in collaboration with:

Enzalutamide for the treatment of metastatic hormone relapsed prostate cancer previously treated with a docetaxel-containing regimen

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam and Maastricht University

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ABBREVIATIONS

ABI	Abiraterone
Abiraterone	Abiraterone acetate
ACD	Appraisal Consultation Document
ADT	Androgen Deprivation Therapy
AE	Adverse Events
AFT	Accelerated Failure Time
AIC	Akaike Information Criterion
AJCC	American Joint Committee on Cancer
ANCOVA	Analyses of covariance
AR	Androgen Receptor
ASCO	American Society of Clinical Oncology
ASCO-GU	American Society of Clinical Oncology-Genitourinary
bd/b.i.d	Twice Daily
BIC	Bayesian Information Criterion
BNF	British National Formulary
BPI	Brief Pain Inventory
BPI-SF	Brief Pain Inventory-Short Form
BSC	Best Supportive Care
CAB	Cabazitaxel
CDF	Cancer Drug Fund
CE	Cost effectiveness
CEA	Cost effectiveness analysis
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
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
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)
DARE	Database of Abstracts of Reviews of Effects
DB	Double Blind
DTX	Docetaxel
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
ENZA	Enzalutamide

EoL	End of Life
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
EUR	Erasmus University Rotterdam
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
FBW	Functional Well-Being
G-CSF	Granulocyte Colony-Stimulating Factor
GnRH	Gonadotropin Releasing Hormone
HR	Hazard ratio
HRQoL	Health-related Quality of Life
HRU	Health Resource Utilisation
HTA	Health Technology Assessment
IA	Interim Analysis
IC	Indirect Comparison
ICER	Incremental Cost-effectiveness Ratio
IPD	Individual Patient Data
ITC	Indirect Treatment Comparison
ITT	Intention to Treat
KSR	Kleijnen Systematic Reviews Ltd
LHRH	Luteinising Hormone-Releasing Hormone
LS	Least Squares Mean
LY	Life Years
LYG	Life Years Gained
mCRPC	Metastatic Castrate-Resistant Prostate Cancer
mg	Milligram
mPFS	Modified Progression Free Survival
MMRM	Mixed Model with Repeated Measures
MRI	Magnetic Resonance Imaging
MS	Manufacturer's Submission
MTC	Mixed Treatment Comparison
MTX/MTZ	Mitoxantrone
MUGA	Multi-Gated Acquisition Scan
NHS	National Health Services
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not Reported
od	Once Daily
OL	Open-Label
OPC	One Prior Chemo
OR	Odds Ratio
ORR	Objective response rate
OS	Overall Survival

PAS	Patient Access Scheme
PC	Prostate Cancer
PCS	Prostate Cancer Scale
PCWG2	Prostate Cancer Clinical Trials Working Group
PDis	Progressive Disease
PFS	Progression Free Survival
PLA	Placebo
PO	Per os (oral)
PP	Per Protocol
PR	Partial response
PRED	Prednisone
PRESS	Peer Review of Electronic Search Strategies
PRO	Patient Reported Outcomes
PS	Performance Status
PSA	Prostate-Specific Antigen
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Services
QALY(s)	Quality-adjusted Life Year(s)
QoL	Quality of Life
RAM	Ramucirumab
RCT	Randomised Controlled Trial
RD	Rate Difference
RECIST	Response Evaluation Criteria in Solid Tumours
RIL	Rilotumumab
rPFS	Radiographic Progression Free Survival
RR	Relative Risk
SAE	Serious Adverse Events
SD	Standard Deviation
SDis	Stable Disease
SE	Standard Error
SLR	Systematic Literature Review
SPC	Summary of Product Characteristics
SRE	Skeletal-Related Event
STA	Single Technology Appraisal
TTD	Time to Treatment Discontinuation
TTO	Time Trade-Off
UMC	University Medical Centre
VAS	Visual Analogue Scale
WTP	Willingness to Pay

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1. SUMMARY

1.1 Critique of the decision problem in the manufacturer's submission

The NICE scope encompasses the clinical and cost effectiveness of enzalutamide within its licensed indication for the treatment of metastatic hormone relapsed prostate cancer previously treated with a docetaxel-containing regimen.[1] According to the NICE scope the relevant comparators are: abiraterone in combination with prednisone or prednisolone; mitoxantrone alone or in combination with prednisolone; and best supportive care (BSC, this may include radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies, and corticosteroids). There were a few differences between the NICE and manufacturer's scopes and these are summarised below.

