun 2012 (5)		CUA UK NHS and PSS perspective	That of COU-AA-301	The manufacturer agreed to a PAS. Total costs/QALY as well as disaggregated costs/QALY are kept CIC		ICER provided by manufacturer: £46,617/QALY vs. PRED alone ICER according to ERG: £60,292 (£60,084 - £72,469) MTZ + PRED is largely dominated by ABI+PRED In pts with 1 prior chemo: manufacturer ICER: £52,714 vs. PRED
SMC, Mar 2012 (96), Aug 2012		CUA, perspective not reported	COU-AA-301	Total costs/QALY as well as disaggregated costs/QALY are kept CIC		Initial submission A PAS was submitted by the company. ICER (with PAS) ABI vs. PRED: £52,230 / QALY

Agency, date	Country	Summary of model	Patient population	Costs	QALY/LYs	ICER
(97)						ABI vs. MTZ: £47,239 / QALY.
				Total costs/QALY as well as disaggregated costs/QALY are kept CIC		A PAS was submitted by the company. ABI vs. PRED: £46,421 ABI vs. DEX: £44,606 ABI vs. MTZ+PRED: £41,122 ABI vs. DOC+PRED: £24,205 Average ICER with PAS ABI vs. comparators: £41,641 (if 70% of pts treated with PRED alone, 20% DOC retreatment and 10% MTZ) £34,717 (If 45% of pts treated with PRED alone, 35% with DOC and 20% with MTZ) ICER if PFS utility of 0.85: ABI vs. PRED: £42.5K/QALY ABI vs. MTZ: £37.5K/QALY ABI vs. DOC: £22K ICER if PFS HR of 0.9 MTZ and DOC vs. PRED: ABI vs. MTZ: £46,044/QALY ABI vs. DOC: £27,808
PBAC, Jul 2011 (98)	Australia	CUA, perspective not reported	TROPIC	NA	NA	ICER CAB vs. MIZ: $75,000 and $105,000 / QALY. The PBAC considered that the 43% uptake rate of cabazitaxel is an overestimation and that the increase in significant AEs for many patients will limit the suitability of this treatment.
PBAC Nov 2011 (99)			TROPIC	NA	NA	Revised ICER: $45,000 and $75,000. If utility values are derived using the EQ-5D from the Early Access Program (EAP), the ICER: $15,000 and $45,000 per QALY.
INESSS, Feb 2012 (100)	Canada	CUA, Ministry of health perspective	TROPIC	Cost of CAB: > than ABI ($ 2,380)	NA	ICER: >$180,000 / QALY
INESSS,	Canada	CUA,	TROPIC	NA	NA	ICER CAB vs. MTZ > $98,186/QALY

Agency, date	Country	Summary of model	Patient population	Costs	QALY/LYs	ICER
March 2013 (101)		Ministry of health perspective				Sensitivity analysis: $144,830 and $296,049/QALY gained. 0% likelihood that the cost/QALY gained is <$100,000
NCPE, Mar 2012 (102)	Ireland	CUA, Perspective not reported	TROPIC	NA	NA	ICERs • Basecase (ECOG 0-2): €120,084/QALY • Basecase (ECOG 0-2): €81,474/LYG • The probability that CAB is CE < €20,000-€45,000/QALY is zero. • ECOG 0-1: €113,766/QALY • ECOG 0-1: €77,126/LYG
UVEF, Apr 2012 (103)	Italy	CEA	TROPIC	Costs for 6 cycles: • CAB: € 19,061 • DOC: € 232 • MTZ: € 276 Δ cost: € 18,785 per patient (including the cost of drugs only)	Incremental survival: +2.4 months	ICER: € 93,925 per LYG.
CVZ, Oct 2011 (104)	Netherlands	CUA, Societal perspective	TROPIC	Cost is € 27,540 per patient	+0.345 incremental LYG +0.198 incremental QALY	ICER CAB vs. MTZ: 69,548 EUR /QALY
TLV, Feb 2013 (105)	Sweden	CUA, Healthcare perspective	TROPIC	Price of CAB: 41,538 SEK / package (60 mg).	+0.58 incremental LYG +0.40 incremental QALY	The ICER depends on how well packages can be utilized. ICER • For whole population: 1.18 to 1.44 million SEK. • A major hospital probably comes closer to 1,180,000 SEK/QALY. • Subgroup of pts who initially responded to docetaxel, but progressed within 3 months after the previous docetaxel treatment, the ICER: 860,000 (large hospitals) to 1,000,000 SEK (small hospitals)
NICE, May 2012 (29)	UK	CUA UK NHS and PSS perspective	TROPIC	Total costs European pts with ECOG 0-1 and had received ≥225 mg/m2 of DTX (Base case)	QALY European pts with ECOG 0-1 and had received ≥225 mg/m2 of DTX (Base case)	ICER • European pts with ECOG 0-1 and had received ≥225 mg/m2 of DTX (base case): £78,016 • Patients with ECOG 0-1 and had received ≥225

Agency, date	Country	Summary of model	Patient population	Costs	QALY/LYs	ICER
				• CAB: £35,493 • MTZ: £11,845 • Δ: £22,649 Patients with ECOG 0-1 and had received ≥225 mg/m2 of DTX • CAB: £ 33,474 • MTZ: £11,736 • Δ: £21,739 European pts • CAB: £33,729 • MTZ: £11,615 • Δ: £22,115 Whole TROPIC population • CAB: £33,102 • MTZ: £11,460 • Δ: £21,643	• CAB: 1.117 • MTZ: 0.827 • Δ: 0.290 Patients with ECOG 0-1 and had received ≥225 mg/m2 of DTX • CAB: 1.076 • MTZ: 0.823 • Δ: 0.253 European pts • CAB: 1.063 • MTZ: 0.810 • Δ: 0.253 Whole TROPIC population • CAB: 1.037 • MTZ: 0.800 • Δ: 0.237	mg/m2 of DTX: £86,008 • European pts: £87,348 • Whole TROPIC population: £91,134
SMC, Nov 2011 (106)	UK	CUA	TROPIC	NA	NA	Basecase CAB vs. MTZ: £76,670.

Source: SLR 2013 (31)

Abbreviations: ABI: abiraterone; BIA: budget impact; BSC: best supportive care; CAB: cabazitaxel; CEA: cost effectiveness analysis; CUA: cost utility analysis; CIC: commercial in confidence; DOC: docetaxel; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; LY: life year; LYG: life years gained; MTZ: mitoxantrone; PAS: patient access scheme; PFS: progression free survival; QALY: quality-adjusted life year.

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[2] or Philips et al. (2004)[3]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

A quality assessment of all included studies is provided in appendix 11, section 10.11.

7.2 *De novo analysis*

Patients

7.2.1 What patient group(s) is (are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

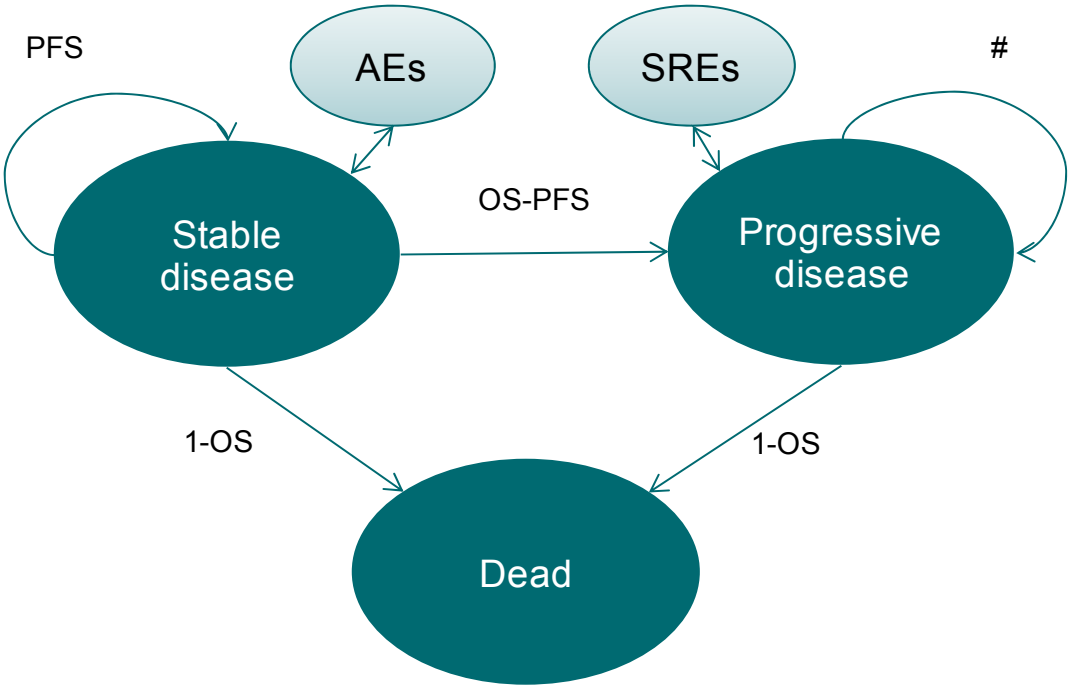
The patient group considered in the economic model is the overall patient population in the AFFIRM study which is: "adult men with mCRPC whose disease has progressed on or after docetaxel therapy" (section 6.3.3). This is the same population as the licensed indication (section 1.3).

[2] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.
[3] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

Figure 17: Model structure of the enzalutamide economic model



Abbreviations: AEs: adverse events; OS: overall survival; PFS: progression free survival; SREs: skeletal related events; # indicates that the proportion is calculated as the remainder not experiencing another event.

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

A Markov model was developed with three health states: Stable Disease (SDis), Progressive Disease (PDis) and Dead. These health states were chosen as they reflect the main objectives in treatment of mCRPC patients: extending survival, and delaying progression. Similar model structures have been used in numerous NICE STAs and multiple technology assessments (MTA) in metastatic cancer (5) (107) (108) (109) (110) (111) and can be considered to be the standard economic modelling approach in oncology (79).

Metastatic CRPC patients enter the model in the SDis state after their disease has progressed on or after docetaxel therapy. They remain in this health state as long as they remain alive and progression free. Patients who die move to the dead health state, whilst patients who progress move to the PDis health state. From the PDis health state, patients may either remain alive in the PDis health state, or die and move to the dead health state. Transition from the PDis health state to the SDis health state is not possible.

Transitions in the model are defined by the OS and PFS curves for each treatment, further described in section 7.3.1. The probability of dying (from both SDis and PDis) is defined as 1 minus the probability of remaining alive (1-OS), and the probability of moving from SDis to PDis is defined as the probability of remaining alive minus the probability of remaining progression free (OS-PFS).

The model compares the intervention enzalutamide, with the comparators stated in the decision problem (section 5): abiraterone and BSC.

7.2.4 Please define what the health states in the model are meant to capture.

As the QoL decreases upon progression (further defined in section 7.3.1.2), it is important to distinguish between SDis and PDis health states. Patients are on treatment for as long as they are in stable disease. In this health state, patients may also experience AEs (grade 3 and higher).

Progression in mCRPC is typically associated with bone metastasis, which can cause SREs (e.g. spinal cord compression, pathological bone fracture). SREs are therefore implemented in the model in the PDis health state.

The model health states also correspond with the structure of the trial, in which OS was the primary endpoint, and PFS was a secondary endpoint.

7.2.5 How does the model structure capture the main aspects of the condition of patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross reference to section 2.1.

The model captures patients with mCRPC whose disease has progressed on or after docetaxel therapy. As discussed in section 2.1, mCRPC is a severe condition, with a poor survival and a large impact on QoL. The model captures these aspects as it evaluated both the survival and the QoL of patients. Both positive effects (treatment) and negative effects (progression, AEs, SREs) on QoL are included.

All patients are assumed to be stable upon starting treatment, and receive enzalutamide, BSC or abiraterone (SDis). The treatment is continued until further progression, after which only palliative care is currently available (PDis). The model therefore captures the important distinction between the pre-progression (SDis) and progression state (PDis), and includes events that may have a potentially large impact on quality of life (AEs, SREs).

7.2.6 Please provide a table containing the following information and any additional features of the model not

previously reported. A suggested format is presented below.

Table 44: Key features of the economic analysis

Factor	Chosen values	Justification	Reference
Time horizon	10 years	This time horizon is assumed to be sufficient to capture the remaining life time of a mCRPC patient, as the median survival in phase III clinical trials for both enzalutamide and abiraterone did not exceed 18.4 months.	AFFIRM (13), COU-AA-301 (25)
Cycle length	3 weeks	Enzalutamide and abiraterone are administered daily and do not require a specific cycle length. A three week cycle has been used in previous models in this indication.	De Bono 2012 (36)
Half-cycle correction	Applied to LY, QALY, and all costs except direct drug costs	A half cycle correction is applied to correct for the fact that patients move between health states continuously instead of at distinct time points. This correction was not applied to direct drug costs to reflect potential wastage as a result of dispensing at the start of each cycle.	NICE guide to the methods of technology appraisal 2013 (112)
Were health effects measured in QALYs; if not, what was used?	Yes	NICE Reference case	NICE guide to the methods of technology appraisal 2013 (112)
Discount of 3.5% for utilities and costs	Yes	NICE Reference case	NICE guide to the methods of technology appraisal 2013 (112)
Perspective (NHS/PSS)	The NHS and personal social services (PSS) in the UK	NICE Reference case	NICE guide to the methods of technology appraisal 2013 (112)

Abbreviations: mCRPC: metastatic castrate resistant prostate cancer; NHS: National Health Service; LY: Life Year; NICE: National Institute for Health and Care Excellence; PSS: personal social services: QALY: quality-adjusted life year

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Dosage and administration of enzalutamide and abiraterone are implemented in the model as per their marketing authorisation (1) (2). The placebo arm of AFFIRM was assumed to represent BSC (this may include radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, hormonal therapies, and corticosteroids) as no active treatment was administered in this arm while all treatments included in the BSC definition were allowed. Radiotherapy is considered part of BSC, and in AFFIRM its administration was reported as an SRE (radiation to bone). The implementation of the intervention and comparators is directly relevant to the specified decision problem.

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators.

No treatment continuation rule has been assumed in the model. However, the model does assume that patients continue treatment up to progression or death (whichever comes first). As progression can be difficult to quantify (as definitions may differ between studies, or as trial definitions may not resemble clinical practice), treatment discontinuation from the trial was considered the best proxy to determine the treatment duration in clinical practice (discussed in detail in section 7.3.1.2).

In AFFIRM patients received their assigned therapy until disease progression was documented and confirmed (i.e., confirmed radiographic progression or the occurrence of a SRE) <u>and</u> the patient was scheduled to initiate another systemic antineoplastic therapy; the occurrence of an AE, where continued administration of study drug was deemed not in the patient's best interest by the Investigator and/or the Sponsor, also resulted in the removal of the patient from therapy (15). According to UK clinical experts (4), it is reasonable to assume that patients would discontinue in clinical practice according to the same or less stringent criteria as in the trial.

7.3 *Clinical parameters and variables*

7.3.1 Please demonstrate how the clinical data were implemented into the model.

The clinical data for the BSC and enzalutamide arms were derived from the AFFIRM study (3). The placebo arm of AFFIRM received no active treatment but was allowed supportive treatments, and was therefore assumed to represent BSC. Inputs on OS, PFS, AEs, and SREs were derived from this trial. Abiraterone data was derived from the COU-AA-301 study (25), and indirectly compared using the control arms in both studies (section 6.7.3).

Survival curves for OS and PFS were derived using the following methodology, and are described in detail in the following sections:

- A reference treatment was selected
- A parametric survival function was fit to the reference treatment
    - Five different survival models (Exponential, Weibull, Log-Logistic, Log-Normal and Generalized Gamma) were fit to the patient level data of the reference treatment
    - One of the functions was selected based on
        - Face validity
        - Clinical validity of the tail (performed by clinical experts)
        - Statistical fit using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)
- The other comparators were implemented by applying a HR to the reference parametric survival function
    - First the proportionality of hazards assumption was tested to see whether it was appropriate to use the HR
        - Alternative methods were employed if the proportionality of hazards assumption was not met

7.3.1.1 **Overall Survival**

In line with the technical support document of the NICE Decision Support Unit guidance (113), BSC was chosen to be the reference arm.

When modelling survival data from oncology trials, the most mature data (i.e., database lock) should be used to provide the best extrapolation of the curves; Therefore, patient-level data on duration of OS based on all deaths at database lock (December 2011, 344 [43.0%] deaths in the enzalutamide arm and 232 [58.1%] deaths in the placebo arm) in the AFFIRM placebo arm was used to fit different accelerated failure time (AFT) parametric models. Five distributions were considered: Exponential, Weibull, Log-Logistic, Log-Normal and Generalized Gamma.

Examination of the goodness of fit showed that the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) of all distributions were similar, except for the Exponential distribution. The Log-Logistic distribution fit the underlying data best (Table 45, numbers in bold). The corresponding parameter estimates of the distributions are presented in Table 46 and a comparison of the observed survival

data from AFFIRM to the predicted estimates for both treatment arms is shown in Figure 18. The red line represents the placebo Kaplan Meier data, the dotted lines show the different predicted curves.

Although all curves had approximately the same median (Table 45), there are considerable differences in the mean OS between the curves. Experts (70) evaluated the plausibility of the slope and the curves' tail, and the proportion alive at 2 and 3 years. The Weibull distribution was chosen over the Log-Logistic distribution to model OS due to the more realistic shape of the 'tail'. The proportion remaining alive with the LogLogistic distribution (also illustrated by the 5 months longer mean OS) was considered unrealistic. The OS Weibull intercept and the OS Weibull scale are [redacted] and [redacted], respectively (corresponding to [redacted]).

Table 45: Goodness of fit for AFFIRM placebo overall survival

	Placebo				
Distribution	**LL**	**AIC**	**BIC**	**Mean OS**	**Median OS**
Exponential	-455.130	912.259	916.248	[redacted]	13.04
Weibull	-426.500	857.001	864.978	[redacted]	12.96
Log-Normal	-425.507	855.013	862.991	[redacted]	12.65
Log-Logistic	-423.667	**851.333**	**859.311**	[redacted]	**12.57**
Gamma	-423.310	852.620	864.586	[redacted]	12.70

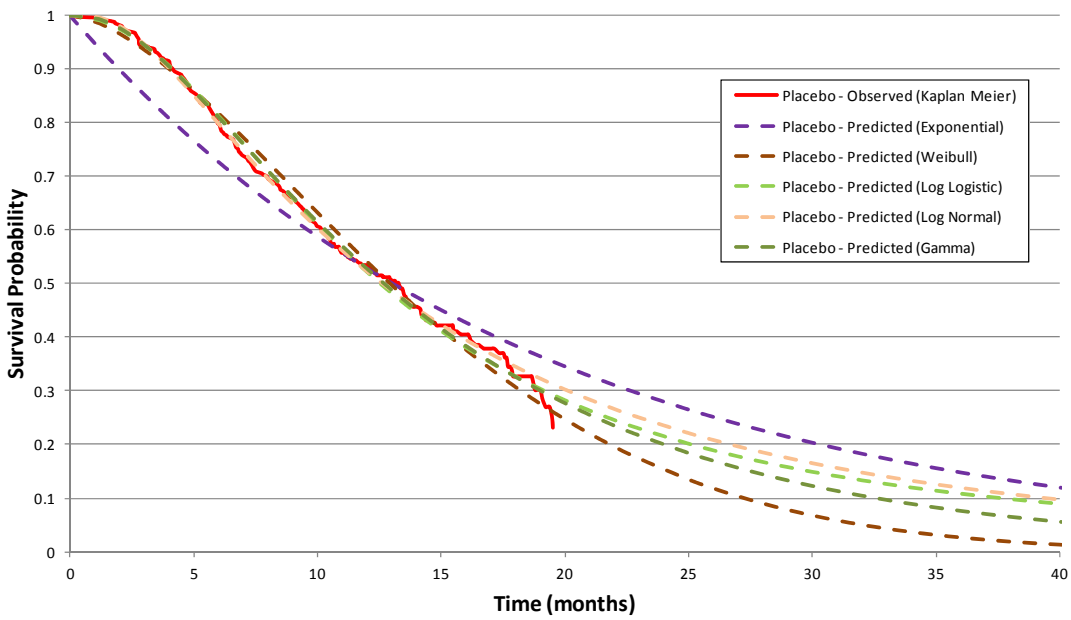
Abbreviations: LL: log likelihood, AIC: akaike information criterion, BIC: Bayesian information criterion; Numbers in bold indicate the lowest information criterion.