The European marketing authorisation (European Medicines Agency, EMA) recommended enzalutamide for the treatment of adult men with metastatic castration-resistant prostate cancer (mCRPC) whose disease has progressed on or after docetaxel therapy. This is consistent with the NICE scope.

The comparators considered in the manufacturer's submission (MS) are: abiraterone and BSC. Mitoxantrone is not considered a relevant comparator to the decision problem by the manufacturer and is not discussed in the MS. The ERG asked the manufacturer to provide a justification for excluding mitoxantrone as a comparator. The manufacturer gave the following response (see Response to Clarification Letter, Question A4, page 8-9[2]):

"Having reviewed the 2013 NICE methods guide (sections 6.2.1 to 6.2.4), Astellas maintains that mitoxantrone is an irrelevant comparator based on the guide's five criteria.

1. *Mitoxantrone has a very small and diminishing place in NHS practice in England;*
2. *Several new alternative treatments are available which have displaced a vast majority of historic mitoxantrone use;*
3. *Existing NICE guidance does not support mitoxantrone in mCRPC;*
4. *Clinical evidence for mitoxantrone in the post-docetaxel setting does not support any survival benefit for mCRPC patients and therefore it cannot be considered a cost-effective choice;*
5. *Mitoxantrone is not licensed for mCRPC."*

The ERG agrees that there is no network linking mitoxantrone trials to enzalutamide and/or abiraterone. In the abiraterone assessment (TA-259) the committee also concluded that there were no trials to link the evidence for mitoxantrone to the COU-AA-301 trial and enable an indirect comparison of abiraterone and mitoxantrone.[3]

The MS, is mainly based on the AFFIRM trial, in which enzalutamide (with or without prednisone) is directly compared with placebo (with or without prednisone). It was assumed that the control arm in the AFFIRM trial represented BSC. An indirect comparison with abiraterone is provided using evidence from the AFFIRM trial and the COU-AA-301 trial, in which abiraterone plus prednisone is compared with placebo plus prednisone. To be able to

perform the indirect comparison 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 versus 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.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The evidence for the clinical effectiveness of enzalutamide came from a multicentre double blind randomised controlled trial (RCT) (AFFIRM) which compared oral enzalutamide (160 mg/day) with placebo when administered to patients with progressive mCRPC previously treated with docetaxel-based chemotherapy. Patients 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. In addition to enzalutamide and placebo, all patients received BSC.

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). Randomisation was stratified by baseline ECOG performance status score (0-1 or 2) and mean BPI-SF Question #3 score averaged over the seven 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 versus ≥ 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. Patients were eligible for enrolment if they had a histologically or cytologically confirmed diagnosis of prostate cancer, castrate levels of testosterone (<50 ng per deciliter [1.7 nmol per liter]), previous treatment with docetaxel, and progressive disease defined according to PCWG2 criteria, including three increasing values for Prostate-Specific Antigen (PSA) or radiographically confirmed progression with or without a rise in the PSA level. The intention to treat (ITT) population consisted of 800 and 399 patients receiving ENZA and PLA respectively. Nearly all patients were white (93%) and 92% had bone disease at entry.

In the manufacturer's submission the population in the AFFIRM study is compared with the population in the COU-AA-301 study for the comparison with abiraterone. According to the manufacturer, the population in AFFIRM closely matches the population in COU-AA-301. In the NICE guidance for abiraterone (TA-259[3]), "The Committee considered the manufacturer's base-case population of patients who had received one prior chemotherapy (OPC) in the COU-AA-301 trial. The Committee noted that this subgroup did not match the population for which abiraterone is licensed (the therapeutic indication in the marketing authorisation does not stipulate only one prior chemotherapy) but probably reflected the

population in England and Wales for whom abiraterone would be considered." In addition, the "Committee accepted that this population was likely to reflect patients who would be treated with abiraterone in UK practice, and who would have better treatment outcomes because they have less advanced disease." In the COU-AA-301 study the OPC sub-population was pre-specified and contributed ~70% of the total; amongst the remaining 30% who received two different chemotherapy regimens one regimen was docetaxel.

If the subgroup of patients who had received one prior chemotherapy in the COU-AA-301 study is considered to have better treatment outcomes because they have less advanced disease then the total population should have more advanced disease and worse treatment outcomes. Therefore, the population in the AFFIRM study is also likely to have more advanced disease and worse treatment outcomes. The implications of this in terms of effectiveness of the interventions are unknown.

The primary endpoint was overall survival (OS), which was defined as the time from randomisation to death from any cause in the ITT population (defined as all randomised patients). An interim analysis was conducted after 308 deaths among patients in the enzalutamide arm and 212 deaths among patients in the placebo arm (14.4 months median follow up).

The key secondary endpoints assessed in AFFIRM were:

- Time to Prostate-Specific Antigen (PSA) progression
- Radiographic PFS (rPFS)
- Time to first Skeletal-Related Event (SRE)
- FACT-P response rate
- Rate of pain palliation at Week 13

The indirect treatment comparison (ITC) was performed for the following outcomes: OS, rPFS, Modified Progression Free Survival (mPFS), time to SRE, Objective response rate (ORR), PSA response, and all grade and grade 3+ specific adverse events (AEs). A summary of the data used in the analysis and the results is provided in Table 1.1 and Table 1.2. All abiraterone-related data including OS correspond to the final analysis as reported in Fizazi 2012[4], Logothetis et al.[5] and the NICE submission[3].

The data cut-off used for the AFFIRM study is the IA (interim analysis) (25 September 2011) for all outcome measures [Scher 2012a[6]] with the exception of OS, where the database lock was used (16 December 2011). The hazard ratio (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.[7]

Table 1.1: OS, rPFS and time to first SRE data included in the ITC with results (HR, [95%CI])

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

Source: Systematic Literature Review (SLR) 2013[8]
Abbreviations: HR: hazard ratio; ITC: Indirect Treatment Comparison; OS: overall survival; rPFS: radiographic progression-free survival; SRE: skeletal-related events; TTD: Time to treatment discontinuation..
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.

Compared to BSC, enzalutamide was associated with significantly better outcomes for OS, rPFS, time to first SRE, mPFS and time to treatment discontinuation (TTD).

Compared to abiraterone, enzalutamide was associated with a significantly higher likelihood of attaining radiographic and modified PFS than abiraterone. In contrast, no significant differences were observed for OS or time to first SRE. An ITC for TTD was not possible because data for TTD was marked as confidential in the COU-AA-301 trial.

Table 1.2: ORR and PSA response data included in the ITC with results

Outcome		AFFIRM		COU-AA-301		Treatment comparison: ENZA vs. ABI
		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]		[redacted]
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]		[redacted]

Source: SLR 2013[8]
Abbreviations: ABI: abiraterone; ENZA: enzalutamide; OR: odds ratio; ORR: objective response rate; PLA: placebo; PRED: prednisone; PSA: prostate specific antigen.
In bold: statistically significant outcomes

Compared to BSC, both ORR and PSA response significantly favour enzalutamide.

Compared to abiraterone, enzalutamide is associated with a significantly higher likelihood to achieve a PSA response (defined as ≥50% decrease confirmed three or four weeks later) than abiraterone. However, no significant differences were observed between enzalutamide and abiraterone for ORR.

Based on the AFFIRM trial, 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%). The overall incidence of adverse events (AEs) with enzalutamide was similar to those of placebo

in the AFFIRM study. The incidence of all grade and of grade 3+ was either comparable or lower in the enzalutamide arm than with placebo.

The indirect comparison shows that enzalutamide has a similar likelihood to be associated with all specific AEs (all grades) of interest to abiraterone except for bone pain and hypokalemia:

- 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% versus 14.2%; p>0.001) or ≥30% (44.9% versus 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]]).