Table 46: Maximum likelihood parameter estimates for AFFIRM placebo overall survival

Parameter	Exponential	Weibull	Log-Normal	Log-Logistic	Gamma
Intercept (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scale (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape (SE)	[redacted]	[redacted]			[redacted]

*Parameter met the 0.05 criterion for statistical significance.
Abbreviations: SE=standard error; Numbers in bold indicate the final model chosen

Figure 18: Comparison of OS K-M estimates with OS parametric models for placebo



In order to test whether survival for patients on enzalutamide could be modelled by applying the HR to the placebo reference curve the proportionality of hazards was checked (appendix 14, section 10.14). As it was found that the proportional hazards assumption was met for enzalutamide vs. placebo, the HR obtained from a stratified Cox proportional hazards model was applied to the BSC Weibull curve (HR =0.618, 95%CI [0.523; 0.730]).

The final OS results of the COU-AA-301 study were reported in the Fizazi 2012 paper (25). Although the paper reported a HR for OS, it also mentioned the proportional hazards requirement was not met, and that the HR should thus be interpreted with caution. The reported Kaplan-Meier graph shows that the abiraterone and prednisone curves separate and then converge again (although patient numbers are small by the time the curves converge); Additional tests also showed that the proportional hazards assumption was not met (appendix 14, section 10.14). As the benefit of abiraterone is decreased in the final section of the curve, applying a fixed HR would likely overestimate abiraterone's benefit. In order to model survival for patients on abiraterone we took the following approach:

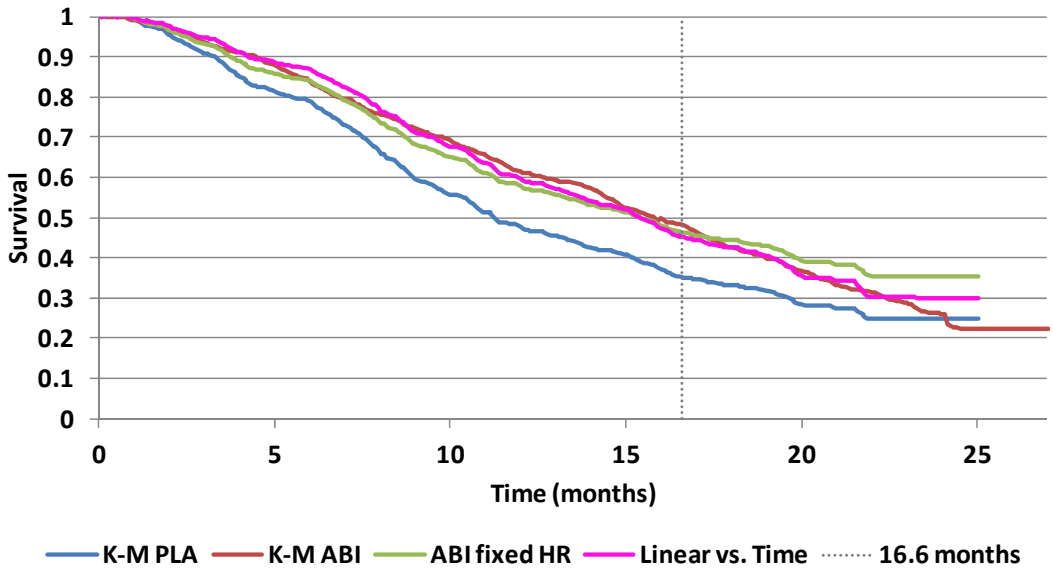
1. the reported OS curves in the Fizazi 2012 paper (25) were digitised using Engauge digitizer v4.1 software (114)
2. Individual Patient Data (IPD) were reconstructed from the K-M curves and the reported number at risk using the method published by Guyot 2012 (115)
3. The IPD data was fitted to estimate the HR.

To capture the HR over time, two methods were employed: 1) fitting a Cox Proportional Hazards model including a time dependent covariate, and 2) using a piecewise HR model (appendix 15, section 10.15). After consultation with an expert in the field of survival modelling (116), the time dependent model was preferred over the piecewise model, as the latter required arbitrary selection of the time intervals on which to model the HR. Using visual inspection of the resulting survival curves, the time dependent (linear vs. time) HR model was selected as providing the best fit (Figure 19). As shown in Table 47, all coefficients were significant. The HR in the model is calculated by HR = exp (-0.65128+0.03923*Time). This function results in HRs starting at 0.52 at the start of the study, ranging to a HR of 1 at 16.6 months, and a HR of 1.39 at 25 months. As no data was reported in the Fizazi paper (25) beyond 25 months, the HR of 1.39 is used for all subsequent cycles in the model. As shown in Figure 19, the point of 16.6 months where the HR is 1 is approximately equal to the time in the reported OS figure where the curves start to converge.

Table 47: Coefficients for the linear function of time model for the abiraterone OS HR

Coefficient	Estimate	p value
Treatment	-0.65128	<.0001
Treatment*Time	0.03923	0.0047

Figure 19: COU-AA-301 OS curves and predictions of abiraterone curve based on a fixed HR (green line), and the time dependent HR (pink line)



Abbreviations: ABI; abiraterone; K-M: Kaplan-Meier; PLA: placebo

In the health economic model, the time dependent HR is directly applied to the reference curve (AFFIRM placebo arm) to generate the abiraterone OS curve.

7.3.1.2 **Progression Free Survival**

PFS is a common endpoint in oncology trials. However, definitions differ between trials, and indications.

The AFFIRM protocol included rPFS as a measure of progression. A mPFS definition was also analysed by combining the secondary endpoints rPFS and time to first SRE, as this definition combines both soft tissue and skeletal progression, and is thus a good measure of clinical worsening. However, neither mPFS nor rPFS were selected for the purpose of the health economic model because:

- Radiographic progression was only measured at 3 month intervals.
- Neither of these endpoints accurately reflects how disease progression (and treatment discontinuation) would be defined in UK clinical practice. UK experts indicated that the decision to discontinue treatment would not be made on a single measure of disease progression (4) (80).

In contrast to rPFS, treatment discontinuation in AFFIRM was a continuous process. In addition, the decision to discontinue treatment in AFFIRM was based on a combination of criteria as patients received their assigned therapy until disease progression was documented and confirmed (i.e., confirmed radiographic progression or the occurrence of a SRE) <u>and</u> the patient was scheduled to initiate another systemic antineoplastic therapy. The occurrence of an AE, where continued administration of study drug was deemed not in the patient's best interest by the Investigator and/or the Sponsor, also resulted in the removal of the patient from

therapy. Therefore, the TTD endpoint was considered a more accurate reflection of clinical practice for modelling purposes.

Investigators from the AFFIRM and COU-AA-301 trial confirmed that the decision to discontinue treatment in these trials would have been made on the same criteria, and that definitions are thus comparable between the trials (4). It was also considered reasonable that patients in clinical practice would discontinue according to the same criteria, or even before all trial discontinuation criteria would be met (4). Using the trial definition of treatment discontinuation may therefore overestimate drug costs.

Similar to the method to model OS, the placebo arm from AFFIRM was assumed to represent BSC, and was used as the reference curve. Five distributions were used to fit different AFT parametric models.

Examination of the goodness of fit (Table 48) showed that the Log-Logistic model has the best statistical fit according to AIC and BIC criteria. However, the Weibull model was selected after validation by clinical experts due to the more realistic shape of the tail (Figure 20) (70). The PFS Weibull intercept and the PFS Weibull scale are [redacted], respectively (corresponding to [redacted]). All model parameters are shown in Table 49.

Table 48: Goodness of fit for AFFIRM placebo time to treatment discontinuation

Distribution	LL	AIC	BIC	Mean TTD	Median TTD
Exponential	-527.262	1056.525	1060.514	[redacted]	3.16
Weibull	-503.312	1010.623	1018.601	[redacted]	3.71
Log-Normal	-476.236	956.472	964.450	[redacted]	3.37
Log-Logistic	-461.470	**926.941**	**934.919**	[redacted]	3.37
Gamma	-475.232	956.463	968.430	[redacted]	3.43

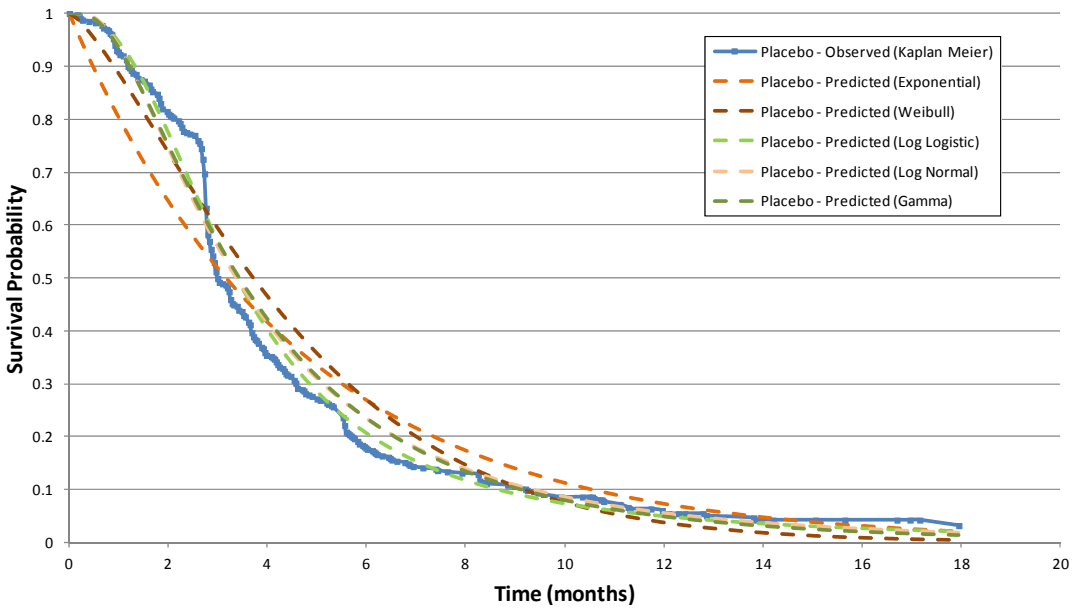
Abbreviation: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; LL: Log Likelihood; Numbers in bold indicate the lowest information criterion.

Table 49: Maximum likelihood parameter estimates for AFFIRM placebo time to treatment discontinuation

Parameter	Exponential	Weibull	Log-Normal	Log-Logistic	Gamma
Intercept (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scale (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape (SE)	[redacted]	[redacted]			[redacted]

*Parameter met the 0.05 criterion for statistical significance.
Abbreviation: SE: standard error; Numbers in bold indicate the final model chosen

Figure 20: Comparison of Treatment Discontinuation K-M estimates with parametric models for placebo



The proportionality of hazard of enzalutamide versus placebo time to treatment discontinuation in AFFIRM was tested (appendix 14, section 10.14). It was found that the proportionality of hazards assumption was met, and therefore the HR obtained from a stratified Cox proportional hazards model was applied to the reference curve (HR = [redacted], 95% CI [redacted]).

Limited data is published on the TTD of abiraterone in the total post-chemotherapy mCRPC setting. The article by Fizazi 2012 (25) reports a median treatment duration of 7.4 months on abiraterone and a median of 3.6 months on prednisone. In the absence of published HRs, the HR can be approximated from the ratio of medians, assuming a constant hazard in each trial arm (i.e., exponential distribution) (117). Applying this method to the reported medians would result in a HR of 0.49. An alternative approach would be using the treatment discontinuation curve used in the abiraterone manufacturer submission (MS) for the one prior chemo (OPC) subgroup (figure 16, abiraterone MS (80)). Using Engauge digitizer v4.1 (114) software, the reported abiraterone and BSC curves were digitised. Subsequently, individual patient data (IPD) was reconstructed using the method described by Guyot et al.(115), and a Cox Proportional Hazards model was fit to the data, resulting in a HR of 0.52 (95% CI 0.44; 0.60) for abiraterone vs. prednisone in the OPC population. To test whether the HR could be applied in the health economic model, the proportionality of hazards was checked, and it was found that the proportional hazards assumption was met.

Both of the methods described above have limitations:

- Median values only describe one point of the discontinuation curve, and disregard a lot of data
- The curves presented in the abiraterone manufacturer submission consisted of model output, and did not present a number at risk over time, which introduces uncertainty
- The presented abiraterone curve was for a subgroup of patients (OPC), and not for all mCRPC patients whose disease has progressed on or after docetaxel therapy, using this value requires the assumption that the

abiraterone OPC population has the same HR for TTD as the total population. However, this can be considered a fair assumption as in AFFIRM the One Prior Chemo population had a similar HR for TTD as the entire (ITT) population (0.335, 95% CI [0.285; 0.393] vs. 0.340, 95% CI [0.297; 0.390]).

The HR derived from the curve in the MS (0.52 [95% CI 0.44; 0.60]) is assumed to be conservative compared to the HR calculated from medians (0.49), as it estimates lower costs for the comparator. Therefore, this HR was selected for use in the model and directly applied to the reference curve (AFFIRM placebo).

Although the median treatment durations for enzalutamide and abiraterone in the trials were not that different (8.3 and 7.4 months), the use of an indirect treatment comparison results in a longer treatment duration for enzalutamide in the model. In clinical practice, both treatments may actually have the same treatment duration.

7.3.1.3 **Adverse Events**

All AEs with a grade ≥3 incidence above 1.0% in the enzalutamide or placebo arm as extracted from the AFFIRM trial data were included. In addition, seizures were added to the list of AEs, as they were classified as important based on expert opinion. AEs are implemented in the SDis health state, and are applied using a cycle probability of each AE calculated from the AE rates in the individual trials.

AE rates for enzalutamide and BSC were calculated based on the number of patients with each AE in AFFIRM and the treatment emergent period (total patient years, [redacted] for enzalutamide and [redacted] for placebo).

Abiraterone incidences for the selected AEs were taken from the Fizazi publication (25) and the abiraterone NICE submission (80). Rates were calculated from the number of patients with each AE and the treatment emergent period (patient years) as reported by Logothetis (67). The rate difference was calculated for abiraterone vs. prednisone, and this difference was added to the AFFIRM placebo AE rates, assuming that both control arms were similar. In reality however, all patients in the COU-AA-301 study were on steroids; therefore, the model could underestimate steroid related AEs for the abiraterone arm.

The number of patients with a grade ≥3 AE in each trial and the calculated rates are shown in Table 50, numbers in bold are the rates used in the model. Overall, the AE rates are similar between enzalutamide and abiraterone, which is in line with the conclusions of the ITC (section 6.9.2.2).

Table 50: Number of patients with grade ≥3 AEs and rates used in model

	AFFIRM (IA) (15)				**COU-AA-301 (Fizazi 2012)** (39)						**ITC**
	ENZ		**PLA**		**ABI**		**PLA**		**ABI-PLA**		**ABI**
	n (pts)	**Rate**	**n (pts)**	**Rate**	**n (pts)**	**Rate**	**n (pts)**	**Rate**	**RD**	**SE RD**	**Indirect rate**
Abdominal pain	4	[redacted]	3	[redacted]	18	0.03	8	0.04	-0.01	0.02	[redacted]
Anaemia	62	[redacted]	38	[redacted]	62	0.10	32	0.16	-0.06	0.03	[redacted]
Arthralgia	20	[redacted]	7	[redacted]	40	0.07	17	0.09	-0.02	0.02	[redacted]
Asthenia	20	[redacted]	10	[redacted]	26	0.04	8	0.04	0.00	0.02	[redacted]
Back pain	38	[redacted]	16	[redacted]	56	0.09	40	0.20	-0.11	0.03	[redacted]
Bone pain	21	[redacted]	14	[redacted]	51	0.08	31	0.16	-0.07	0.03	[redacted]
Dehydration	6	[redacted]	6	[redacted]		0.00		0.00	0.00	0.00	[redacted]
Diarrhoea	9	[redacted]	1	[redacted]	9	0.01	5	0.03	-0.01	0.01	[redacted]
Dyspnoea	6	[redacted]	6	[redacted]	14	0.02	9	0.05	-0.02	0.02	[redacted]
Fatigue	50	[redacted]	29	[redacted]	72	0.12	41	0.21	-0.09	0.04	[redacted]
Febrile neutropenia	0	[redacted]	0	[redacted]	3	0.00	0	0.00	0.00	0.00	[redacted]
Hypertension	16	[redacted]	5	[redacted]	10	0.02	1	0.01	0.01	0.01	[redacted]
Hypokalaemia	7	[redacted]	3	[redacted]	35	0.06	3	0.02	0.04	0.01	[redacted]
Leukopenia	2	[redacted]	0	[redacted]		0.00		0.00	0.00	0.00	[redacted]
Nausea	12	[redacted]	13	[redacted]	17	0.03	11	0.06	-0.03	0.02	[redacted]
Neutropenia	6	[redacted]	0	[redacted]	1	0.00	1	0.01	0.00	0.01	[redacted]
Oedema Peripheral/Fluid retention	7	[redacted]	3	[redacted]	20	0.03	4	0.02	0.01	0.01	[redacted]
Pain	6	[redacted]	2	[redacted]	7	0.01	8	0.04	-0.03	0.01	[redacted]
Pain in extremity	14	[redacted]	13	[redacted]	24	0.04	20	0.10	-0.06	0.02	[redacted]
Pulmonary embolism	6	[redacted]	4	[redacted]		0.00		0.00	0.00	0.00	[redacted]
Seizure	7	[redacted]	0	[redacted]		0.00		0.00	0.00	0.00	[redacted]
Thrombocytopaenia	8	[redacted]	3	[redacted]	11	0.02	2	0.01	0.01	0.01	[redacted]
Vomiting	9	[redacted]	10	[redacted]	21	0.03	12	0.06	-0.03	0.02	[redacted]
Total	336	[redacted]	186	[redacted]	497	0.82	257	1.27	-0.44	0.09	[redacted]

Abbreviations: ENZ: enzalutamide: PLA: placebo; ABI: abiraterone; ITC: indirect treatment comparison; pts: patients; RD: rate difference; SE: standard error

7.3.1.4 **Skeletal Related Events**

The model includes the following SREs: spinal cord compression, pathologic bone fractures (non-vertebral), radiation to bone, surgery to bone. It should be noted that this is a slightly different definition from the definition in the AFFIRM protocol as change of antineoplastic therapy to treat bone pain was not considered a SRE in the model.

As SREs are typically a result of progression of metastatic bone disease, SREs were applied to the PDis health state. SRE rates are calculated from the individual trials and applied in the model as a cycle probability.

SRE rates for enzalutamide and BSC were calculated from the number of events in AFFIRM, and the treatment emergent period (patient years).

The SRE rates for abiraterone were calculated from the number of events and the treatment emergent period as reported by Logothetis et al. (67). The rate difference vs. prednisone was calculated for abiraterone, and applied to the rates of the AFFIRM placebo arm.

The number of events in each study and the calculated rates are shown in Table 51. The numbers in bold are the rates used in the model. Enzalutamide and abiraterone have similar SRE rates, and show a reduced rate compared to BSC.