The likelihood of enzalutamide to be associated with any of the grade 3+ AEs assessed is not statistically different from that of abiraterone. No significant differences were observed in the incidences of SREs between enzalutamide and abiraterone (OR: [redacted] [95% CI [redacted]]). In both studies, the proportion of patients who discontinued treatment due to an AE was lower with study intervention (enzalutamide and abiraterone) than the comparator. The ITC showed no significant differences in the rate of treatment discontinuation (tolerability) (OR: [redacted], 95% CI [[redacted]]).

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The submission appears to be complete in that it included the only RCT comparing enzalutamide with placebo (the AFFIRM trial) for mCRPC patients who had failed to respond during or following docetaxel therapy, and presented a systematic review looking for evidence that might allow an indirect comparison of the effectiveness of enzalutamide versus abiraterone and mitoxantrone. AFFIRM was a double blind study reporting the objective outcomes of all-cause mortality and time to radiological progression or death. The AFFIRM trial provided persuasive evidence that enzalutamide confers a survival advantage over BSC, showing a significant difference in overall survival (HR of 0.62 [0.52; 0.73]). The effect was consistent across subgroups, however black and other racial groups were under represented in the trial population and it cannot be certain that the effect is necessarily generalisable to these groups.

The indirect comparison with abiraterone is straightforward, using the "adjusted" indirect comparison methodology described by Bucher.[9] The ERG agrees that this is an appropriate method, and it was performed correctly.

The results of the indirect comparison showed that enzalutamide was associated with a significantly higher likelihood of attaining radiographic and modified PFS than abiraterone.

In contrast, no significant differences were observed for OS or time to first SRE. Enzalutamide is associated with a significantly higher likelihood to achieve a PSA response (defined as ≥50% decrease confirmed three or four weeks later) than abiraterone. However, no significant differences were observed between enzalutamide and abiraterone for ORR.

The indirect comparison shows that enzalutamide has a similar likelihood to be associated with all specific AEs (all grades) of interest to abiraterone except for bone pain (more likely with enzalutamide) and hypokalemia (less likely with enzalutamide). The likelihood of enzalutamide to be associated with any of the grade 3+ AEs assessed is not statistically different from that of abiraterone, while the rate of treatment discontinuation (tolerability) showed no statistically significant difference either.

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

The literature search for relevant cost effectiveness studies was appropriate and did not identify any studies that included enzalutamide as a comparator. Hence, a de novo economic analysis was performed.

The manufacturer presented a comparison of enzalutamide, abiraterone and BSC. Mitoxantrone was not included as a comparator, although it was listed in the scope. The Markov state transition model follows the structures used in other NICE STAs in metastatic cancer (health states are stable disease, progressive disease and death) and is appropriate in the view of the ERG. The model applied a 10-year time horizon, which reflects life expectancy, coupled with a three weekly cycle. The backbone of the model is made up by survival curves for PFS and OS. Time in the progressive disease state was calculated as the difference between OS and PFS. In addition to disease progression and survival, AEs (grade ≥3) in stable disease, SREs in progressive disease, and an 'on treatment utility gain' for enzalutamide and abiraterone is taken into account. The effectiveness estimates in the model are based on the patient level data on OS and TTD (as a proxy for PFS) of the AFFIRM trial for enzalutamide and BSC and published results of the COU-AA-301 study for the effectiveness of abiraterone versus BSC.

Utility data was collected using the EQ-5D among a subset of the patients in the AFFIRM study. Response was just above 60% among the patients asked. It should be noted that overall only for a very small proportion of the patients in AFFIRM complete (none of the five items missing) EQ-5D forms were available (at baseline between 13% and 16% for the placebo and enzalutamide arm respectively). The AFFIRM EQ-5D data were used to estimate baseline utility. The 'on treatment utility gain' for enzalutamide was based on AFFIRM data using FACT-P mapping. Utility values for the progressive disease health state, 'on treatment utility gain' for abiraterone, AEs, and SREs could not be estimated from AFFIRM data and were taken from the literature.

The list price of enzalutamide is £2,734.67 for each 28 day pack. The manufacturer has agreed a Patient Access Scheme (PAS) with the Department of Health, which is reflected in the base case analysis. The PAS consists of a [redacted] discount, resulting in a price per pack of

enzalutamide of [redacted]. [redacted]. Treatment specific costs further include costs for monitoring and concomitant medication. Monitoring costs are less for enzalutamide as compared to abiraterone as a result of a lower frequency, and in line with the abiraterone STA.[3] Costs of concomitant medication were based on the AFFIRM study and assumed the same for both enzalutamide and abiraterone (except that prednisolone was added to the concomitant medication costs of abiraterone). Total technology costs per cycle amounted to [redacted] (first three months) and [redacted] (subsequent months) for enzalutamide, to [redacted] (first three months) and [redacted] (subsequent months) for abiraterone, and to £112 for BSC. Post-progression (post-study) treatment costs were not taken into account. The impact of this assumption was tested in univariate (for one comparator at the time) sensitivity analyses showing that this impacted the ICERs (MS: Table 83 & Table 84; p. 181-182). However, when including post-progression treatment costs for all comparators in the model alike, the impact on the ICERs was only modest (MS: Table 88; p.187). Post-progression monitoring costs were assumed to be equal to pre-progression monitoring costs in BSC. Terminal treatment costs of £3,133 per patient were calculated in the same manner as in the abiraterone STA[3] and taken into account as a transition cost to the death state. Costs for AEs were based on resource use reported in the cabazitaxel STA,[10] the abiraterone STA[3] and updated NHS prices (2011-2012). The resource use associated with SREs was taken from Botteman 2011[11] and recalculated using 2011-2012 NHS reference prices.

The base case expected outcome is that, with the PAS, the cost effectiveness of enzalutamide is £14,576 per QALY against abiraterone, and £43,239 against BSC. For a threshold of £20,000 per QALY the probability that enzalutamide is cost effective is 83% against abiraterone, and 0% against BSC. For a threshold of £50,000 per QALY the probability that enzalutamide is cost effective against BSC is 80%. The manufacturer presented a large number of sensitivity (using the 95% CI limits as inputs) and scenario analyses. The most influential variable in the sensitivity analyses for the comparison of enzalutamide versus abiraterone is the HR for OS of abiraterone versus BSC (ICER spread £11,843 to £46,022). For enzalutamide compared to BSC, the HR for OS for enzalutamide versus BSC is considered the most influential variable (ICER spread £34,692 to £58,042). In the clarification letter the ERG requested the probabilistic results of the scenario analyses, which were provided by the manufacturer. For the comparison of enzalutamide versus abiraterone, the results of the scenario analyses varied from £8,881 (Log Logistic instead of Weibull model for OS) to £20,932 (Log Logistic instead of Weibull model for PFS). For the comparison of enzalutamide versus BSC, the results of the scenario analyses varied between £25,525 (Log Logistic instead of Weibull model for OS) and £51,075 (on treatment utility gain excluded).

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

Although the ERG agrees that because of the limited use of mitoxantrone in clinical practice and limited evidence available, a comparison would be seen as secondary, the ERG has the opinion that the MS should comply with the scope. Also after request for clarification the

manufacturer did not include mitoxantrone as a comparator. Therefore, the ERG modelled mitoxantrone as a comparator in a similar manner as done in the abiraterone STA.[3]

The manufacturer's submission was in line with the NHS reference case, apart from omitting mitoxantrone as a comparator, selecting the subgroup with OPC to estimate the HR for PFS of abiraterone versus BSC, and using mapped EQ-5D utility based on FACT-P data for 'on treatment utility gain' and disutility of SREs.

The AFFIRM and COU-AA-301 trials are reasonably comparable with regard to population, interventions and outcomes allowing an indirect comparison. Both modified PFS and radiographic PFS are disregarded in the modelling, instead TTD is used as a proxy for PFS. The manufacturer argues that TTD as measured in the trials best reflected UK practice. The ERG agrees that among the measures for disease progression available TTD is to be preferred, although this estimate remains uncertain. The OS and curves for BSC are based on the AFFIRM trial. Several models were fitted, of which the Log-Logistic models had the best statistical performance. The manufacturer however chose to use the Weibull models based on expert opinion. After further clarification was provided, the ERG agrees that the Weibull models are more realistic. The effectiveness of abiraterone versus BSC was estimated from the COU-AA-301 study. The OS HR of abiraterone versus BSC was appropriately modelled as time-dependent. However, this resulted in a HR of 1.39 at 25 months (end of follow up in the trial), which was then kept constant in the model for the remaining time horizon. The ERG asked for further clarification as this extrapolation is based on very few patients. The manufacturer did not provide additional arguments. In the ERGs opinion a conservative approach is preferred by keeping a HR of 1.00 for OS of abiraterone versus BSC after 25 months, i.e., both abiraterone and BSC produce the same hazard function after month 25.