Table 51: Number of events and rates for SREs used in the model

	AFFIRM (IA) (15)				**COU-AA-301 (Logothetis 2012)** (67)						**ITC**
	ENZ		**PLA**		**ABI**		**PLA**		**ABI-PLA**		**ABI**
SREs	**n (events)**	**Rate**	**n (events)**	**Rate**	**n (events)**	**Rate**	**n (events)**	**Rate**	**RD**	**SE RD**	**Indirect rate**
Spinal cord compression	72	[redacted]	31	[redacted]	45	0.07	28	0.14	-0.07	0.03	[redacted]
Pathologic bone fractures	41	[redacted]	15	[redacted]	36	0.06	8	0.04	0.02	0.02	[redacted]
Radiation to bone	238	[redacted]	111	[redacted]	145	0.24	92	0.46	-0.22	0.05	[redacted]
Surgery to bone	24	[redacted]	3	[redacted]	10	0.02	2	0.01	0.01	0.01	[redacted]
Total	375	[redacted]	160	[redacted]	236	0.39	130	0.65	-0.26	0.06	[redacted]

Abbreviations: ABI: abiraterone; ENZ: enzalutamide; PLA: placebo; RD: rate difference; SE: standard error

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Transition probabilities were calculated from the survival curves described in section 7.3.1. In summary, the model uses the following survival curves (Table 52):

Table 52: Survival curves used for each arm for OS and PFS

Comparator Outcome	BSC	Enzalutamide	Abiraterone
OS	Weibull parametric fit of AFFIRM placebo arm	Constant HR applied to BSC reference curve	Time dependent HR applied to BSC reference curve
PFS	Weibull parametric fit of AFFIRM placebo arm	Constant HR applied to BSC reference curve	Constant HR applied to BSC reference curve

Abbreviations: BSC: best supportive care; HR: hazard ratio; OS: overall survival; PFS: progression free survival

The cumulative hazard $H(t)$ and the survival function $S(t)$ for the Weibull parametric fit can be defined in terms of these parameters:

$$H(t) = \lambda t^{\gamma}$$

$$S(t) = \exp\left(-\lambda t^{\gamma}\right)$$

The lambda (λ) and gamma (γ) were calculated from the intercept and scale parameters reported in section 7.3.1 using: λ=exp (-intercept/scale) and γ=1/scale.

The transition probability for a given value of t can then be calculated using the formulas shown below, assuming a cycle length u.

$$tp(t) = 1 - \exp\left\{H(t-u) - H(t)\right\}$$

$$= 1 - \exp\left\{\lambda(t-u)^{\gamma} - \lambda t^{\gamma}\right\}$$

For enzalutamide and abiraterone curves, where a HR was applied to the reference curve, the transition probability can be calculated using:

$$tp(t) = 1 - \exp\left\{HR * \left(\lambda(t-u)^{\gamma} - \lambda t^{\gamma}\right)\right\}$$

Furthermore, transition to the death state (from both SDis and PDis) was defined as 1 minus the probability of overall survival (1-OS). Transition from SDis to PDis was defined as the probability of overall survival, minus the probability of remaining in SDis (OS - PFS). This probability was limited to non-negative numbers to account for potential crossing of the curves at longer follow-ups with some parameterisations.

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Yes, transition probabilities for OS and PFS vary over time as defined by the survival curves

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No intermediate outcome measures were linked to final outcomes. OS and PFS were modelled using independent survival curves.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

A series of advisory boards were held to validate the health economic model and its inputs: Dec. 2011(118), Apr. 2012 (119), Jun. 2012 (120), Sep. 2012 (70), Apr. 2013 (4). For each advisory board clinical experts participated as well as health economic experts. Clinical experts were selected based on their experience with mCRPC and consisted of clinical oncologists, radiologists, and urologists.

The assumptions employed in the health economic model were made in a manner consistent with the published literature and previous NICE appraisals. These assumptions were then presented at the advisory board, as well as the clinical results from the AFFIRM study. Feedback from the advisory boards was incorporated in the health economic model and presented at the final advisory board in April 2013 (4).

Clinical parameters validated by the clinical experts include (but are not limited to) the plausibility of the parametric fits for OS and PFS, the applicability of rPFS, mPFS and TTD, similarity of discontinuation (TTD) criteria in clinical trials, similarity between treatment discontinuation in clinical trial and clinical practice and the model structure.

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table 53: Summary of variables applied in the economic model

Variable	Value	Distribution / 95% CI	Source / Reference
General inputs			7.2.6
Cycle length (wks)	3	NA	
Time horizon (yrs)	10	NA	
Discount rate for costs (%)	3.50%	NA	
Discount rate for effects (%)	3.50%	NA	
Overall Survival			7.3.1.1
OS BSC	Weibull [redacted]	Multivariate Normal	AFFIRM, data on file
OS enzalutamide	HR of 0.618	Lognormal distribution, 95% CI: [0.52; 0.73]	AFFIRM, data on file
OS abiraterone	Time dependent HR. HR = exp(-0.65128+0.03923*Time)	Multivariate Normal	COU-AA-301, derived from Fizazi 2012 (25)
PFS			7.3.1.2
PFS BSC	Weibull [redacted]	Multivariate Normal	AFFIRM, data on file
PFS enzalutamide	HR of [redacted]	Lognormal distribution, 95% CI: [redacted]	AFFIRM, data on file
PFS abiraterone	HR of 0.52	Lognormal distribution, 95% CI: [0.44; 0.60]	COU-AA-301, derived from abiraterone manufacturer submission (80)
Costs (£)			7.5
Treatment (costs per cycle)			7.5.5
BSC	0	NA	
Enzalutamide	[redacted]	NA	
Abiraterone	[redacted]	NA	
Concomitant medication (costs per cycle)			7.5.5
BSC	41	Gamma distribution. 95% CI assumed ±25%	
Enzalutamide	42	Gamma distribution. 95% CI assumed ±25%	
Abiraterone	41	Gamma distribution. 95% CI assumed ±25%	
Routine visits (cost per cycle)			7.5.5

Variable	Value	Distribution / 95% CI	Source / Reference
BSC	71	Gamma distribution. 95% CI assumed ±25%	
Enzalutamide			
First three months	142	Gamma distribution. 95% CI assumed ±25%	
Subsequent months	71	Gamma distribution. 95% CI assumed ±25%	
Abiraterone			
First three months	245	Gamma distribution. 95% CI assumed ±25%	
Subsequent months	127	Gamma distribution. 95% CI assumed ±25%	
BSC - Progressed Disease	71	Gamma distribution. 95% CI assumed ±25%	7.5.6
Terminal treatment (transition cost)	3,133	Gamma distribution. 95% CI assumed ±25%	7.5.6
Hospitalisations (costs per cycle)			7.5.6
Stable Disease	0	NA	
Progressed Disease	0	NA	
Utility			7.4
Stable Disease	[redacted]	Beta distribution, SE: [redacted]	7.4.3
Utility benefit on treatment			
Enzalutamide	[redacted]	Normal distribution, 95% CI: [[redacted]]	7.4.3
Abiraterone	0.04	Normal distribution, 95% CI: [0.032; 0.048]	7.4.9
Disutility for PDis	-0.085	Normal distribution, SE assumed 20% of mean: 0.017	7.4.7
Disutility for AEs			7.4.8
Abdominal pain	-0.069	Normal distribution, SE = 0.012	
Anaemia	-0.119	Normal distribution, SE = 0.047	
Arthralgia	-0.069	Normal distribution, SE = 0.012	
Asthenia	-0.131	Normal distribution, SE = 0.030	
Back pain	-0.069	Normal distribution, SE = 0.012	
Bone pain	-0.069	Normal distribution, SE = 0.012	
Dehydration	-0.151	Normal distribution, SE = 0.020	
Diarrhoea	-0.137	Normal distribution, SE = 0.034	
Dyspnoea	-0.050	Normal distribution, SE = 0.012	
Fatigue	-0.131	Normal distribution, SE = 0.030	
Febrile neutropenia	-0.120	Normal distribution, SE = 0.016	
Hypertension	-0.153	Normal distribution, SE = 0.049	
Hypokalaemia	0	Not varied	
Leukopenia	-0.090	Normal distribution, SE = 0.015	
Nausea	-0.152	Normal distribution, SE = 0.028	

Variable	Value	Distribution / 95% CI	Source / Reference
Neutropenia	-0.090	Normal distribution, SE = 0.015	
Oedema Peripheral/Fluid retention	0	Not varied	
Pain	-0.069	Normal distribution, SE = 0.012	
Pain in extremity	-0.069	Normal distribution, SE = 0.012	
Pulmonary embolism	-0.145	Normal distribution, SE = 0.025	
Seizure	-0.140	Normal distribution, SE = 0.020	
Thrombocytopaenia	-0.090	Normal distribution, SE = 0.015	
Vomiting	-0.076	Normal distribution, SE = 0.016	
Duration of AEs (in days)			7.4.8
Abdominal pain	10.5	No distribution assumed	
Anaemia	10.5	No distribution assumed	
Arthralgia	10.5	No distribution assumed	
Asthenia	91.25	No distribution assumed	
Back pain	10.5	No distribution assumed	
Bone pain	10.5	No distribution assumed	
Dehydration	10.5	No distribution assumed	
Diarrhoea	10.5	No distribution assumed	
Dyspnoea	10.5	No distribution assumed	
Fatigue	91.25	No distribution assumed	
Febrile neutropenia	10.5	No distribution assumed	
Hypertension	10.5	No distribution assumed	
Hypokalaemia	30.42	No distribution assumed	
Leukopenia	91.25	No distribution assumed	
Nausea	10.5	No distribution assumed	
Neutropenia	10.5	No distribution assumed	
Oedema Peripheral/Fluid retention	10.5	No distribution assumed	
Pain	10.5	No distribution assumed	
Pain in extremity	10.5	No distribution assumed	
Pulmonary embolism	10.5	No distribution assumed	
Seizure	10.5	No distribution assumed	
Thrombocytopaenia	10.5	No distribution assumed	
Vomiting	10.5	No distribution assumed	
AE rates enzalutamide			7.3.1.3
Abdominal pain	[redacted]	Lognormal, in(SE) = [redacted]	
Anaemia	[redacted]	Lognormal, in(SE) = [redacted]	
Arthralgia	[redacted]	Lognormal, ln(SE) = [redacted]	
Asthenia	[redacted]	Lognormal, ln(SE) = [redacted]	
Back pain	[redacted]	Lognormal, ln(SE) = [redacted]	
Bone pain	[redacted]	Lognormal, in(SE) = [redacted]	
Dehydration	[redacted]	Lognormal, in(SE) = [redacted]	
Diarrhoea	[redacted]	Lognormal, in(SE) = [redacted]	
Dyspnoea	[redacted]	Lognormal, ln(SE) = [redacted]	
Fatigue	[redacted]	Lognormal, ln(SE) = [redacted]	
Febrile neutropenia	[redacted]	NA	
Hypertension	[redacted]	Lognormal, ln(SE) = [redacted]	
Hypokalaemia	[redacted]	Lognormal, ln(SE) = [redacted]	
Leukopenia	[redacted]	Lognormal, ln(SE) = [redacted]	

Variable	Value	Distribution / 95% CI	Source / Reference
Nausea	[redacted]	Lognormal, ln(SE) = [redacted]	
Neutropenia	[redacted]	Lognormal, ln(SE) = [redacted]	
Oedema Peripheral/Fluid retention	[redacted]	Lognormal, ln(SE) = [redacted]	
Pain	[redacted]	Lognormal, ln(SE) = [redacted]	
Pain in extremity	[redacted]	Lognormal, ln(SE) = [redacted]	
Pulmonary embolism	[redacted]	Lognormal, ln(SE) = [redacted]	
Seizure	[redacted]	Lognormal, ln(SE) = [redacted]	
Thrombocytopaenia	[redacted]	Lognormal, ln(SE) = [redacted]	
Vomiting	[redacted]	Lognormal, ln(SE) = [redacted]	
AE rates BSC	[redacted]		7.3.1.3
Abdominal pain	[redacted]	Lognormal, ln(SE) = [redacted]	
Anaemia	[redacted]	Lognormal, ln(SE) = [redacted]	
Arthralgia	[redacted]	Lognormal, ln(SE) = [redacted]	
Asthenia	[redacted]	Lognormal, ln(SE) = [redacted]	
Back pain	[redacted]	Lognormal, ln(SE) = [redacted]	
Bone pain	[redacted]	Lognormal, ln(SE) = [redacted]	
Dehydration	[redacted]	Lognormal, ln(SE) = [redacted]	
Diarrhoea	[redacted]	Lognormal, ln(SE) = [redacted]	
Dyspnoea	[redacted]	Lognormal, ln(SE) = [redacted]	
Fatigue	[redacted]	Lognormal, ln(SE) = [redacted]	
Febrile neutropenia	[redacted]	NA	
Hypertension	[redacted]	Lognormal, ln(SE) = [redacted]	
Hypokalaemia	[redacted]	Lognormal, ln(SE) = [redacted]	
Leukopenia	[redacted]	NA	
Nausea	[redacted]	Lognormal, ln(SE) = [redacted]	
Neutropenia	[redacted]	NA	
Oedema Peripheral/Fluid retention	[redacted]	Lognormal, ln(SE) = [redacted]	
Pain	[redacted]	Lognormal, ln(SE) = [redacted]	
Pain in extremity	[redacted]	Lognormal, ln(SE) = [redacted]	
Pulmonary embolism	[redacted]	Lognormal, ln(SE) = [redacted]	
Seizure	[redacted]	NA	
Thrombocytopaenia	[redacted]	Lognormal, ln(SE) = [redacted]	
Vomiting	[redacted]	Lognormal, ln(SE) = [redacted]	
AE abiraterone rate difference vs. BSC			7.3.1.3
Abdominal pain	-0.010	Normal, SE = 0.02	
Anaemia	-0.058	Normal, SE = 0.03	
Arthralgia	-0.019	Normal, SE = 0.02	
Asthenia	0.003	Normal, SE = 0.02	
Back pain	-0.108	Normal, SE = 0.03	
Bone pain	-0.071	Normal, SE = 0.03	
Dehydration	0.000	NA	
Diarrhoea	-0.010	Normal, SE = 0.01	
Dyspnoea	-0.022	Normal, SE = 0.02	
Fatigue	-0.086	Normal, SE = 0.04	
Febrile neutropenia	0.005	Normal, SE = 0.00	
Hypertension	0.012	Normal, SE = 0.01	
Hypokalaemia	0.043	Normal, SE = 0.01	

Variable	Value	Distribution / 95% CI	Source / Reference
Leukopenia	0.000	NA	
Nausea	-0.027	Normal, SE = 0.02	
Neutropenia	-0.003	Normal, SE = 0.01	
Oedema Peripheral/Fluid retention	0.013	Normal, SE = 0.01	
Pain	-0.028	Normal, SE = 0.01	
Pain in extremity	-0.060	Normal, SE = 0.02	
Pulmonary embolism	0.000	NA	
Seizure	0.000	NA	
Thrombocytopaenia	0.008	Normal, SE = 0.01	
Vomiting	-0.025	Normal, SE = 0.02	
Costs for AEs (£)			7.5.7
Abdominal pain	697	Gamma, SE based on IQR = 258	
Anaemia	1,249	Gamma, SE based on IQR = 360	
Arthralgia	101	Gamma, SE based on IQR = 50	
Asthenia	12	Gamma, SE based on IQR = 4	
Back pain	460	Gamma, SE based on IQR = 190	
Bone pain	460	Gamma, SE based on IQR = 190	
Dehydration	1,569	Gamma, SE based on IQR = 409	
Diarrhoea	606	Gamma, SE based on IQR = 343	
Dyspnoea	0	NA	
Fatigue	12	Gamma, SE based on IQR = 4	
Febrile neutropenia	4,384	Gamma, SE based on IQR = 2016	
Hypertension	552	Gamma, SE based on IQR = 216	
Hypokalaemia	163	Gamma, SE based on IQR = 84	
Leukopenia	237	Gamma, SE based on IQR = 100	
Nausea	606	Gamma, SE based on IQR = 343	
Neutropenia	237	Gamma, SE based on IQR = 100	
Oedema Peripheral/Fluid retention	914	Gamma, SE based on IQR = 339	
Pain	101	Gamma, SE based on IQR = 50	
Pain in extremity	101	Gamma, SE based on IQR = 50	
Pulmonary embolism	1,849	Gamma, SE based on IQR = 478	
Seizure	1743	Gamma, SE based on IQR = 446	
Thrombocytopaenia	570	Gamma, SE based on IQR = 198	
Vomiting	606	Gamma, SE based on IQR = 343	
SRE Disutilities			7.4.3
Spinal cord compression	[redacted]	Normal, SE = [redacted]	
Pathologic bone fractures	[redacted]	Normal, SE = [redacted]	
Radiation to bone	[redacted]	Normal, SE = [redacted]	
Surgery to bone	[redacted]	Normal, SE = [redacted]	

Variable	Value	Distribution / 95% CI	Source / Reference
SRE duration (in days)			7.4.9
Spinal cord compression	30.42	No distribution assumed, SA range: 0-90	
Pathologic bone fractures	30.42	No distribution assumed, SA range: 0-90	
Radiation to bone	30.42	No distribution assumed, SA range: 0-90	
Surgery to bone	30.42	No distribution assumed, SA range: 0-90	
SRE costs			7.5.7
Spinal cord compression	6,047	Gamma, SE based on IQR = 3,655	
Pathologic bone fractures	5,042	Gamma, SE based on IQR = 1,445	
Radiation to bone	116	Gamma, SE based on IQR = 36	
Surgery to bone	3,888	Gamma, SE based on IQR = 1,656	
SRE rate enzalutamide			7.3.1.4
Spinal cord compression	[redacted]	Lognormal, ln(SE) = [redacted]	
Pathologic bone fractures	[redacted]	Lognormal, ln(SE) = [redacted]	
Radiation to bone	[redacted]	Lognormal, ln(SE) = [redacted]	
Surgery to bone	[redacted]	Lognormal, ln(SE) = [redacted]	
SRE rate BSC			7.3.1.4
Spinal cord compression	[redacted]	Lognormal, ln(SE) = [redacted]	
Pathologic bone fractures	[redacted]	Lognormal, ln(SE) = [redacted]	
Radiation to bone	[redacted]	Lognormal, ln(SE) = [redacted]	
Surgery to bone	[redacted]	Lognormal, ln(SE) = [redacted]	
SRE rate difference abiraterone			7.3.1.4
Spinal cord compression	-0.066	Normal, SE = 0.03	
Pathologic bone fractures	0.020	Normal, SE = 0.02	
Radiation to bone	-0.221	Normal, SE = 0.05	
Surgery to bone	0.007	Normal, SE = 0.01	

Abbreviations: AE: adverse events; BSC: best supportive care; CI: confidence interval; HR: hazard ratio; PFS: progression free survival; SRE: skeletal related event; OS: overall survival; SDis: stable disease; PDis: progressed disease; SE: standard error; wks: weeks; yrs: years.

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

As not all patients in AFFIRM had progressed or died at the end of the study, extrapolation was required. As described in section 7.3.1, clinical outcomes are extrapolated beyond the trial follow-up duration by fitting parametric curves to the observed data of the reference arm. OS and PFS for BSC is assumed to follow a Weibull distribution, and the HRs used to model enzalutamide OS and PFS and abiraterone PFS are assumed to remain constant over time. The HR to model the effect of abiraterone on OS is determined by a time dependent function, and is not extrapolated beyond 25 months. A comparison of curve fittings to Kaplan-Meier plots is provided in section 7.3.1.1 and 7.3.1.2.