Given the relatively small number of patients asked and the considerable non response, the ERG has some concerns regarding the applicability of the baseline utility value [redacted] (SE = [redacted]) for the population in clinical practice. As the population in the AFFIRM trial could have been fitter than generally seen in clinical practice, the utility value of [redacted] could be an overestimation of the quality of life of the patient population. Furthermore, the ERG questioned the application of the 'on treatment utility gain' for abiraterone ([redacted] (95% CI: [redacted]]) and enzalutamide ([redacted] (95% CI: [redacted]]) for the following reasons. Firstly, details on the internal mapping algorithm and further details used to calculate the enzalutamide 'on treatment utility gain' were missing (and not provided after clarification questions). Secondly, the 'on treatment utility gain' for enzalutamide and abiraterone versus BSC are likely to be an overestimation of the real 'on treatment utility gain' as part of this utility benefit is already captured by the utility decrements used for AEs in the stable disease health state. This creates potential for double counting. Thirdly, the evidence base to assume a different 'on treatment utility gain' for enzalutamide and abiraterone is extremely thin as the estimate for abiraterone is taken from a Dutch submission report that does not include any details with regard to the methods used. In response to questions for clarification the manufacturer argues that excluding the 'on treatment utility gain' would underestimate the

total impact of AEs as only AEs grade ≥3 are taken into account. The ERG agrees with this. However, in light of the weak evidence for the 'on treatment utility gain' for both enzalutamide and abiraterone and the risk of double counting, the ERG prefers taking a conservative approach and disregarding the 'on treatment utility gain' in the base case scenario.

The ERG viewed the resource use and costs as reasonable.

It should be noted that the cost effectiveness of abiraterone versus BSC in this analysis is estimated to be £102,751. This seems to be a less favourable result than in the abiraterone STA, although this is difficult to judge due to large amount of data on abiraterone that is CIC information.[12] As a result, it was impossible to exactly pin-point the sources of differences underlying the analyses undertaken for this STA, and the analyses undertaken in the abiraterone STA. In general, a less favourable cost effectiveness of abiraterone against BSC is likely to favour enzalutamide in the comparison against abiraterone.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

- The report was written in a clear and transparent manner.
- The MS provided sufficient detail for the ERG to appraise the majority of searches. All relevant databases were searched and most of the search strategies were adequate.
- A good quality double blind RCT demonstrated a clear survival gain from use of enzalutamide over placebo.
- The RCT provided evidence that enzalutamide delayed disease progression.
- The drug is orally administered and thereby potentially convenient for patients, clinicians and the NHS when compared with alternative cytotoxic agents requiring IV infusion.
- A thorough systematic review was completed looking for evidence that might allow a network meta-analysis to be conducted to determine the effectiveness of enzalutamide relative to the designated comparators.
- An indirect comparison with abiraterone showed that enzalutamide is at least as effective as abiraterone in terms of OS, rPFS, mPFS, time to SRE, ORR, and PSA response.
- Enzalutamide has a similar safety profile as abiraterone and is unlikely to be associated with some of the adverse effects that can result from the use of cytotoxic therapies for this condition.
- The economic model was appropriately simple and transparent.
- A PAS of [redacted] was agreed with the Department of Health and included in the submission.

1.6.2 Weaknesses and areas of uncertainty

- Regarding the literature searches, the ERG noted a number of errors regarding line combinations, which may have been consequential to the final recall of results. The ERG was unable to say whether these errors were errors in reporting or mistakes made during the search process.