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Table 54: Assumptions in the economic model

Assumption	Justification	Reference
The population of AFFIRM is reflective of the UK population of adult men with mCRPC whose disease has progressed on or after docetaxel therapy	AFFIRM only included patients with mCRPC who received at least one prior chemotherapy. Clinical experts in the UK confirmed that the AFFIRM population reflected that of the UK clinical practice (15 sites) (section 6.10.2).	Clinical experts (4)
Treatment discontinuation in the best proxy for disease progression	Oncologists actively treating PC in the UK confirmed that disease progression in PC in clinical practice is not a decision made using any single assessment measure alone (e.g. by radiographic or PSA progression alone) because of the advanced nature of disease in this patient population. Disease progression was based on the treatment discontinuation criteria in the trial.	Abiraterone Manufacturer Submission (80), UK clinical experts (4)
Post study treatment in AFFIRM was assumed to have had no impact on OS	Although any effect of post-study treatment would be inherently included in the survival curves, this is a conservative assumption as more placebo patients received post study treatment. In addition clinical experts indicated that post-study abiraterone (21% in enzalutamide arm vs 24% in placebo arm) would have had a larger impact on the placebo OS than on enzalutamide OS. As the impact of post-study treatment cannot be quantified without increasing uncertainty, no impact of OS has been included in any of the analyses and all patients were assumed to receive BSC upon treatment discontinuation. However, a sensitivity analysis has been included in	Scher 2012a(3), UK clinical experts (4)

Assumption	Justification	Reference
	which the costs of the post-study treatment as per AFFRIM are included.	
Patients in the Progressive Disease health state receive BSC, irrespective of the prior treatment, and do not receive another active treatment.	No data on the treatment pathway is available and no treatment is currently recommended in the guidelines for patients who fail on their post-docetaxel treatment. Abiraterone received a positive decision by NICE, however, clinical experts consider it unlikely that patients will be prescribed abiraterone after enzalutamide due to the high costs and unknown benefit.	Clinical experts (4), NICE PC guideline (28)
Patients can experience AEs only in the stable disease health state.	It is assumed that any incremental differences in AE rates between comparators would occur only when patients are actively receiving treatment.	Clinical experts (70)
Only grade ≥3 AE are taken into account.	Any incremental difference in Grade 1/2 AEs was not assumed to impact cost effectiveness results. This was also confirmed by UK clinical experts.	Clinical experts (70)
Patients in the progressive disease can only experience SREs; no other complications are taken into account.	As patients have discontinued active treatment in progressive disease, no incremental differences in AEs are expected. As SREs are one of the key markers of bone progression, they are only expected to occur once patients' progress.	Clinical experts (70)
The effects of the included SRE's have a 1-month impact in terms of QoL and costs.	No data on the duration of SREs was collected in AFFIRM. Based on literature data, a one month duration was considered reasonable. Clinical experts confirmed this was a reasonable assumption, but would expect some variation between types of SREs.	Botteman 2010 (121); Clinical experts (4).
SREs result in an additional decrement in utility over the decrement of progression	Both SREs and progression was associated with a significant decrease in utility. Available literature also indicates these events results in a decrease in QoL.	Section 7.4.5
Approximation of OS and PFS curves assumed a parametric function	Not all patients have died, progressed, or discontinued treatment at the end of AFFIRM. Therefore, in line with NICE DSU guidance on survival modelling, the available survival data was fitted to parametric functions. A Weibull function was selected by clinical experts.	Clinical opinion, NICE DSU guidance on survival modelling (113)
The placebo arm in AFFIRM and the placebo + prednisolone arm in COU-AA-301 study are comparable.	All baseline demographics are similar between AFFIRM and COU-AA-301. Abiraterone needs to be taken with steroids which is not the case for enzalutamide. Therefore a different percentage of patients in control arm of AFFIRM and the COU-AA-301 study received steroids (n=182/399, 45.6% vs. n=398/398, 100%). While there is no controlled evidence to suggest that steroids may impact PFS or OS, it can be argued that steroids would have some benefit on clinical outcome. Experts noted that many patients would have already received steroids and progressed on this treatment earlier on in the disease (4) and that the benefit of steroids is likely negligible in this patient population.	Section 6.7 (25)(3), clinical experts (4).
The decision to discontinue treatment in AFFIRM and COU-AA-301 was made on the same criteria	Both trials used comparable discontinuation criteria, in addition, investigators in both studies confirmed that little difference was expected in the criteria for discontinuation between the two studies.	AFFIRM clinical study protocol (41), Fizazi 2012 (25), investigators from AFFIRM and COU-AA-301

Abbreviations: AE: adverse events; BSC: best supportive care; DSU: decision support unit; FACT-P: functional assessment of cancer therapy – prostate; mCRPC: metastatic castrate-resistant prostate cancer; NICE: national institute for health and care excellence; OS: overall survival; PFS: progression free survival; PSA: prostate specific antigen; SRE: skeletal related event; UK: United Kingdom.

7.4 *Measurement and valuation of health effects*

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

The QoL in PC patients decreases in the last phase of life (122). Bone metastases result in a significantly worse HRQoL, as found in a study by Hechmati et al.(123) comparing patients with bone metastases to patients at high risk of bone metastases. Pain in mCRPC is often a result of bone metastasis, and has a significant impact on the HRQoL (122). Finally treatment may also interfere with a patient's QoL. A study in German mCRPC patients (124) found that patients on chemotherapy had worse HRQoL than chemo-naïve patients or than patients who had been previously treated with chemotherapy.

7.4.2 Please describe how a patient's HRQoL is likely to change over the course of the condition.

As mentioned in section 7.4.1, QoL decreases in the last phase of life, especially during the last year before death (122). This is also shown in the AFFIRM study, where a marked and statistically significant deterioration in QoL in all FACT-P scores (except for social well-being) versus baseline in the placebo arm at all timepoints was observed (section 7.4.3).

The decline in QoL in mCRPC is associated with further progression; therefore, delaying progression is also expected to have a substantial effect on QoL. As indicated in section 7.4.3, progression was also shown to cause a significant decline in utility value in the AFFIRM study (section 7.4.3).

HRQoL data derived from clinical trials

7.4.3 If HRQoL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQoL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

QoL data was collected in the AFFIRM study through FACT-P and EQ-5D questionnaires.

Although the disease specific FACT-P questionnaire was collected from all 1,199 AFFIRM patients, the collection of EQ-5D questionnaire was only instituted at all sites in France, Germany, Italy, Spain, and the UK via Amendment 2.0 to the protocol. As a result of this amendment, 331 patients (111 in the placebo arm and 220 in enzalutamide arm, Table 55) of the total ITT population of the AFFIRM study) were requested to fill in the EQ-5D questionnaire.

Table 55: HRQoL instruments assessment schedule

PRO instrument	Patients	Week 1	Week 13	Week 17	Week 21	Week 25 and every subsequent 12 weeks
EQ-5D*	331	X	X			X
FACT-P	1,199	X	X	X	X	X

*Note: only sites from France, Germany, Italy, Spain, and the UK collected EQ-5D data.
Abbreviations: EQ-5D: European Quality of Life Five-Domain Scale; FACT-P: Functional Assessment of Cancer Therapy – Prostate.

The number of patients with evaluable EQ-5D forms (i.e., with the 5 domain items correctly answered) at baseline was 209 (67 [60.4%] in the placebo arm and 142 [64.5%] in the enzalutamide arm). The EQ-5D utility scores were calculated using the UK time trade-off (TTO) value set (125).

As a result of the limited number of patients completing the EQ-5D questionnaire, the FACT-P responses were mapped to EQ-5D values using an internal mapping algorithm (47) (section 7.4.4). This allowed analysis of health state utilities from a larger number of patients (1,199 patients) than using the EQ-5D (331 patients). However, as mapping utility values always introduces uncertainty, the EQ-5D values were preferred for the health economic model, and the mapped values are only used for analyses where the number of EQ-5D responses was insufficient.

The baseline utility value in AFFIRM was [redacted] using the actual EQ-5D (N = 209, SE = [redacted]), and [redacted] using the mapped values (N = 1,008, SE = [redacted]).

As HRQoL was only collected for patients on treatment, it was not possible to calculate the disutility for treatment discontinuation based on this definition, and a literature utility value was preferred for the economic model. For the purpose of sensitivity analysis, the impact of progression was calculated according to mPFS criteria (radiographic progression, first SRE or death). The disutility for progression was calculated in the following way:

- All patients included in AFFIRM who were alive and showed radiographic progression or a SRE were identified.
- Linear mixed-effects model was used to model each patient's longitudinal trajectory of the collected and mapped EQ-5D utility values over time before the event of interest (i.e., radiographic progression or SRE).
- The utility decrement was derived using the trajectory adjusted mean change, defined as the mean deviation of the post-event utility from the expected value based on all patients' pre-event trajectory.

The derived utility decrement for progression was [redacted] using the mapped values (N = 466, SE = [redacted]), and [redacted] using the actual EQ-5D (N = 106, SE = [redacted]). However, it should be noted that this analysis only provides the utility decrement up to the start of progression, while it is likely that the utility further decreases over time in the months before death. Therefore it was decided to take the utility decrement from the literature in the base case model analysis (see section 7.4.7).

Enzalutamide patients showed a significant advantage in pain palliation at Week 13 (as measured by question 3 of the BPI) with [redacted] achieving palliation on enzalutamide vs. [redacted] on placebo (difference [redacted], 95% CI: [[redacted]], p = [redacted]). In addition, enzalutamide was associated with a significantly higher proportion of patients with a positive QoL response than placebo (n=275/652, 42.2% vs. n=36/248, 14.5%; p=0.0018), and significantly better QoL than placebo in FACT-P total score and all sub-domains (physical, functional and emotional wellbeing and prostate cancer scale) at all time points except for social wellbeing which did not change. As these QoL advantages could lead to a utility benefit over placebo, the QoL of enzalutamide and placebo patients was compared using a MMRM model. To derive the treatment arm effect for patients in stable disease, the individual patient changes from baseline utility as implied by the FACT-P mapping function are calculated and regressed on the baseline utility with a dummy variable for the enzalutamide treatment arm. The analysis was performed using a repeated measures analysis including covariates for treatment, time, baseline utility and baseline covariates (ECOG status, prior chemotherapy regimens [1 or ≥2], pain, age and fatigue).

Only those assessments prior to the documented disease progression were included in the analysis. The LS mean estimates for mean changes from baseline for enzalutamide versus placebo was estimated to be [redacted] (95% CI: [[redacted]]). The adjusted LS means change from baseline was [redacted] (95% CI [[redacted]], p=[redacted]) for placebo compared with an increase of [redacted] (95% CI [[redacted]], p=[redacted]) for enzalutamide (Figure 21).

Figure 21: Adjusted mean change from baseline in mapped EQ-5D utility index score

[redacted]

Source: PRO Report 2012 (37)
Note(s): ** p-value<0.005, results for within group comparison
Abbreviations: EQ-5D: European Quality of Life Five-Domain Scale; LS mean: least squared mean.

Similar to the calculation of the disutility for progression, separate disutilities were calculated for individual SREs using a trajectory adjusted mean change. As insufficient EQ-5D data was available, the following disutilities were calculated based on the mapped utilities: spinal cord compression: [redacted] (95% CI: [redacted]); pathologic bone fracture: [redacted] (95% CI:[redacted]); radiation or surgery to the bone: [redacted] (95% CI: [redacted]).

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

Three statistical techniques were used to estimate patients' EQ-5D index scores determined using the UK-tariff: (a) generalized estimating equations (GEE) (b) two-part model combining logistic regression and GEE (c) separate mapping algorithms for patients with poor health defined as FACT-P ≤76 (group-specific model).

For each method, the following 4 models were compared:

- Model 1: FACT-P total score and baseline variables (age, weight at baseline, ECOG status at baseline, number of prior chemotherapy regimens, pain score at baseline [assessed from question #3 of the BPI questionnaire] and fatigue severity at baseline) - full model (all covariates included).

- Model 2: FACT-P total score and baseline variables - restricted model (i.e., the variables with non significant parameter estimate at 0.05 were removed from the model).

- Model 3: The 5 FACT-P subscales (physical, emotional, functional, and social well-being and prostate cancer subscale) and baseline variables - full model.

- Model 4: The 5 FACT-P subscales and baseline variables - restricted model.

The models were cross-validated using a 10-fold in-sample cross-validation. Details on model development and selection are provided in Skaltsa et al. (51).

The number of mCRPC patients in the estimation sample, i.e., with both FACT-P and EQ-5D non-missing scores simultaneously at one or more timepoints during the study, was 236 patients. The group-specific model including the FACT-P subscale scores and baseline variables (Table 56) had the best predictive performance with R^2=0.718 and Root Mean Square 0.162, and was used for all subsequent analyses.

Mapped utility values were used for the decrement due to SREs, and for use in scenario analyses.

Table 56: Coefficients for the group-specific model with FACT-P sub domains as covariates.

Variables	Coefficients	SE	p-value	Coefficients	SE	p-value
	Poor health (FACT-P<76)			**Good health (FACT-P>=76)**		
Intercept	-0.2343	0.5003	0.6396	-0.3475	0.2229	0.1191
ECOG at baseline (0-1 vs. 2)	0.2225	0.1104	0.0438	0.0839	0.0823	0.3082
Number of prior chemotherapy regimens (1 vs. >=2)	-0.0700	0.1135	0.5377	-0.0087	0.0198	0.6602
Age	-0.0095	0.0055	0.0876	0.0025	0.0016	0.1115
Weight	0.0023	0.0025	0.3447	0.0015	0.0009	0.0734
Baseline average pain score (<4 vs. >=4)	-0.1125	0.0741	0.1287	0.0568	0.0282	0.0438
Fatigue severity (No fatigue vs. Fatigue)	-0.1416	0.1104	0.1996	0.0291	0.0183	0.1108
Physical WB	0.0277	0.0091	0.0022	0.0111	0.0036	0.0021
Social/Family WB	0.0006	0.0091	0.9442	-0.0006	0.0019	0.7362
Emotional WB	0.0214	0.0113	0.0577	0.0089	0.0031	0.0037
Functional WB	0.0160	0.0104	0.1247	0.0048	0.0024	0.0452
PCS	0.0124	0.0077	0.1073	0.0060	0.0018	0.0008

Abbreviations: ECOG: eastern cooperative oncology group; GEE: generalized estimating equations; FACT-P: functional assessment of cancer therapy – prostate; PCS: prostate cancer subscale; SE: standard error; WB: well-being.

HRQoL studies

7.4.5 Please provide a systematic search of HRQoL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

A systematic search of HRQoL data is provided in appendix 12, section 10.12.

7.4.6 Provide details of the studies in which HRQoL is measured.

Studies measuring HRQoL in PC are described in appendix 12, section 10.12.8. The studies presenting utilities in mCRPC are summarised in Table 57.

Table 57: Studies measuring QoL in metastatic or castrate resistant patients

Study	Utility Weight				Method
Bayoumi (2000) (126)				0.4	Distant symptomatic prostate cancer , hormone resistant
Bennet (1997) (127)				0.42	TTO (Median), Physicians Opinion (N=47)
				0.05	Pts w/ Localised PC Opinion (N=27)
				0.05	Pts w/ Metastatic PC Opinion (N=17)
Chapman (1998) (128)				0.2	TTO (mean), Impersonal (N=31)
				0.35	TTO (mean), Personal (N=28)
Chapman (1999) (129)				0.23	TTO patient opinion (n=57)
Kobayashi (2007)				0.5	Metastatic prostate cancer
Reed (2011)(130)				0.25	Metastatic prostate cancer
Sandblom (2004) (122)	**16-12M**	**12-8M**	**8-4M**	**4-0M**	Time before death
	0.58	0.58	0.54	0.46	EQ-5D (mean), Value
	0.57	0.57	0.53	0.45	EQ-5D (mean), VAS
Volk (2004) (131)				0.55	TTO (mean), Husbands (N=168)
				0.66	TTO (mean), Wives (N=168)
				0.62	TTO (mean), Couples (N=168)
Stewart (2005) (132)				0.25	SG (mean), Patients (N=162)
Sullivan (2007)(133)				0.635	EQ-5D (mean baseline) Total patients (N=280)
				0.715	EQ-5D (mean baseline) UK patients (N=29)
Abiraterone submission to CVZ (2012) (92)				0.80	COU-AA-301 mapped utility
				0.715	mCRPC post progression
Cabazitaxel submission to NICE (2011) (134)				-0.07	Utility decrement for progression derived from Sullivan (2007)(133)
				-0.085	Utility decrement for progression derived from Sandblom (2004)(122)

Abbreviations: CVZ: *college voor Zorgverzekeringen*, Dutch health care insurance board; M: months; mCRPC: metastatic castrate-resistant prostate cancer; SG: standard gamble; TTO: time trade off; pts: patients; VAS: visual analogue scale.

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Only the Sandblom 2004 (122) and Sullivan 2007 (133) studies reported the EQ-5D in mCRPC patients. The baseline utility in the Sullivan 2007 study is comparable to the baseline utility in AFFIRM. Sandblom measured EQ-5D in the last months before death and found a utility 16-12 months before death that was slightly lower than the AFFIRM baseline utility.

Janssen presented in their submission to *College voor Zorgverzekeringen (CVZ,* the Dutch Health Care Insurance Board) (92) the baseline utility in the COU-AA-301 study using a mapping algorithm. The reported baseline utility is considerably higher than the baseline EQ-5D in AFFIRM. However, FACT-P results from the COU-AA-301 study were mapped to EQ-5D using an external mapping algorithm, and may thus be influenced by the mapping. In Janssen's submission to NICE the mapped baseline utility value from the COU-AA-301 study was also used for the pre-progression health state (value commercial in confidence [CIC]) (80). The ERG noted that this value was "similar or higher than that for similarly aged men in the general

population, which may be implausible" (135). The abiraterone submission used an average from the utility 8-4 months and 4-0 months before death from the study by Sandblom (122) for the post-progression utility (utility value of 0.5). The ERG noted that this resulted in a decrease in utility, and that the utility decrement upon progression appeared quite large (135).

As the baseline EQ-5D from AFFIRM was derived from a reasonably sized sample of European post-chemo mCRPC patients, this was considered the most appropriate utility for the stable disease health state of the economic model.

Utility decrements for progression have been derived from the Sullivan 2007 (133) study and from the Sandblom 2004 (122) study as described in the cabazitaxel NICE submission (134). Both approaches result in comparable utility decrements. An alternative approach, employed in the abiraterone submission is to use the absolute utility value from the Sandblom study; however, this would not take into account the lower baseline value in this study. For the purpose of the economic model the utility decrement derived from the Sandblom study (-0.085) was considered the most appropriate value, as the collected time intervals (16-8 and 8-0 months before death) approximately match the time in stable and progressive disease for AFFIRM patients.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQoL.

AEs may have a strong negative impact on the QoL of patients; therefore, it is important to account for the disutility associated with them. In the absence of disutilities from AFFIRM (aside from SRE values), the utility data for experiencing an AE was sourced from literature. When disutilities were found in different sources, the average value was used. Durations were based on the values reported in the abiraterone ERG report (135). The disutilities and durations used were further validated by experts (70), and are reported in Table 58.

Table 58: Disutility and duration of adverse events

AE	Disutility	SE	Justification / Source	Duration (days)
Abdominal pain	-0.069	0.012	Assumed same as pain/arthralgia (Doyle 2008) (136)	7-14
Anaemia	-0.119	0.047	Swinburn 2010 (137)	7-14
Arthralgia	-0.069	0.012	Doyle 2008 (136)	7-14
Asthenia	-0.131	0.03	Assumed equal to fatigue: Lloyd 2006 (138), Nafees 2008 (139), Swinburn 2010 (137)	91.25
Back pain	-0.069	0.012	Doyle 2008 (136)	7-14
Bone pain	-0.069	0.012	Doyle 2008 (136)	7-14
Dehydration	-0.151	0.02	Based on clinical expert opinion that stomatitis cases are often filed under dehydration: Lloyd 2006 (138)	7-14
Diarrhoea	-0.137	0.034	Nafees et al, 2008 (139), Swinburn 2010 (137), Lloyd 2006 (138)	7-14
Dyspnoea	-0.050	0.012	No disutility as per NICE abiraterone ERG report(135)	7-14
Fatigue	-0.131	0.03	Lloyd 2006 (138), Nafees 2008 (139), Swinburn 2010 (137)	91.25

Febrile neutropenia	-0.120	0.016	Lloyd 2006 (138) and Nafees 2008 (139)	7-14
Hypertension	-0.153	0.049	Swinburn 2010 (137)	7-14
Hypokalaemia	0		No (dis-)utilities reported, assumed to have no detrimental impact on QoL	7-14
Leukopenia	-0.090	0.015	Assumed equal to neutropenia: Nafees 2008 (139)	7-14
Nausea	-0.152	0.028	Nafees 2008 (139), Swinburn 2010 (137)	7-14
Neutropenia	-0.090	0.015	Nafees 2008 (139)	7-14
Oedema Peripheral/Fluid retention	0		No (dis-)utilities reported, assumed to have no detrimental impact on QoL	
Pain	-0.069	0.012	Doyle 2008 (136)	7-14
Pain in extremity	-0.069	0.012	Doyle 2008 (136)	7-14
Pulmonary embolism	-0.145	0.025	Average of Gould et al (1999) (140) and Treasure et al (2009) (141) as per NICE Cabazitaxel MS (134)	7-14
Seizure	-0.140	0.02	Epilepsy utilities change with frequency of attacks. An average utility (based on EQ-5D) for epilepsy patients is 0.81 (Stavem) (142). Other sources give an average of 0.83 (Messori) (143), with a min of 0.66. Based on 0.96 for seizure free life, a decrement of 0.96-0.82= 0.14.	7-14
Thrombocytopaenia	-0.090	0.015	Assumed same as neutropenia: Nafees 2008 (139)	7-14
Vomiting	-0.076	0.016	Lloyd 2006 (138) and Nafees 2008 (139)	7-14

Abbreviations: AE: adverse events; EQ-5D: European quality of life five-domain scale; MS: manufacturer submission; NICE: national institute for health and care excellence; SE: standard error.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Table 59: Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	CI / SE	Reference in submission	Justification
Stable Disease	[redacted]	SE = [redacted]	7.4.3	The baseline utility (EQ-5D) values in AFFIRM represent patients in SDis.
Disutility progression	-0.085	SE assumed 20% of mean = 0.017	7.4.7	As no QoL data was collected beyond progression, only the utility decrease upon the first sign of progression could be calculated, and not the utility while in progressive disease. Therefore literature data were preferred: Decrease in utility from 16-8 months before death to 8-0 months before death in Sandblom study (122) was assumed to represent utility decrement for progression.
On treatment benefit for enzalutamide	[redacted]	[redacted]	7.4.3	Enzalutamide showed a significant effect on pain, resulting in a significant utility gain over placebo in AFFIRM based on mapped FACT-P utilities.
On treatment benefit for abiraterone	0.04	0.032 - 0.048	Abiraterone CVZ submission (92)	Abiraterone showed a statistically significant utility gain over placebo in the COU-AA-301 study based on mapped FACT-P utilities.
SRE disutilities				
Radiation or surgery to bone	[redacted]	95% CI [redacted]	7.4.3	SREs in AFFIRM were associated with a significant decline in utility.
Pathologic bone fractures	[redacted]	95% CI [redacted]	7.4.3	
Spinal cord compression	[redacted]	95% CI [redacted]	7.4.3	
Duration of SRE disutility	1 month		Botteman 2011 (121)	Duration was based on literature data. No other sources were identified.
AE disutilities	See Table 58		7.4.8	Literature values were used as impact of individual SAEs could not be measured in AFFIRM due to frequency of HRQoL measurements (12 weeks).

Abbreviations: AE: Adverse Event; CI: Confidence Interval; SE: Standard Error; SRE: Skeletal Related Event

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Using the methodology described in section 7.3.5 the applicability of the utility values for the health economic model, the mapping methodology, and the method to derive the on treatment utility gain, and disutilities for progression and SREs were validated.

In addition, the QoL analyses were performed in cooperation with several clinical experts. In particular Dr. D. Cella, who developed the Functional Assessment of Cancer Therapy (FACT) questionnaires, aided the design of the QoL analyses (47).

7.4.11 Please define what a patient experiences in the health states in terms of HRQoL. Is it constant or does it cover potential variances?

A patient in SDis experiences a constant utility, consisting of the SDis utility value and an on treatment utility benefit for patients treated with enzalutamide or abiraterone. The utility in SDis may be decreased for a number of days due to the occurrence of AEs.

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[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Once patients progress to the PDis health state they no longer experience any on treatment utility benefit. Furthermore their utility is decreased due to the progression. The utility in PDis is constant, but may be decreased for a duration of 1 month due to the occurrence of SREs.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

An effect of AEs on QoL was identified in the literature (144). However, the model only includes AEs of grade 3 and higher as mild (grade 1 or 2) AEs were not expected to lead to incremental differences between the comparators. In addition, the model assumes that the utility in the PDis state is constant over time, whereas studies found that the utility decreases in the last months of life (145) (146). This effect was not included as no reliable data was available to incorporate these effects in the analysis, and it was not expected to influence the incremental results.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Patients enter the model in the SDis health state, the baseline QoL is the utility of this health state. Any QoL events (i.e., AEs, treatment gain, progression) were taken from this baseline.

7.4.14 Please clarify whether HRQoL is assumed to be constant over time. If not, provide details of how HRQoL changes with time.

HRQoL is assumed constant over time in each health state.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

The values have not been amended.

7.5 *Resource identification, measurement and valuation*

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

The only tariff that is relevant to mCRPC patients in the post-chemotherapy setting is the chemotherapy tariff. However, this is only relevant to those patients receiving subsequent chemotherapy.

The clinical management of mCRPC patients is currently costed using NHS reference costs for scheduled monitoring, chemotherapy administration, management of AEs and SREs, and terminal treatment costs (147).

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

The chemotherapy tariff would only be applicable for patients receiving chemotherapy. The following costs sources are used in the economic model:

- British National Formulary (BNF) 65, March 2013 (34), and Electronic Market Information Tool (eMit) (148) for drug costs.
- NHS reference costs 2011-2012 for diagnostic imaging and tests, palliative care, and AE and SRE management costs (147).

Unit costs for Health and Social Care 2012 for outpatient visits and home care (33).

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

A systematic search of health resource utilisation (HRU) data identified 4 studies (34) (149) (150) (151) (Table 60). In addition to these studies, two NICE STAs [cabazitaxel (29) and abiraterone (5)] were identified estimating resource utilisation in men with mCRPC whose disease has progressed on or after docetaxel therapy.

Hwang et al reported that in the last 6 months of life, 98% of patients with CRPC needed a clinic visit (median of 19) and 32% of them an emergency room visit. The majority of patients (95%) also needed at least one hospitalisation (median: 2) and 40% had referral to a hospice for a median length of stay of 35 days. The majority of patients received opioids (90%) and 50% received courses of palliative radiation in their last 6 months of life (152).

Dass et al assessed the HRU by patients with mCRPC in an observational, retrospective, year-long study conducted in 47 centres specialised in PC in 6 countries: Belgium, France, Germany, Sweden, the Netherlands, and the UK (149). Rates of PCr-related surgery were highest in the post-chemotherapy setting (11.3%) or patients on chemotherapy (12.9%) than in chemo-naïve patients (5.9%) while palliative radiotherapy was more common in patients who had never received chemotherapy (28.2% vs. 19.1% and 14.5%). In terms of hospitalisation, the proportion of patients needing to be hospitalised was lower among patients on chemotherapy at the time of the study (23.5% vs. 43.7% and 43.5%). Conversely, more patients in this subgroup needed emergency room visits (14.5% vs. 7.4% and 9.9%).

Duran et al compared the HRU of patients with SRE in the US and Europe. In Europe more patients with SRE needed inpatient stays (29.5% vs. 14.7%) and fewer patients an outpatient stay (74.1% vs. 88.1%) than in the US. The proportion of patients with

at least one visit to the emergency room was comparable in both geographical regions. The proportion of patients on bisphosphonates either oral or IV was 70% in the US and 63.0% in Europe (150).

According to the model developed by Reed et al, the mean length of stay in hospital in patients treated with zoledronic acid (5.7 days) was not statistically different from that in patients on placebo (8.0 days; p=0.1910) (151).

Table 60: Studies reporting health resource utilisation

Study, Year **Country** **Description**	**HRU**
Hwang 2004 (152) US Retrospective cohort of 89 consecutive CRPC patients seen at a VA New Jersey medical centre from 1994 to 1999.	No costs are provided. <u>HRU in last 6 mo:</u> Clinic visits: 98% of patients, median of 19 visits ER visits: 32% of patients, median of 1 visit Hospitalisations: 95% of patients, median of 2 hospitalisations Hospice referral: 40% of patients with a median LOS of 35 days. <u>Tx administered</u> 90% of patients received opioids and the opioid dose increased over time. 50% of patients received courses of palliative radiation in their last 6 months of life. Corticosteroids: 43% Blood transfusion: 57% of patients.
Dass 2012 (149) No country provided • Mean age: 73.0 years • Mean time since PC diagnosis: 6.6 years Chemo consisted principally of DOC: 82.0%.	No costs provided Rates of PC surgery • Without Prior chemo: 5.9% • Past chemo: 11.3% • Ongoing chemo: 12.9% Palliative radiotherapy • Without Prior chemo: 28.2% • Past chemo: 19.1% • Ongoing chemo: 14.5% Hospitalisation rates • Without Prior chemo: 43.7% • Past chemo: 43.5% • Ongoing chemo: 23.5% Mean Hospitalisation durations • Without Prior chemo: 6.1 • Past chemo: 6.8 • Ongoing chemo: 5.7 Emergency room visits • Without Prior chemo: 7.4% • Past chemo: 9.9% • Ongoing chemo: 14.5%
Duran 2012 (150) US and EU (Germany, United Kingdom, Spain, and Italy) Pts with advanced cancer and bone metastases with solid tumours	<u>US: SREs (n=354)</u> % of SREs with inpatient stay: 14.7% • Mean inpatient stays: 0.18 % of SREs with outpatient visits: 88.1% • Mean visits: 9.1 • Median visits: 9.0 % of SREs with ER visits: 4.0% • Mean visits: 0.05 • Median visits: 0.0 Biphosphate use (PO or IV): 70% <u>EU: SREs (n = 893)</u> % of SREs with inpatient stay: 29.5% • Mean stays: 0.32

Study, Year Country Description	HRU
	% of SREs with outpatient visits 74.1% • Mean visits: 4.8 • Median visits: 2.0 % of SREs with ER visits: 4.1% • Mean: 0.04 • Median: 0.0 Biphosphate use (PO or IV): 63.0%
Reed 2004 (151) Argentina, Austria, Australia, Belgium, Brazil, Canada, Chile, France, Germany, Italy, New Zealand, Peru, Sweden, Switzerland, UK, US, Uruguay Median age (pts with resource use data): 73 yrs Costs reported in 2002 US$	Length of hospital stay (mean) • ZOL: 5.7 days • PLA: 8.0 days • p=0.1910
Abiraterone MS, 2012 (80)	Estimated HRU: <u>Abiraterone first three months:</u> 1 outpatient visit every 2 weeks 1 LFT every 2 weeks, 1 kidney function test every four weeks Full blood count (FBC) 1 every 6 weeks <u>Abiraterone subsequent months:</u> 1 outpatient visit every month LFT, kidney function test every four weeks FBC 1 every 6 weeks <u>Mitoxantrone:</u> 1 outpatient visit every 3 weeks LFT ,kidney function test every 3 weeks FBC, every 6 weeks <u>Prednisone:</u> 1 outpatient visit every 6 weeks LFT, kidney function test every 6 weeks FBC, every 6 weeks <u>All</u> CT; MRI; ECG; Ultrasound; Bone scan; 1 in 5% each every 6 weeks PSA: 1 every 6 weeks
Cabazitaxel MS, 2011 (134)	One chemotherapy administration per 3 weeks. Other frequencies CIC

Abbreviations: CIC: commercial in confidence; DOC; docetaxel; ER; emergency room; FBC: full blood count; HRU: health resource utilisation; LFT: liver function test; LOS: length of stay; MS: manufacturer submission; PC: prostate cancer; PLA: placebo; SRE: skeletal related event; ZOL: zoledronic acid.

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Using the methodology described in section 7.3.5, the values for resource utilisation were discussed with clinical experts. In particular the resource utilisation for regular monitoring as reported in the abiraterone manufacturer submission (80) was discussed with the experts, and modified according to the consensus at the advisory board (4). In addition, the included cost categories, the concomitant medication, the terminal treatment costs and the exclusion of additional hospitalisation costs were validated at the advisory boards (4) (70).

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

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[6] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Technology costs

The list price of enzalutamide is £2,734.67 for each 28 day pack (112 tablets of 40 mg). Astellas has agreed a PAS with the Department of Health, which is reflected in the base case of the health economic model. The PAS consists of a [redacted] discount, resulting in a price per pack of enzalutamide of [redacted]

Abiraterone is available with a list price of £2,930 for each 30 day pack (120 tablets of 250 mg). The manufacturer of abiraterone has agreed on a confidential PAS with the Department of Health. [redacted]

Monitoring

The monitoring requirements and frequency was based on the abiraterone STA (Table 38 MS (80)), and modified based on the experience of UK clinical experts (Table 61). According to UK clinical experts actively treating patients with mCRPC (4), it was highly unlikely that monitoring would be alternated between a clinical oncologist and a nurse specialist; therefore, the model assumes that all monitoring is performed by a clinical oncologist. As enzalutamide does not require the additional monitoring required for abiraterone (2), the monitoring frequency was estimated at once every four weeks in the first three months, and once every 8 weeks thereafter. Unit costs for routine monitoring are shown in Table 62.

Table 61: Medical Resource Utilisation for monitoring of mCRPC patients on treatment

Resource	Enzalutamide				BSC	
	First 3 months		Months 4+			
	Frequency (every X weeks)	% of pts	Frequency (every X weeks)	% of pts	Frequency (every X weeks)	% of pts
Outpatient visit consultant	4	100%	8	100%	8	100%
CT scan	4	5%	8	5%	8	5%
Radiographic/MRI scan	4	5%	8	5%	8	5%
ECG	4	5%	8	5%	8	5%
Ultrasound	4	5%	8	5%	8	5%
Bone scan	4	5%	8	5%	8	5%
Full blood count	4	100%	8	100%	8	100%
Liver function test	4	100%	8	100%	8	100%
Kidney function test	4	100%	8	100%	8	100%
PSA	4	100%	8	100%	8	100%
Cost (£) per 3 weeks	**141.81**		**70.90**		**70.90**	
Resource	**Abiraterone**					
	First 3 months		**Months 4+**			
	Frequency (every X weeks)	**% of pts**	**Frequency (every X weeks)**	**% of pts**		
Outpatient visit consultant	2	100%	4	100%		
CT scan	4	5%	8	5%		
Radiographic/MRI scan	4	5%	8	5%		
ECG	4	5%	8	5%		
Ultrasound	4	5%	8	5%		
Bone scan	4	5%	8	5%		
Full blood count	4	100%	8	100%		
Liver function test	2	100%	4	100%		
Kidney function test	4	100%	4	100%		
PSA	4	100%	8	100%		
Cost (£) per 3 weeks	**245.42**		**127.32**			

Abbreviations: BSC: best supportive care; CT: computed tomography; ECG: electrocardiogram; MRI: magnetic resonance imaging; PSA: prostate specific antigen

Table 62: Unit costs for routine monitoring

Resource	Cost (£)	Code	Source
Outpatient visit consultant	132.00	15.5	PSSRU 2012(33)
CT scan	104.97	DIAGIM_OP RA10Z	NHS reference costs 2011-2012(147)
Radiographic/MRI scan	199.34	DIAGIM_OP RA03Z	NHS reference costs 2011-2012(147)
ECG	145.15	OPROC EA47Z	NHS reference costs 2011-2012(147)
Ultrasound	51.27	DIAGIM_OP RA23Z	NHS reference costs 2011-2012(147)
Bone scan	185.51	DIAGIM_OP RA36Z	NHS reference costs 2011-2012(147)
Full blood count	3.09	DAPS DAP823	NHS reference costs 2011-2012(147)
Liver function test	6.15	DAPS DAP841	NHS reference costs 2011-2012(147). 5 tests required as reported in abiraterone manufacturer submission(80)
Kidney function test	12.30	DAPS DAP841	NHS reference costs 2011-2012(147). Assumed 10 tests, similar to abiraterone manufacturer submission(80)
PSA	1.23	DAPS DAP841	NHS reference costs 2011-2012(147).

Abbreviations: CT: computed tomography; ECG: electrocardiogram; MRI: magnetic resonance imaging; NHS: National Health Service; PSA: prostate specific antigen; PSSRU: Personal Social Services Research Unit.

Concomitant medication

Concomitant medication was based on the AFFIRM trial. In the health economic model, 6 concomitant medications have been included: anti-histamines, H2-antagonists, anti-emetic drugs, corticosteroids, granulocyte colongy-stimulating factors (G-CSFs) and bisphosphonates (Table 63). Apart from the need for all abiraterone patients to receive prednisolone, concomitant medication use in the abiraterone arm was assumed equal to concomitant use in the enzalutamide arm (as per AFFIRM). Dosing was taken from the British National Formulary (BNF 65) and costs were taken from eMit and BNF 65 (Table 64) (34).

Table 63: Use of concomitant medications

Commends	**% requiring concomitant treatment**		
	ENZ	**ABI**	**BSC**
Antihistamine	10%	10%	10%
H2-antagonist	52%	52%	52%
Anti-emetic	14%	14%	14%
Corticosteroid (prednisolone)	47%	100%	47%
G-CSF	0%	0%	0%
Biphosphonates	47%	47%	47%
Cost per 3 weeks (£)	**50.37**	**57.28**	**50.37**

Abbreviations: ABI: abiraterone; BSC: best supportive care; G-CSF: Granulocyte colony-stimulating factor; ENZ: enzalutamide.

Table 64: Unit costs associated with concomitant medication

Resource	**Cost per mg (£)**	**Dose (mg) per (3 week) cycle**	**Cost (£)/Cycle**	**Source**
Antihistamine (chlorphenamine) 4mg every 4-6 hours, assumed for 5 days each cycle	0.002	96	0.19	eMit 2013 (148)
H_2-antagonist (ranitidine) 150mg BD, assumed for 5 days each cycle	0.00006	1,500	0.09	eMit 2013 (148)
Anti-emetic (ondansetron) 4 mg every 12 hours for up to 5 days; max of 32mg/day	0.013	40	0.51	eMit 2013 (148)
Corticosteroid (prednisolone) twice daily oral 5 mg	0.0019	210	0.39	eMit 2013 (148)
G-CSF (filgrastim) 500,000 units/kg daily for up to 14 days	0.18 / mcg	300 mcg	52.71	BNF65 (34)
Bisphosphonates (zoledronic acid) 4mg infusion every 6 weeks	43.54	2	87.07	BNF65 (34); frequency according to abiraterone manufacturer submission to NICE (80)

Abbreviations: BD: twice daily; BNF: British National Formulary; G-CSF: granulocyte colony-stimulating factor; mg: milligram; mcg: microgram

A summary of the total treatment costs is shown in Table 65.

Table 65: Costs (£) per 3 week cycle in SDis

Items	ENZ (£)	ABI (£)	BSC (£)
Technology cost per 3 week cycle	[redacted]	[redacted]	0
Administration cost	0	0	0
Monitoring cost (Table 61)	142* 71**	245* 127**	71
Concomitant medication (Table 64)	41	42	41
Total	[redacted]	[redacted]	**112**

Abbreviations: ENZ: enzalutamide; BSC: best supportive care; ABI: abiraterone; * First three months; ** Subsequent months.

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

In addition to the treatment specific costs mentioned in section 7.5.5, the model includes costs for routine monitoring and medication in the PDis state, and costs for the terminal phase of life.

Medication in the PDis health state

Medication in the PDis state is assumed to consist only of the concomitant medication of the BSC arm (Table 63). As no active treatment is currently recommended in the UK for post-chemotherapy mCRPC patients after progression, no costs were included for active treatment.