- All Cochrane Library search strategies were not adequate, involved incorrect PubMed syntax and could not be replicated by the ERG. The omission of MeSH and Emtree terms, lack of alternative spelling variations and incorrectly-used truncations were of further concern.
- Lack of a head-to-head comparison of enzalutamide versus abiraterone.
- Mitoxantrone (listed in the scope) was disregarded as a comparator in the economic analysis.
- Lack of reliable utility data:
  - to estimate baseline utility and utility after progression in this population in UK clinical practice.
  - to model the 'on treatment' quality of life impact of treatment with enzalutamide, apart from the impact already modelled based on AEs grade ≥3 (so without running the risk of double counting).
  - to estimate the relative 'on treatment utility gain' of enzalutamide versus abiraterone.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has added mitoxantrone alone or in combination with prednisone as a comparator to the health economic model to comply with the scope. With this adapted model, the following additional analyses are undertaken:

- Constant HR of 1.00 for OS of abiraterone versus BSC beyond 25 months,
- Using the whole population to estimate the HR for PFS of abiraterone versus BSC,
- Excluding on treatment utility gain,
- All the above as ERG base case.

In the ERG base case the ICER of enzalutamide versus mitoxantrone amounts to £37,840 (extended dominated), the ICER versus abiraterone decreased to £14,488 (extended dominated), and the ICER of enzalutamide versus BSC increased to £51,124. As mitoxantrone is extended dominated, adding it as a comparator did not change the relative cost-effectiveness of enzalutamide versus abiraterone and versus BSC.

Table 1.3: Overview of additional and exploratory analyses undertaken by the ERG

Treatment	Expected outcomes		Enzalutamide compared to		
	Costs	QALYs	Δ Costs	Δ QALYs	ICER
MS Base case					
Enzalutamide	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	14,576**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	43,239
Adding mitoxantrone*					
Enzalutamide	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	14,599**
Mitoxantrone	10,722	0.75	[redacted]	[redacted]	33,585**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	43,288

Treatment	Expected outcomes		Enzalutamide compared to		
	Costs	QALYs	Δ Costs	Δ QALYs	ICER
Constant HR of 1.00 for OS of abiraterone versus BSC after 25 months					
Enzalutamide	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	15,020**
Mitoxantrone	10,761	0.751	[redacted]	[redacted]	33,582**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	43,398
Whole population HR of 0.49 for abiraterone instead of OPC subgroup					
Enzalutamide	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	12,461**
Mitoxantrone	10,750	0.752	[redacted]	[redacted]	33,510**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	43,285
Exclude 'on treatment utility gain'					
Enzalutamide	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	16,464**
Mitoxantrone	10,744	0.737	[redacted]	[redacted]	37,703**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	51,014
ERG base case					
Enzalutamide	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	14,488**
Mitoxantrone	10,732	0.736	[redacted]	[redacted]	37,840**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	**51,124**

Abbreviations: BSC: best supportive care. * Differences to the Manufacture's base case are due to PSA. ** Extended dominated

The ERG performed exploratory analyses with regard to the TTD (as a proxy for PFS) HR of enzalutamide versus BSC and the baseline utility. If the HR is 0.23 or lower (base case value [redacted]) the ICER of enzalutamide versus BSC is higher than £50,000. It is to be noted that in the model enzalutamide becomes less cost effective if it becomes less effective in terms of PFS, while OS remains equal. A baseline utility of 0.58 or lower results in an ICER of enzalutamide versus BSC higher than £50,000.

In conclusion, the additional analyses showed that changing assumptions and inputs in a way that, according to the ERG, is more appropriate increases the ICER of enzalutamide versus BSC from £43,239 to £51,014 per QALY; abiraterone and mitoxantrone are both extended dominated. In the additional analyses the ICER of enzalutamide versus abiraterone is highest when excluding the treatment specific estimates of 'on treatment utility gain' (£16,464 instead of £14,576 in the MS). Exploratory analyses show that the cost-effectiveness of enzalutamide versus BSC is most sensitive to the baseline utility value and the PFS HR of enzalutamide versus BSC.

2. BACKGROUND

This report provides a review of the evidence submitted by Astellas in support of enzalutamide (trade name XTANDI™) for the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men whose disease has progressed during or following docetaxel therapy.