Post study treatment was allowed in the AFFIRM study (Table 66). For purposes of the model, it has been assumed that this had no effect on OS. In reality, this is unlikely, and as significantly more patients in the placebo arm received post study treatment, this is likely to bias against enzalutamide in the analysis. As the impact of post study treatment cannot be excluded without increasing uncertainty, no adjustments have been made to the survival curves to account for this. As no reliable data is available on the duration of post study treatment and on post study treatment in the COU-AA-301 study, no costs were included for post-study treatment in the base case.

A scenario analysis is included to show the impact of including the costs for post study treatment.

Table 66: Post study treatment for AFFIRM patients

Post study treatment	Enzalutamide arm	BSC arm
Abiraterone	20.90%	24.30%
Cabazitaxel	9.80%	13.80%
Docetaxel	8.50%	14.30%
Mitoxantrone	2.60%	8.00%
Total	**41.80%**	**60.40%**

Abbreviations: BSC: best supportive care.

Monitoring in the PDis health state

The monitoring required for patients in the PDis health state was assumed to be the same as the pre-progression BSC monitoring. The frequency and costs are summarised in Table 61 and Table 62 (section 7.5.5). The average monitoring cost per cycle is £70.90.

Terminal Treatment costs

As resource use and associated costs usually show a peak in the months immediately prior to death for patients with PC (153), a terminal care cost for a patient's last months has been considered in the model. Following the estimates in the abiraterone submission (80), patients were assumed to receive home care by a nurse twice per day (assumed once during the day and once in the evening), for 14 days each month during the last 3 months of life. Fifty percent of patients typically die in a hospital (palliative care unit) and 50% die in a hospice centre. The duration of stay in each of these locations was assumed to be 14 days. Costs for a one hour home care visit in both a day and evening settings (averages to £18.50 per hour) were obtained from the Personal Social Services Research Unit (PSSRU) 2012 (33). Daily cost of both a hospice centre and a palliative care unit of a hospital was £112.75, based on the NHS Reference costs. This results in a terminal treatment cost of £3,133 per patient, which is applied in the model as a transition cost to the death state.

Table 67: List of health states and associated costs in the economic model

Health states	Items	Value (£)	Reference in submission
Stable Disease	All costs are treatment specific	-	Section 7.5.5
Progressed Disease (£/cycle)	Monitoring	71	Section 7.5.5
	BSC	41	Section 7.5.5
Dead (£, transition cost to de dead state)	Terminal Treatment	3,133	PSSRU 2012 (33), NHS Reference costs 2011-2012 (147)

Abbreviations: BSC: best supportive care; NHS: National Health Service; PSSRU: Personal Social Services Research Unit.

Hospitalisations

No costs for hospitalisations were included in the base case. UK clinical experts confirmed that all hospitalisations would have been captured by AEs, SREs and terminal treatment costs.

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Assumptions regarding HRU costs associated with AEs included in the model were presented in detail in the cabazitaxel STA (29). The cost of these AEs was calculated based on this HRU, applying the updated NHS prices (147). For AEs not reported in the cabazitaxel submission, costs were taken from the abiraterone ERG report (135).

Table 68: Costs associated with AEs (grade ≥ 3)

AE	Cost (£)	Lower quartile cost (£)	Upper quartile cost (£)	Reference
Abdominal pain	697	523	871	NHS reference costs 2011-2012 Total HRGs: PA29Z
Anaemia	1,249	968	1,454	NHS reference costs 2011-2012; NEI_L; HRG code: SA04F Iron Deficiency Anaemia without CC, non-elective inpatient (long-stay),
Arthralgia	101	79	146	NHS Reference Costs 2011-2012; CLFUMFF; HRG code: 191, Pain management, multi-professional non-admitted face-to-face
Asthenia	12	9	15	NICE ERG report abiraterone, table 24, p. 64. IQR assumed ±25%
Back pain	460	275	532	NHS Reference Costs 2010-2011, NEI_S HC32C
Bone pain	460	275	532	NHS Reference Costs 2010-2011, NEI_S HC32C
Dehydration	1,569	1,212	1,764	NHS reference costs 2011-2012 ; NEI_L; HRG code: average of KC05B and E
Diarrhoea	606	352	815	NHS reference costs 2011-2012 ; NEI_L; HRG code: FZ43C
Dyspnoea	0	-	-	NICE ERG report abiraterone, table 24, p. 64
Fatigue	12	9	15	NICE ERG report abiraterone, table 24, p. 64. IQR assumed ±25%
Febrile neutropenia	4,384	2,739	5,458	NHS reference costs 2011-2012 ; NEI_L; HRG code: PA45Z
Hypertension	552	294	585	NHS reference costs 2011-2012 ; NEI_S; HRG code: EB04I
Hypokalaemia	163	46	159	NHS reference costs 2011-2012; HICOSTDRUGS_OP; HRG code: XD26Z
Leukopenia	237	127	262	Costs assumed to be equal to neutropenia NHS reference costs 2011-2012;

AE	Cost (£)	Lower quartile cost (£)	Upper quartile cost (£)	Reference
				HICOSTDRUGS_APC; HRG code: XD25Z
Nausea	606	352	815	Costs assumed to be equal to diarrhoea NHS reference costs 2011-2012 ; NEI_L; HRG code: FZ43C
Neutropenia	237	127	262	NHS reference costs 2011-2012; HICOSTDRUGS_APC; HRG code: XD25Z
Oedema Peripheral/Fluid retention	914	686	1,143	NICE ERG report abiraterone, table 24, p. 64
Pain	101	79	146	NHS Reference Costs 2011-2012; CLFUMFF; HRG code: 191, Pain management, multi-professional non-admitted face-to-face
Pain in extremity	101	79	146	Costs assumed to be equal to arthralgia/pain NHS Reference Costs 2011-2012; CLFUMFF; HRG code: 191, Pain management, multi-professional non-admitted face-to-face
Pulmonary embolism	1,849	1,449	2,094	NHS reference costs 2011-2012; NEI_L; HRG code: average of DZ09A/B/C
Seizure	1,743	1,282	1,884	NHS reference costs 2011-2012; NEI_L; HRG code: AA26A
Thrombocytopaenia	570	307	574	NHS reference costs 2011-2012; NEI_S; HRG code: SA12F
Vomiting	606	352	815	Costs assumed to be equal to diarrhoea NHS reference costs 2011-2012 ; NEI_L; HRG code: FZ43C

Abbreviations: AE: adverse event; HRG: healthcare resource group; NHS: National Health Service.

Costs for SREs were included in the health economic model. The costing was derived from Botteman 2011 (121), and recalculated using the 2011-2012 NHS Reference costs (147).

Table 69: Costs for SREs in the model

SRE	Cost (£)	Lower quartile unit cost (£)	Upper quartile unit cost (£)	Reference
Spinal Cord Compression	6,047	2,640	7,570	HRG HC28b–Spinal Cord conditions with CC. NHS Trusts Non-Elective Inpatient (Long Stay) HRG Data
Pathological Bone Fracture	5,042	3,828	5,777	Average of HRG code HD39C, HD39B, HD39A weighted by the number of treatment in each HRG. Plus for patients with non-vertebral fractures (assumed 50%) the cost of outpatient care for long-bone fractures for 3 months (£5,073), assumed to be incurred by 61% of patients with non-vertebral fractures (total of £5,073 * 61% = £3,095) (based on Ross et al. set of assumptions)

SRE	Cost (£)	Lower quartile unit cost (£)	Upper quartile unit cost (£)	Reference
Radiation to the Bone	116	90	139	Average of HRG code SC21Z, SC22Z, SC23Z, SC24Z, SC25Z, SC26Z, SC27Z, SC28Z,b weighted by the number of treatment in each HRG. NHS National Schedule of Reference Costs, Radiotherapy Treatment: Outpatient
Surgery to the Bone	3,888	2,456	4,689	HRG HD39A–Pathological Fractures or Malignancy of Bone and Connective Tissue with Major CC. NHS Trusts Non-Elective Inpatient (Long Stay) HRG Data, 2010-2011

Abbreviations: HRG: healthcare resource group; NHS: National Health Service; SRE: skeletal related event

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

None

7.6 *Sensitivity analysis*

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated,

including a description of the alternative scenarios in the analysis.

The key uncertainties around structural assumptions relate to:

- The parametric fitting of the OS and PFS data;
- Limitations of the ITC against abiraterone;
- How progression in the model is defined;
- Uncertainty around the mapping and the health state utilities for SDis and PDis;
- Potential double counting of disutilities for AEs and SREs;
- Uncertainty around the abiraterone PAS.

The scenario analyses conducted to investigate these uncertainties are described in Table 70. The methods to perform each analysis are provided in appendix 16, section 10.16.

Table 70: Scenario analyses

	Analysis	Rationale / methods
1	Vary time horizon to 4, 6 and 8 years	NICE reference case
2	Vary discount rate for costs and effects to 0%, 1.5% and 5%	NICE reference case
3	Use a fixed HR for abiraterone OS	The proportionality was not met, and the time dependent HR provided a better fit according to Figure 19. This scenario shows the impact of a scenario in which the actual reported HR is used.
4	Apply an ITC on mean OS to the abiraterone arm	As an alternative to the method shown above, an ITC on mean OS has been suggested. Weibull curves fit to the individual arms of the COU-AA-301 study were used to calculate mean OS. An ITC was performed using the AFFIRM mean OS (from a Weibull distribution). The indirect estimate of mean OS was used to derive Weibull parameters according to the methods described in section 7.1.3.1.3.1 of the ERG report on cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer (154).
5	Use Log Logistic model for OS reference curve (AFFIRM placebo)	Although the Weibull parametric fit resulted in the most plausible extrapolation according to clinical opinion, the Log Logistic model had the best statistical fit.
6	Use mPFS instead of TTD for PFS	Progression according to the modified criteria may be considered by some to be more reflective of clinical progression. Curves were fit to the AFFIRM mPFS data. For enzalutamide, an individual Weibull curve was used, as the proportionality of hazards was not met. For abiraterone the HR for mPFS reported in the abiraterone appraisal consultation document (ACD) was used (5).
7	Use Log Logistic model for PFS reference curve (AFFIRM placebo)	Although the Weibull parametric fit resulted in the most plausible extrapolation according to clinical opinion, the Log Logistic model had the best statistical fit.
8	No disutility for AEs	There may be some double counting between AEs and the on treatment benefit analysed in AFFIRM. However, most AEs have a duration < 2 weeks, whereas QoL was measured every 12 weeks. It is therefore unlikely that many AEs were captured in

	Analysis	Rationale / methods
		the on treatment utility benefit. This analysis shows the impact of not applying AE disutilities.
9	No disutility for SREs	There may be some double counting between the effect measured for progression and the disutility for SREs. This analysis shows the impact of not applying a utility decrement for SREs.
10	No disutility for AEs or SREs	Reasons stated for scenario 10 and 11.
11	Utility values for health states used in abiraterone submission	Test the impact of alternative data sources
12	Use mapped utility values for baseline and progressed disease utility	Mapped utility values were available for more patients than the EQ-5D. This analysis includes the mapped baseline utility. In addition the impact of progression, as derived by the analysis on mapped utilities is included in this analysis.
13	Exclude on treatment utility gain	Show the impact of the improved utility
14	Same on treatment utility gain for enzalutamide and abiraterone	A higher on treatment utility gain was found for enzalutamide than for abiraterone. The analysis uses the enzalutamide on treatment utility gain for abiraterone.
15	Assume routine visits are alternated between nurse and consultant	Uncertainty around monitoring frequency in clinical practice.
16	Include active treatment post-progression	Although no active treatment is available in the UK post progression, a proportion of patients in both arms in AFFIRM received post study treatment (section 7.5.6). In this scenario, costs were included according to the percentage of patients receiving post study treatment in AFFIRM. The same costs were assumed for abiraterone as for enzalutamide.

Abbreviations: AE: adverse events; EQ-5D: European quality of life five-domain scale; ITC: indirect treatment comparison; mPFS: modified progression free survival; PFS: progression free survival; OS: overall survival; SRE: skeletal related events.

In addition to the scenarios mentioned above, one additional scenario was run for the comparison of enzalutamide with abiraterone. Astellas received feedback from some clinical experts that they believe enzalutamide and abiraterone have an equal impact on PFS and OS. Although the ITC revealed a significant difference on rPFS and a trend towards longer OS, some experts believe any differences may be explained by differences in the patient population. To show the impact of such a scenario on the cost-effectiveness, a cost-minimisation analysis was run assuming the enzalutamide OS and PFS curves for abiraterone. This scenario conservatively assumed the same AE and SRE rates, and the same on treatment utility gain for abiraterone and enzalutamide.

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

All model inputs were varied in univariate sensitivity analyses. Although most parameters were varied over their lower and upper 95% confidence level, some values were varied over extreme ranges to show the impact of the parameter (i.e., discount rate, time horizon). An overview of those parameters is shown in appendix 17, section 10.17 the distribution of all other parameters is shown in Table 53 (section 7.3.6).

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

Probabilistic Sensitivity Analysis was performed on the base case using 10,000 Monte Carlo simulations. All distributions for the probabilistic analysis are shown in section 7.3.6. The results of the probabilistic analysis are shown in 7.7.8.

7.7 *Results*

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

Link between clinical- and cost-effectiveness results.

Costs, QALYs and incremental cost per QALY.

Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.

A statement as to whether the results are based on a PSA.

Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.

Scatter plots on cost-effectiveness quadrants.

A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table 71 shows that the median OS in the model is close to the reported literature values for enzalutamide and BSC. Although the median PFS is equal to the median time to treatment discontinuation for enzalutamide, the median for BSC is slightly longer in the model. This is a result of the shape of the Kaplan Meier curve for treatment discontinuation. However, the mean treatment duration in AFFIRM is close to the modelled treatment duration ([redacted]), thereby confirming the validity of the modelled curve.

Table 71: Summary of model results compared with clinical data

Outcome	Clinical trial result (Months, Median [95% CI])	Model result (Months, Median [95% CI])
BSC		
TTD	[redacted]	[redacted]
OS	13.31 (11.24; 14.19)	13.0
Enzalutamide		
TTD	[redacted]	[redacted]
OS	17.84 (16.72; 18.83)	17.5

Abbreviations: BSC: best supportive care; CI: confidence interval; TTD: time to treatment discontinuation; OS: overall survival.

Abiraterone was implemented in the model through an indirect comparison using the placebo arm in AFFIRM as the reference curve. Comparing the model results with those from the COU-AA-301 trial would therefore equate to a naïve comparison. The results in Table 72 are therefore only presented for face validity.

Table 72: Summary of model results compared with clinical data of treatments compared using indirect comparison

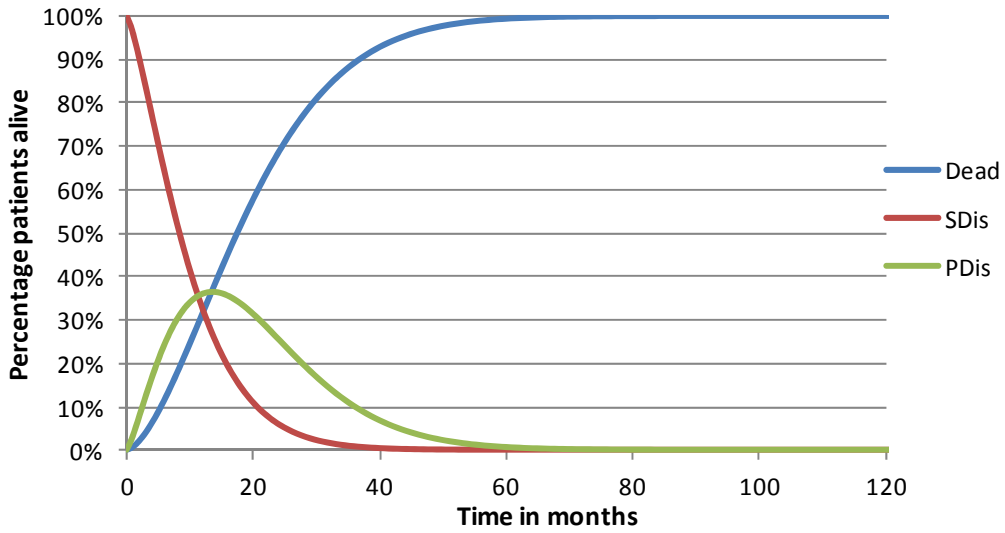
Outcome	Clinical trial result (Months, Median [95% CI])	Model result (Months, Median [95% CI])
Abiraterone		
TTD	7.4	6.1
OS	15.8 (14·8–17.0)	15.2

Abbreviations: CI: confidence interval; TTD: time to treatment discontinuation; OS: overall survival.

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

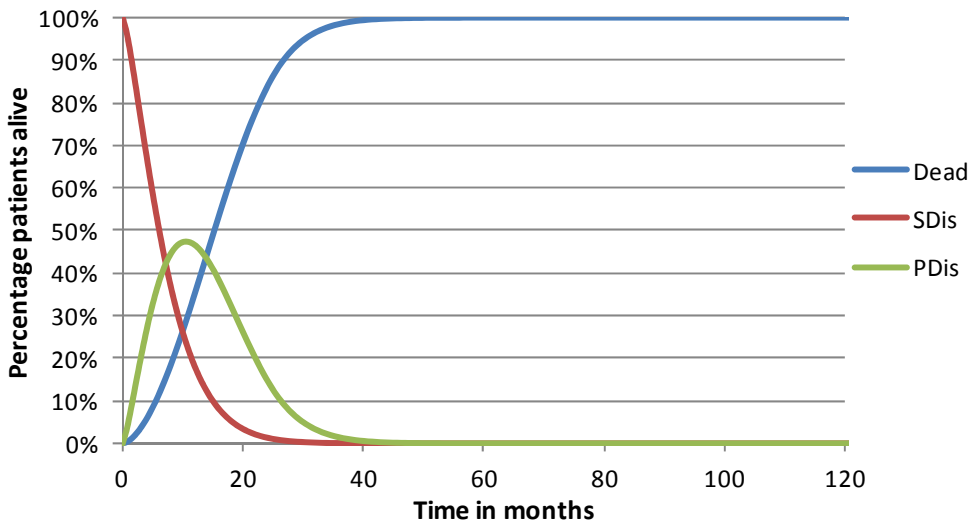
Markov traces for enzalutamide and its comparators are provided in Figure 22 to Figure 24. Patients treated with enzalutamide remain longer in the SDis health state than patients on abiraterone or BSC. The benefit of enzalutamide is also illustrated by the longer time to death.

Figure 22: Markov trace for enzalutamide



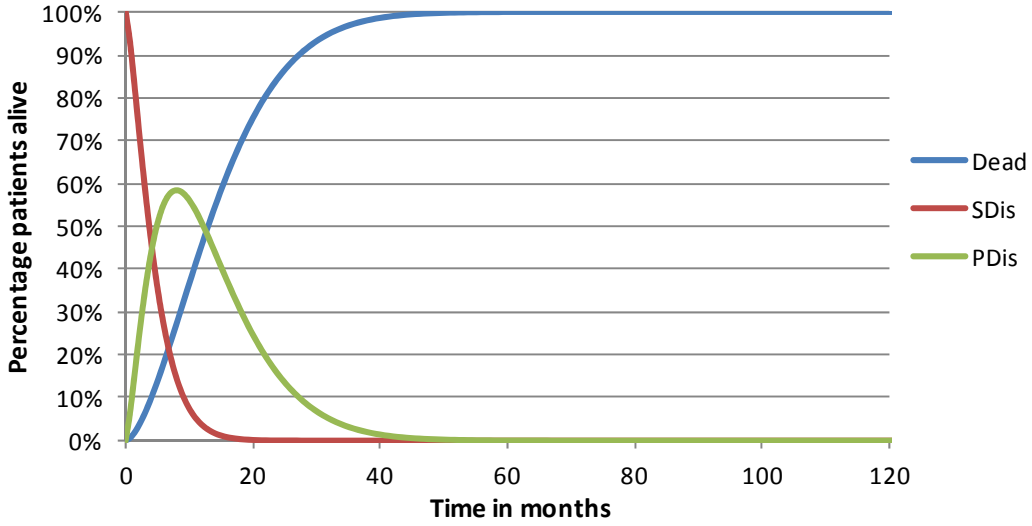
Abbreviations: PDis: progressive disease; SDis: stable disease.

Figure 23: Markov trace for abiraterone



Abbreviations: PDis: progressive disease; SDis: stable disease.

Figure 24: Markov trace for BSC



Abbreviations: PDis: progressive disease; SDis: stable disease.

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

QALY gain over time for all comparators is shown in Figure 25 to Figure 27. QALYs are accrued in the SDis health state (red line) and the PDis health state (green line). QALY decrements due to AEs and SREs are also shown in the graphs (orange and purple line). The total QALYs gained over time is shown by the blue line. Please note that the QALY over time in these graphs is not discounted.

In line with patients treated with enzalutamide having a longer time in SDis, and a higher on treatment utility than patients treated with the comparators, enzalutamide results in more QALYs gained in the SDis health state. As the overall incidence and duration of the AEs and SREs is low, their impact is relatively small. Enzalutamide results in the highest cumulative QALYs as a result of longer OS and PFS, and due to the higher on treatment utility gain.

Figure 25: QALY gain over time for enzalutamide

Abbreviations: AE: adverse event; PDis: progressive disease; SDis: stable disease; SRE: skeletal related event.

Figure 26: QALY gain over time for abiraterone

Abbreviations: AE: adverse event; PDis: progressive disease; SDis: stable disease; SRE: skeletal related event.

Figure 27: QALY gain over time for BSC

[redacted]

Abbreviations: AE: adverse event; PDis: progressive disease; SDis: stable disease; SRE: skeletal related event.

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Table 73: Model outputs by clinical outcomes - enzalutamide

Outcome	LY	QALY	Cost (£)
SDis	[redacted]	[redacted]	[redacted]
PDis	[redacted]	[redacted]	4,427
AEs	-	[redacted]	254
SREs	-	[redacted]	951
Total (Overall survival)	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; LY: life year; PDis: progressive disease; SDis: stable disease; SRE: skeletal related event; QALY: quality-adjusted life year.

Table 74: Model outputs by clinical outcomes - abiraterone

Outcome	LY	QALY	Cost (£)
SDis	[redacted]	[redacted]	[redacted]
PDis	[redacted]	[redacted]	4,321
AEs	-	[redacted]	292
SREs	-	[redacted]	979
Total (Overall survival)	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; LY: life year; PDis: progressive disease; SDis: stable disease; SRE: skeletal related event; QALY: quality-adjusted life year.

Table 75: Model outputs by clinical outcomes - BSC

Outcome	LY	QALY	Cost (£)
SDis	[redacted]	[redacted]	[redacted]
PDis	[redacted]	[redacted]	4,583
AEs	-	[redacted]	235
SREs	-	[redacted]	1,406
Total (Overall survival)	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; LY: life year; PDis: progressive disease; SDis: stable disease; SRE: skeletal related event; QALY: quality-adjusted life year.

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 76: Summary of QALY gain by health state - enzalutamide vs. abiraterone

Health state	QALY ENZ	QALY ABI	Increment	Absolute increment	% absolute increment
SDis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SREs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABI:, abiraterone; AE: adverse event; ENZ: enzalutamide; LY: life years; PDis: progressive disease; SDis: stable disease; SRE: skeletal related event; QALY: quality-adjusted life year

Table 77: Summary of QALY gain by health state - enzalutamide vs. BSC

Health state	QALY ENZ	QALY BSC	Increment	Absolute increment	% absolute increment
SDis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SREs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; ENZ: enzalutamide; LY: life year; PDis: progressed disease; SDis: stable disease; SRE: skeletal related event; QALY: quality-adjusted life year.

Table 78: Summary of costs by health state - enzalutamide vs. abiraterone

Health state	Cost ENZ (£)	Cost ABI (£)	Increment (£)	Absolute increment (£)	% absolute increment
SDis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDis	4,427	4,321	106	106	[redacted]
AEs	254	292	-38	38	[redacted]
SREs	951	979	-28	28	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABI: abiraterone; AE: adverse event; ENZ: enzalutamide; PDis: progressive disease; SDis: stable disease; SRE: skeletal related event

Table 79: Summary of costs by health state - enzalutamide vs. BSC

Health state	Cost ENZ (£)	Cost BSC (£)	Increment (£)	Absolute increment (£)	% absolute increment
SDis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDis	4,427	4,583	-156	156	[redacted]
AEs	254	235	19	19	[redacted]
SREs	951	1,406	-455	455	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; ENZ: enzalutamide; PDis: progressive disease; SDis: stable disease; SRE: skeletal related event

Table 80: Summary of predicted resource use by category of cost - enzalutamide vs. abiraterone

Item	Cost ENZ (£)	Cost ABI (£)	Increment (£)	Absolute increment (£)	% absolute increment
Active treatment - SDis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant medication - SDis	614	457	157	157	[redacted]
Medication - PDis	541	490	51	51	[redacted]
Routine visits - SDis	1,309	1,803	-494	494	[redacted]
Routine visits - PDis	926	840	87	87	[redacted]
AE	254	292	-38	38	[redacted]
SRE	951	979	-28	28	[redacted]
Terminal care	2,960	2,991	-31	31	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABI: abiraterone; AE: adverse event; ENZ: enzalutamide; PDis: progressive disease; SDis: stable disease; SRE: skeletal related event

Table 81: Summary of predicted resource use by category of cost - enzalutamide vs. BSC

Item	Cost ENZ (£)	Cost BSC (£)	Increment (£)	Absolute increment (£)	% absolute increment
Active treatment - SDis	[redacted]	0	[redacted]	[redacted]	[redacted]
Concomitant medication - SDis	614	288	326	326	[redacted]
Medication - PDis	541	583	-42	42	[redacted]
Routine visits - SDis	1,309	457	852	852	[redacted]
Routine visits - PDis	926	998	-72	72	[redacted]
AE	254	235	19	19	[redacted]
SRE	951	1,406	-455	455	[redacted]
Terminal care	2,960	3,002	-42	42	[redacted]
Total	[redacted]	6,970	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; ENZ: enzalutamide; PDis: progressive disease; SDis: stable disease; SRE: skeletal related event

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental

analysis ranking technologies in terms of dominance and extended dominance.

The results of the base case analysis are presented in Table 82 below. Abiraterone has an ICER of £102,751 against BSC. Enzalutamide has an ICER of £14,795 against abiraterone and £43,587 against baseline (BSC). A comparison of these results with those from other economic evaluations is provided in section 7.10.1.

Table 82: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER versus baseline (QALYs)	ICER incremental analysis (QALYs)
A: BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Not applicable	Not applicable
B: Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	102,751	102,751
C: Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,587	14,795

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; QALYs: quality-adjusted life years; Ext. dom.: extended dominance; ICER incremental analysis: compares the treatment in the current row with the last non-dominated treatment option

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Figure 28: Tornado diagram showing all parameters with a minimum ICER spread of £1,000 on enzalutamide vs. abiraterone

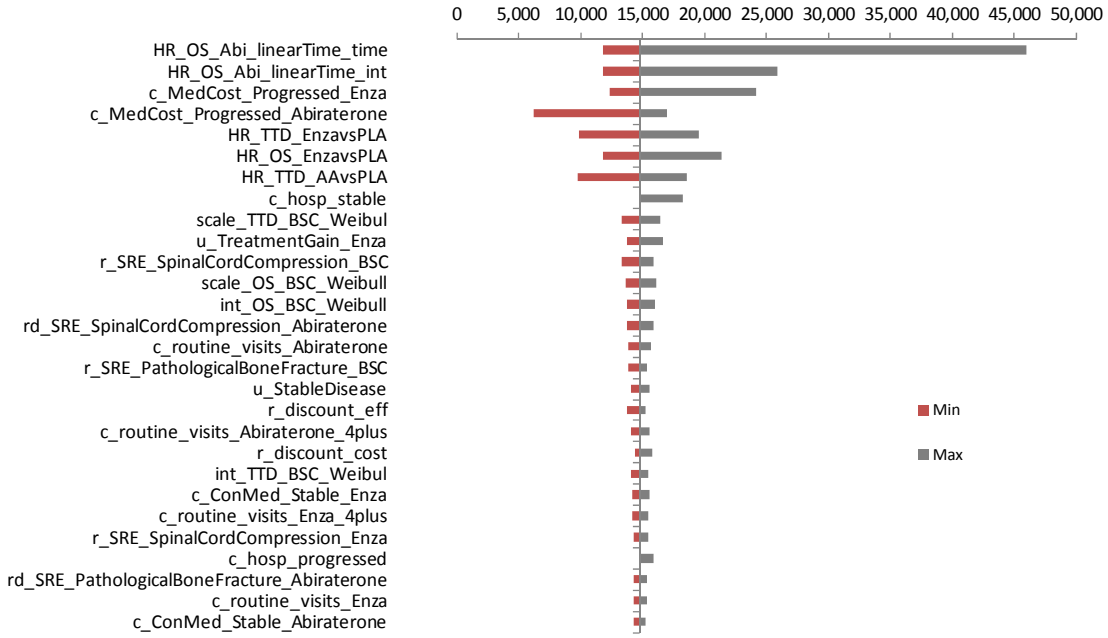


Table 83: Description of ten most influential parameters in model for comparison enzalutamide vs. abiraterone

Name	Description	Model Input [low;high]	ICER low; high (£/QALY)
Base Case			**14,795**
HR_OS_Abi_linearTime_time	Intercept from the linear vs. Time model to calculate the Abiraterone OS HR	0.039 [0.012; 0.067]	46,022; 11,843
HR_OS_Abi_linearTime_int	Intercept from the linear vs. Time model to calculate the Abiraterone OS HR	-0.651 [-0.955; -0.348]	25898; 11,801
c_MedCost_Progressed_Enza	Medication costs incurred by patients who moved to the progressed disease health state after enzalutamide treatment	41.42 [0.00; 200.00]	12336; 24,209
c_MedCost_Progressed_Abiraterone	Medication costs incurred by patients who moved to the progressed disease health state after abiraterone treatment	41.42 [0.00; 200.00]	17,023; 6,262
HR_TTD_EnzavsPLA	HR of TTD for enzalutamide vs. Placebo	[redacted]	19,602; 9,868
HR_OS_EnzavsPLA	HR overall survival for enzalutamide vs. placebo as per AFFIRM results	0.618 [0.523; 0.730]	11,821; 21,379
HR_TTD_AAvsPLA	HR TTD of abiraterone applied directly to the survival curve of placebo as modelled from AFFIRM data	0.520 [0.444; 0.600]	9,753; 18,635
c_hosp_stable	3-weekly unscheduled hospitalisation costs for patients in stable disease	0.00 [0.00; 200.00]	14,795; 18,294
scale_TTD_BSC_Weibul	Scale of TTD Weibull model for BSC	[redacted]	13,326; 16,488
u_TreatmentGain_Enza	Treatment gain of enzalutamide over BSC	[redacted]	16,666; 13,765

*Please note that the impact of correlated parameters (e.g. HR_OS_Abi_linearTime_time) is actually smaller than shown here, as the intercept is not varied at the same time.
Abbreviations: BSC; best supportive care; HR: hazard ratio; OS: overall survival; TTD: time to treatment discontinuation.

Figure 29: Tornado diagram showing all parameters with a minimum ICER spread of £1,000 on enzalutamide vs. BSC

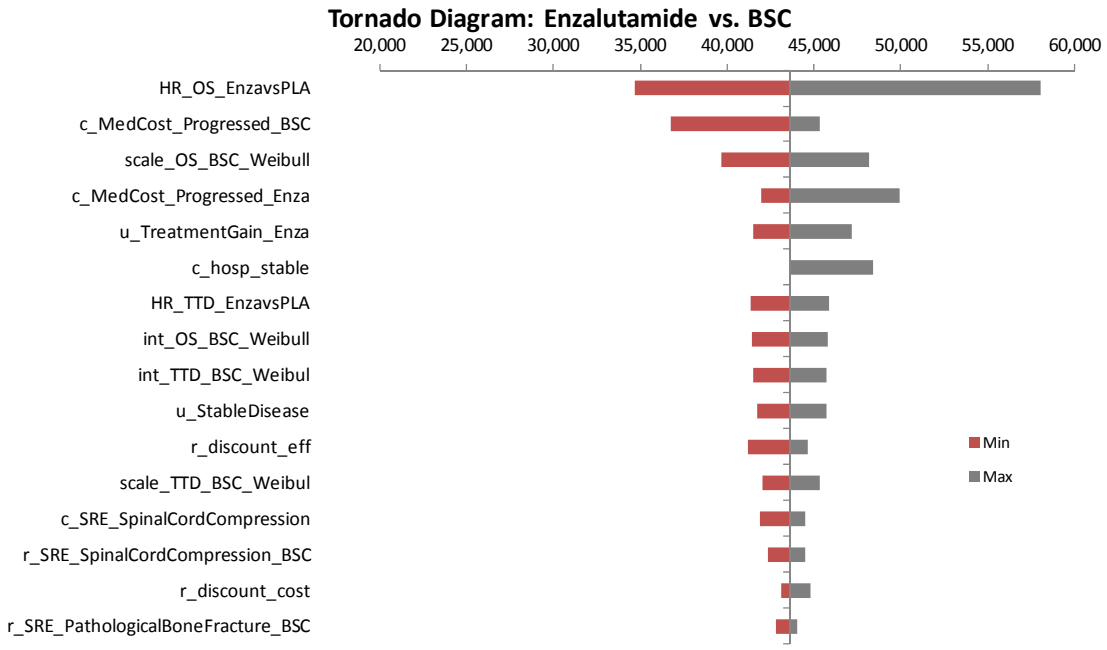


Table 84: Description of ten most influential parameters in model for comparison enzalutamide vs. BSC

Name	Description	Model Input [low; high]	ICER low; high (£/QALY)
Base Case			**43,587**
HR_OS_EnzavsPLA	HR overall survival for enzalutamide vs. placebo as per AFFIRM results	0.618 [0.523; 0.730]	34,692; 58,042
c_MedCost_Progressed_BSC	Medication costs incurred by patients who moved to the progressed disease health state on best supportive care	41.42 [0.00; 200.00]	45,369; 36,764
scale_OS_BSC_Weibull	Scale of OS Weibull model for BSC	[redacted]	48,127; 39,660
c_MedCost_Progressed_Enza	Medication costs incurred by patients who moved to the progressed disease health state after enzalutamide treatment	41.42 [0.00; 200.00]	41,933; 49,920
u_TreatmentGain_Enza	Treatment gain of enzalutamide over BSC	[redacted]	47,148; 41,498
c_hosp_stable	3-weekly unscheduled hospitalisation costs for patients in stable disease	0.00 [0.00; 200.00]	43,587; 48,399
HR_TTD_EnzavsPLA	HR of TTD for enzalutamide vs. Placebo	[redacted]	45,834; 41,363
int_OS_BSC_Weibull	Intercept of OS Weibull model for BSC	[redacted]	45,811; 41,448
int_TTD_BSC_Weibul	Intercept of TTD Weibull model for BSC	[redacted]	41,502; 45,746
u_StableDisease	Utility of being in the stable disease health state	[redacted]	45,730; 41,697

Abbreviations: BSC; best supportive care; HR: hazard ratio; OS: overall survival; TTD: time to treatment discontinuation.

7.7.8 Please present the results of a probabilistic sensitivity analysis, and include scatter plots and cost-effectiveness acceptability curves.

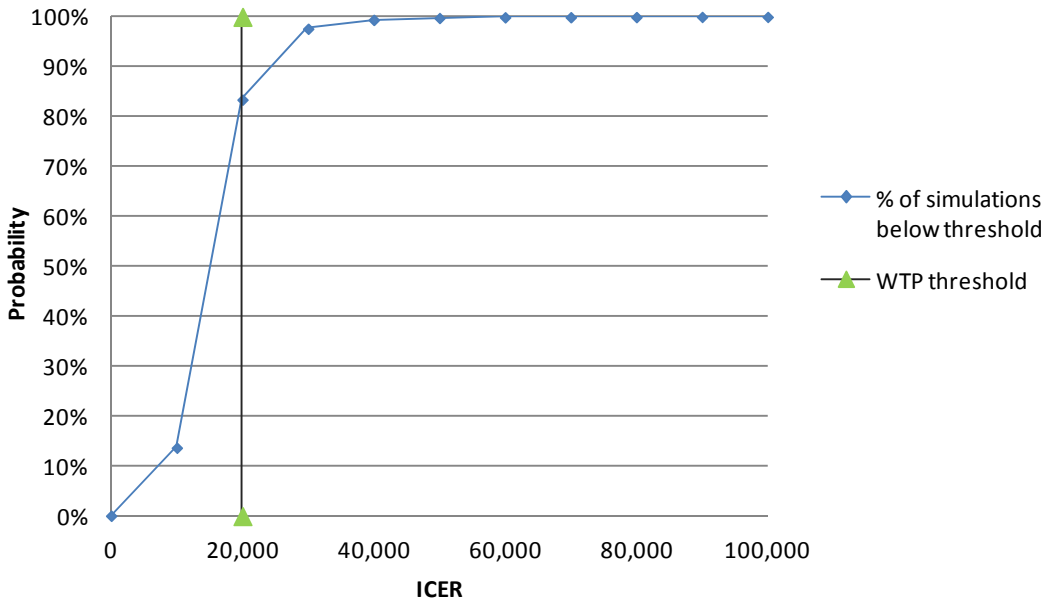
Scatter plots and cost-effectiveness acceptability curves (CEAC) are shown in Figure 30 to Figure 33. A summary of the Probabilistic Sensitivity Analysis results, and a comparison with the deterministic results is provided in Table 86 and Table 87. Willingness to pay (WTP) thresholds are shown in each curve; a WTP of 50,000 £/QALY is shown for comparison with BSC due to the applicability of the end of life criteria (section 7.10.4), and a WTP of £20,000 £/QALY is shown for comparison with abiraterone. The probability of being cost-effective at different WTP thresholds is shown in Table 85.

Figure 30: Results of 10,000 runs - enzalutamide vs. abiraterone

[redacted]

Abbreviations: QALY: quality adjusted life year; WTP: willingness to pay.

Figure 31: CEAC enzalutamide vs. abiraterone



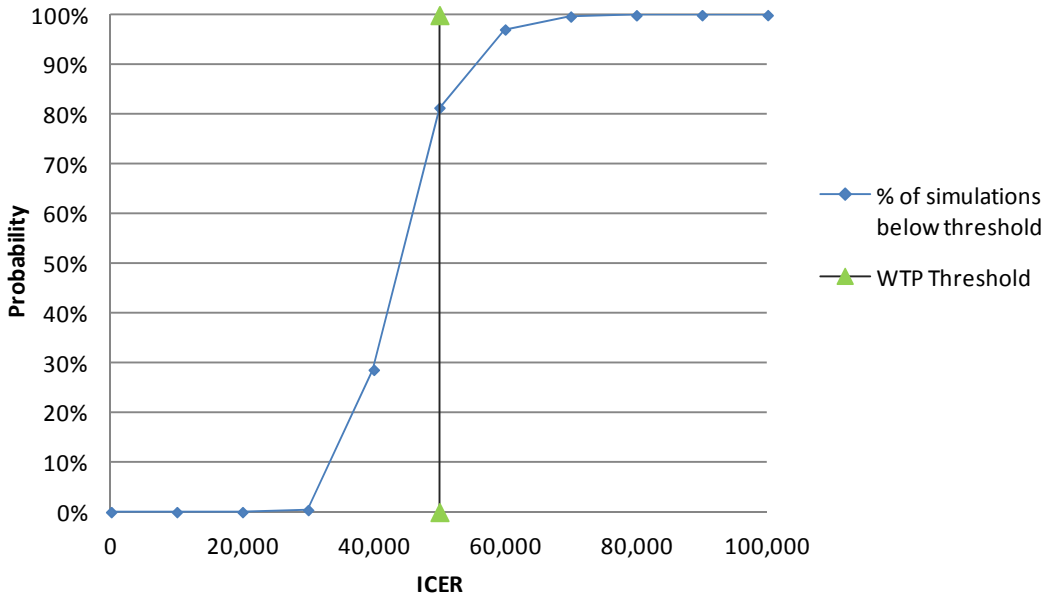
Abbreviations: ICER: incremental cost-effectiveness ratio; WTP: willingness to pay.

Figure 32: Results of 10,000 runs - enzalutamide vs. BSC

[redacted]

Abbreviations: BSC: best supportive care; QALY: quality adjusted life year; WTP: willingness to pay.

Figure 33: CEAC enzalutamide vs. BSC



Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; WTP: willingness to pay.

Table 85: Probability of being cost effective for all comparisons

WTP (£/QALY)	Probability of enzalutamide being cost effective against	
	BSC	ABI
20,000		83%
30,000		98%
50,000	81%	100%

Abbreviations: ABI: abiraterone; BSC: Best Supportive Care; WTP: Willingness to pay.

Table 86: Summary of probabilistic sensitivity analysis results – enzalutamide vs. abiraterone

	Enzalutamide		Abiraterone		Incremental		
	Costs	QALYs	Costs	QALYs	Costs	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,795
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,576
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,762
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,690
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,004
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	40,908
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,921

Abbreviations: LCL: lower confidence level; UCL: upper confidence level; PSA: probabilistic sensitivity analysis; QALY: quality adjusted life year.

Table 87: Summary of probabilistic sensitivity analysis results – enzalutamide vs. BSC

	Enzalutamide		BSC		Incremental		
	Costs	QALYs	Costs	QALYs	Costs	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,587
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,239
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,048
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	54,009
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,649
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	61,606
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,437

Abbreviations: BSC: best supportive care; LCL: lower confidence level; UCL: upper confidence level; PSA: probabilistic sensitivity analysis; QALY: quality adjusted life year.

7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

The results of the scenario analyses are shown in Table 88, the rationale for each analysis is described in Table 70 and the methods are described in appendix 16, section 10.16.

Table 88: Results of scenario analyses

	Analysis	ICER Enzalutamide vs. Abiraterone (£)	ICER Enzalutamide vs. BSC (£)
	Base Case	**14,795**	**43,587**
1	Time Horizon 4 years	14,828	44,469
	Time Horizon 6 years	14,793	43,611
	Time Horizon 8 years	14,795	43,587
2	Discount rate costs and effects – 0%	14,718	42,343
	Discount rate costs and effects – 1.5%	14,752	42,879
	Discount rate costs and effects – 5%	14,827	44,113
3	Use a fixed HR for abiraterone OS	19,972	43,587
4	Apply on ITC on mean OS to the abiraterone arm	18,034	43,587
5	Use Log Logistic model for OS reference curve (AFFIRM placebo)	8,899	25,623
6	Use mPFS instead of TTD for PFS	13,476	43,396
7	Use Log Logistic model for PFS reference curve (AFFIRM placebo)	21,215	47,807
8	No disutility for AEs	14,783	43,540
9	No disutility for SREs	14,801	43,802
10	No disutility for AEs or SREs	14,789	43,754
11	Utility values for health states used in abiraterone CVZ submission	12,882	38,399
	Pre-progression value of 0.80 post-progression of 0.50	13,702	37,147
12	Use mapped utility values for baseline ([redacted]) and progressed disease (decrement of [redacted]) utility	14,421	43,036
13	Exclude on treatment utility gain	16,720	51,343
14	Same on treatment utility gain for enzalutamide and abiraterone	15,652	43,587
15	Assume routine visits are alternated between nurse and consultant	15,494	43,026
16	Include active treatment costs post-progression	12,920	36,987

Abbreviations: AE: adverse events; EQ-5D: European quality of life five-domain scale; ICER: incremental cost effectiveness ratio; ITC: indirect treatment comparison; mPFS: modified progression free survival; PFS: progression free survival; OS: overall survival; SRE: skeletal related events.

In addition to the scenarios described above, one additional analysis will be described in more detail.

As some clinical experts believe enzalutamide and abiraterone have an equal impact on PFS and OS, a cost-minimisation analysis was run assuming the enzalutamide OS and PFS curves for abiraterone. This scenario conservatively assumed the same AE and SRE rates, and the same on treatment utility gain for abiraterone and enzalutamide.

As shown in Table 89, both treatments now have the same technology acquisition costs. However, as there is still a difference in the requirement for steroids and in the monitoring frequency, the total costs are lower for enzalutamide leading to cost

savings of £1,007. As both treatments result in the same LYs and QALYs, the enzalutamide arm is less costly and as effective as abiraterone.

Table 89: Results of cost-minimisation scenario

	Enzalutamide	Abiraterone
Technology acquisition cost	13,676	13,676
Other costs	7,555	8,561
Total costs	21,231	22,238
Difference in total costs	-	-1,007
LYG	1.575	1.575
LYG difference	-	0.000
QALYS	1.063	1.063
QALY difference	-	0.000
ICER	-	Dominant

7.7.10 What were the main findings of each of the sensitivity analyses?

As shown in section 7.7.8, enzalutamide has a high probability (83%) of being cost-effective against abiraterone at a WTP of £20,000 per QALY gained, further increasing to 98% at a WTP of £30,000.

BSC was not considered a relevant comparators by clinicians, as practically all patients eligible for enzalutamide would currently receive abiraterone. However, this treatment was included as per the scoping process, and in the probabilistic analysis, enzalutamide showed a high probability of being cost-effective (81% against BSC) at a WTP of £50,000 per QALY gained. This threshold (£50,000 per QALY gained) was also used for the recommendation of abiraterone, and is appropriate as enzalutamide meets all end of life criteria for the comparison against BSC (section 7.10.4).

Uncertainty around input values was tested in the deterministic sensitivity analysis. The most influential model parameters were those that were directly taken from the trial (HR for OS and PFS). Overall, most parameters showed only a limited impact, and did not cross major cost-effectiveness thresholds. It should be noted that the impact of correlated parameters (such as the intercept and time covariate of the abiraterone time dependent HR) should be interpreted with caution as only one parameter at a time is varied in this analysis, thus overestimating the actual impact. This is further demonstrated in the probabilistic sensitivity analysis, where high ICERs (such as those in the tornado for correlated parameters) were rare.

The impact of structural assumptions was shown in section 7.7.9. The results were shown to be insensitive to discount rate and time horizon. The two scenario analyses on abiraterone OS show that the model is relatively robust to the methods chosen to model OS.

As the proportionality of hazards assumption was not met for abiraterone OS, a time dependent HR was applied in the model. Applying a fixed HR overestimates the OS benefit of abiraterone, but would still result in an ICER under £20,000, further showing the robustness of the results.

UK experts selected a Weibull model for the OS and PFS reference curves, due to the more realistic shape of the tail. The best statistical fit – Log Logistic – would result

in (unrealistically) long tails. Applying this fit for OS would result in lower ICERs, due to larger OS gains, whereas applying this fit for PFS, overestimates the time on treatment and results in higher ICERs. However, the extreme scenario in which the Log Logistic model is used for PFS still shows an ICER close to the £20,000 / QALY threshold.

TTD was considered the most accurate reflection of progression (and thus discontinuation) in clinical practice. When mPFS is used instead of treatment discontinuation, the ICER further decreases to £13,476 vs. abiraterone and to £43,396 vs. BSC. This shows that the cost-effectiveness would be similar, should discontinuation in clinical practice resemble more closely mPFS instead of the trial defined TTD.

The model is relatively insensitive to the utility decrement for AEs, and SREs, which shows that potential double counting in utility values is not likely to have a big impact on the incremental cost effectiveness results. When the mapped values are used instead of the baseline EQ-5D value for SDis and literature value for the PDis health state, the ICER decreases. Also using the same on treatment utility gain for enzalutamide and abiraterone has limited impact on the incremental results. This shows that the model is robust to alternative assumptions for the utility calculation.

Using the utility values from the abiraterone submissions reduced the ICERs. This was a result of the larger QALY gain due to the higher utilities. Even when the (highly criticised) post-progression value of 0.5 used in abiraterone's NICE submission was used the ICER remained similar to the base case.

UK experts considered it unlikely that routine monitoring visits would be alternated between nurse and consultant, and the HRU in the model was adapted to reflect this. Should the assumption of alternated visits from the abiraterone submission be applied, this would result in a small decrease in the ICER vs. BSC and a small increase in the ICER vs. abiraterone as a result of the differences in total monitoring costs.

The model assumed no active treatment post-progression, as no treatment is currently recommended in the UK post-progression. However, patients received post study treatment in AFFIRM. For purposes of modelling, this was not assumed to impact OS. However, as outlined in section 7.5.6, this is likely to bias against enzalutamide. Although the impact of post study treatment on OS cannot be quantified with certainty, we have included a scenario analysis in which the costs for post study treatment were included. This showed decreased ICER against BSC, due to the higher use (and thus higher costs) of post study treatment in the BSC arm.

In conclusion, the sensitivity analyses showed a high probability of enzalutamide being cost-effective at accepted thresholds, with robust results, and a limited influence of either parameter inputs, or structural assumptions.

7.7.11 What are the key drivers of the cost-effectiveness results?

Key drivers of the cost-effectiveness results against BSC and abiraterone are the HR for OS, the HR for TTD and the on treatment utility gain. All of these inputs were directly derived from the AFFIRM and COU-AA-301 trials.

7.8 *Validation*

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The model programming was internally validated by an experienced health economist not involved in the project. Extreme value scenarios were performed, as well as validation of internal consistency, face validity and source validation of input data. The modelling methods and results were also reviewed by an external health economic expert, as well as by two health economists who participated in the advisory boards (4) (70).

7.9 *Subgroup analysis*

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

Individual utilities for health states and patient preference.

Subgroups based solely on differential treatment costs for individuals according to their social characteristics.

Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

No subgroup analyses were undertaken. The subgroup in which abiraterone is accepted – the one prior chemo population - was not considered a relevant subgroup. Clinicians confirmed that there is no differentiation between these patients and the entire population, which was also confirmed in the AFFIRM OS subgroup analysis (Figure 11, section 6.5.3). Also, no subgroups were identified in the NICE scope.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Not applicable.

7.9.3 Please describe how the statistical analysis was undertaken.

Not applicable.

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

Not applicable.

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

No obvious subgroups were excluded, as shown in section 6.5.3, enzalutamide has a comparable benefit in all sub-populations.

7.10 *Interpretation of economic evidence*

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

No economic evaluations have been published for enzalutamide for the treatment of mCRPC in adult men whose disease has progressed on or after docetaxel therapy. The manufacturer submission of abiraterone to NICE calculated an ICER of £52,851 for abiraterone vs. BSC in the one prior chemo population, however, it is difficult to compare this with the ICER calculated in this analysis. Not only was a different subgroup modelled, but also many inputs are different (i.e., utility values) as shown in Table 90. In addition, many inputs in the abiraterone submission were CIC, which makes a comparison of the ICERs even more complicated.

Table 90: Comparison of key model aspects abiraterone and enzalutamide submission

Model Aspect	Abiraterone submission to NICE	Enzalutamide submission to NICE (this analysis)
Population	OPC subgroup	Entire post-chemo mCRPC population
Interventions considered	BSC Abiraterone Mitoxantrone	BSC Enzalutamide Abiraterone
Technique for survival modelling	Kaplan Meier curves were extrapolated with exponential distribution	In line with NICE DSU guidance: BSC reference treatment modelled through Weibull parametric fit Enzalutamide and BSC modelled by applying a HR to the reference parametric fit
Definition of PFS	Time to treatment discontinuation	Time to treatment discontinuation
Baseline utility	Mapped COU-AA-301 value: CIC	Baseline AFFIRM EQ-5D: [redacted]
Utility for progressed disease	Absolute utility value (0.50) from Sandblom study (122)	Utility decrement (-0.085) derived from Sandblom study (122)

Abbreviations: BSC: best supportive care; CIC: commercial in confidence; mCRPC: metastatic castrate-resistant prostate cancer; OPC: one prior chemo.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

Yes, the economic evaluation includes the entire population of adult men with mCRPC whose disease has progressed on or after docetaxel therapy.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

One of the main strengths of the analysis is the comprehensive methods with which survival was modelled. The survival extrapolation has been performed according to the guidance of the NICE DSU, and has been validated by an external expert. Extensive sensitivity analysis showed the robustness of the survival extrapolation. In addition, utility data from the AFFIRM study was used, thereby ensuring that the utility values are reflective of the population of interest. In the trial, enzalutamide showed a significant impact on QoL compared to BSC, which justifies the use of an on treatment utility gain in the analysis. Furthermore, the modelled population is comparable to the UK patient population.

The external validity of the model was good: all modelled medians were close to the reported values. In addition, the model was validated by UK clinical and health economic experts. All sensitivity and scenario analyses showed that the results are robust, and insensitive to changes in model inputs.

The key limitation relates to the lack of head to head comparison with abiraterone, thereby requiring an ITC. Another limitation is the availability of published data on the abiraterone treatment duration and the amount of data on abiraterone that was CIC.

The analysis used actual EQ-5D utility values, as these are generally preferred over mapped values. Although this data was available for only a subset of patients, mapping would have introduced additional uncertainty in the analysis. It should be noted however, that the mapped values were in line with the EQ-5D values. The scenario analysis using the mapped EQ-5D values, also confirmed the limited impact of the mapping.

As no resource utilisation was collected in the AFFIRM trial, literature data was used, which was modified based on the input from UK clinical experts. Although it may be argued that using literature data introduces additional uncertainty, resource utilisation from clinical trials would also be biased due to protocol driven monitoring. An alternative assumption on monitoring was tested in a scenario analysis, and resulted in similar cost-effectiveness estimates.

7.10.4 End of life consideration

Enzalutamide was shown to be a cost-effective treatment option when compared to abiraterone. Although clinical experts indicated that almost all patients eligible for enzalutamide would currently receive abiraterone, a small proportion may not be eligible for this treatment and may currently receive BSC. When compared with BSC, enzalutamide showed an ICER which is similar to other cancer drugs recommended by NICE that have met EoL criteria. Enzalutamide meets all criteria to be considered by NICE under the Supplementary Advice on appraising EoL medicines as presented below:

- **The treatment is indicated for patients with a short life expectancy, normally less than 24 months**
  As indicated by the median survival in the control arms of the COU-AA-301 study (25) and the AFFIRM study (3), patients currently treated with BSC have a short life expectancy of approximately one year.

- **The treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment**
  Enzalutamide showed an increase in median OS in the AFFIRM study of more than three months. In the economic model this translated into a gain of [redacted] or [redacted].

- **The technology is licensed or otherwise indicated, for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England.**
  As indicated in section 2.2, the potential patient population for enzalutamide in 2013 is estimated at 2,977 patients. Only a very small proportion of these patients would currently receive BSC.

7.10.5 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Head to head trials could overcome the limitations of the ITC, also a trial with longer follow-up would reduce uncertainty regarding the extrapolation of survival curves.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

As discussed in section 2.2, mCRPC will have an annual prevalence of 12,029 in the England and Wales in mid 2013, with an annual incidence (defined as patients with non-metastatic CRPC) of 3,433 (22).

Of these men, 33% will receive docetaxel chemotherapy (23). It is estimated that 75% of these patients may be candidates for further treatment with enzalutamide based on 1-year survival data following docetaxel (21) giving a potential patient population of 2,977.

Table 91: Eligible patient population for treatment of mCRPC patients, mCRPC whose disease has progressed on or after docetaxel therapy

	2013	2014	2015	2016	2017	2018
Estimated number of mCRPC patients	12,029	12,143	12,255	12,365	12,472	12,576
% receiving docetaxel	33%	33%	33%	33%	33%	33%
Number receiving docetaxel	3,970	4,007	4,044	4,081	4,116	4,150
Assume 75% of these are eligible for enzalutamide or abiraterone	2,977	3,005	3,033	3,060	3,087	3,113
Eligible patient population	2,977	3,005	3,033	3,060	3,087	3,113

Source: Office of National Statistics (155); Stats Wales (156); Kantar data (22).

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

The budget impact of enzalutamide is based on the assumption that all patients (approximately 2,977 [75%]) who have progressed on or after docetaxel based chemotherapy currently receiving treatment with abiraterone.

8.3 What assumption(s) were made about market share (when relevant)?

The market share estimates in Table 92 are based on enzalutamide receiving positive NICE guidance in Q1 2014.

Table 92: Market share estimates for patients with mCRPC whose disease has progressed on or after docetaxel therapy

	2013	2014	2015	2016	2017	2018
Estimated market share enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated market share abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients receiving treatment with enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients receiving treatment with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

We assume no patients received mitoxantrone or BSC after docetaxel containing chemotherapy treatment. Although some physicians use mitoxantrone (unlicensed in mCRPC) in the absence of a licensed alternative, no clinical evidence is available to support any survival benefit in mCRPC patients. Patients are treated with either abiraterone or enzalutamide. This assumption is based on the outcomes of a UK advisory board (4) where physicians reported that while some mCRPC patients may still receive mitoxantrone, it is likely that this treatment choice was initiated prior to the availability of abiraterone.

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

Costs of treatment and monitoring associated with enzalutamide are discussed in section 7.5.5. Additional INR monitoring may be needed if enzalutamide is co-administered with an anticoagulant metabolised by CYP2C9 (such as warfarin or acenocoumarol). Enzalutamide does not require additional LFT and cardiovascular monitoring, which are required for abiraterone (1). The frequency of monitoring enzalutamide was estimated at once every four weeks in the first three months, and once every 8 weeks thereafter. The cost of treatment and monitoring for enzalutamide were aligned with the median treatment duration from the AFFIRM trial of 8.3 months (7).

No additional costs related to AEs and SREs are included. Enzalutamide is assumed to have no incremental impact on the cost of treating AEs and SREs when compared to abiraterone in men with mCRPC whose disease has progressed on or after docetaxel therapy.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on

national reference costs or the PbR tariff, which HRGs reflected activity?

Unit costs for treatment and monitoring can be found in section 7.5.7.

8.6 Were there any estimates of resource savings? If so, what were they?

Enzalutamide requires less frequent monitoring than abiraterone (section 7.5.5), resulting in a cost saving of £34.30 per month for the first three months (every 4 weeks with enzalutamide and every 2 weeks with abiraterone) and a saving of £28 per month for subsequent months thereafter (monitoring needed every 8 weeks with enzalutamide and every 4 weeks with abiraterone).

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The incremental budget impact, based on the market share difference of enzalutamide when compared to abiraterone is presented in Table 93.

Table 93: The incremental budget impact difference of enzalutamide when compared to abiraterone

	2014	2015	2016	2017	2018
Market Share					
With PAS					
Without PAS					

Note: The budget impact difference assumes a median duration of 8.3 months for enzalutamide and 7.4 months for abiraterone. As mean duration for abiraterone has not been published, the median duration for both drugs was used.
Abbreviations: PAS: Patient Access Scheme.

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

An estimate of 5-10% of mCRPC patients require hospital transportation for monitoring visits; as less monitoring visits are required for enzalutamide treated patients, it is likely that less hospital transportation is required for these patients (4). These specific costs have not been accounted for within the health economic model, or budget impact calculation. During an advisory board, clinicians informed that the abiraterone monitoring requirements place a large burden on staff resourcing. There have been occasional reports of clinics having to hire an extra nurse to carry out all monitoring obligations (4). As enzalutamide does not require these additional monitoring visits, this is an opportunity for resource savings.

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