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer's description of mCRPC during or following failure of docetaxel therapy is appropriate to the decision problem. The overview of the disease is given in section 2.1 of the MS and summarised below.

Prostate cancer is a disease in which tumours develop in the prostate gland. The manufacturer states that in early stages prostate cancer is localised to the prostate gland and driven by androgens.[13] The disease can be cured in early stages with surgery or radiotherapy but; patients with inoperable locally advanced or metastatic disease at diagnosis or who have inoperable recurrent disease are treated with Androgen Deprived Therapy (ADT) which slows the tumour growth and delays progression.[13] However, as the disease continues to progress the tumour stops responding to ADT and becomes castration-resistant.[13] Amongst the patients who are diagnosed with castration resistant prostate cancer (CRPC), most patients (84%) will also have metastatic disease (which means tumour spread outside the prostate) and of those with no metastases at diagnosis, 33% may develop it within two years. The CRPC tumours which are resistant to ADT may respond to therapy with anti-androgens (or anti-androgen withdrawal), inhibitors of androgen production and estrogenic agents that further inhibit luteinising hormone.[13] After receiving hormonal manipulations the majority of patients receive chemotherapy involving docetaxel as the disease continues to progress. Enzalutamide (Xtandi, Astellas Pharma) is an androgen receptor antagonist which can inhibit the androgen receptor signalling pathway thus may reduce the growth of tumours.[1]

Section 1.2 in the manufacturer's submission states:

"Enzalutamide, formerly known as MDV3100, 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."

Section 2.3 in the MS states that there are no published data on life expectancy of mCRPC patients in England and Wales.[13] The five year relative survival of patients with metastatic prostate cancer (not necessarily castrate resistant) in England between 1999 and 2002 was 32.6 (95% CI 30.4-34.9).[14] The median overall survival (time from randomisation to death of any cause)[15] was 15.8 months with abiraterone and 11.2 months with placebo plus prednisone in the COU-AA-301 study.[4, 13] The MS states that the patient population in COU-AA-301 study was relevant to the UK population as 14.8% patients were from the UK. Hence, experts

believed it can be assumed that the survival estimates in England and Wales will not differ from the overall survival estimates in the COU-AA-301 study.[13]

According to the NICE scope, there were around 37,000 people diagnosed with prostate cancer in 2009, and over 9,600 deaths from prostate cancer in 2010.[1] The MS states that the prevalence of mCRPC in England and Wales will be 12,029 in 2013.[13] The annual incidence of mCRPC was 3,433 (defined as patients with non metastatic CRPC).[13] It is not clear how annual incidence of metastatic CRPC can be defined as non metastatic CRPC. Also, the reference given in the MS to support these findings was not valid (referenced in the MS as "Kantar Health Data. [accessed April 2013]. Available at: http://www.kantarhealth.com/"). The MS states that around 33% mCRPC patients will receive docetaxel chemotherapy and 75% of these patients have been estimated as candidates for second-line treatment with enzalutamide based on one year survival data following docetaxel giving a potential patient population of 2, 977.[13]

The ERG is aware of the abiraterone assessment by NICE (TA-259[3]). The population under consideration in that assessment was the same as the one considered in this submission. The number of estimated mCRPC patients eligible for the treatment of interest in the abiraterone assessment was similar compared to the estimate in this submission. This information is summarised in Table 2.1.

Table 2.1: Difference between estimate of mCRPC patients between enzalutamide and abiraterone submissions[12, 13]

	Enzalutamide submission	**Abiraterone submission**
Prevalence of mCRPC in England and Wales	12,029 (No valid reference in the MS estimate in 2013)	10,448 (NICE estimate in 2006)
Eligible for docetaxel	33% eligible (3,969 patients)	40% eligible (4,400 patients)
Eligible for second-line treatment of interest	75% of 3, 969 mCRPC patients eligible (2,977patients)	75% of 4,400 mCRPC patients eligible (3,300 patients)

Overall, the evidence presented in this section of the submission is in line with the background information given in the final scope.[1] This is also consistent with the ERG's understanding of the problem.

2.2 Critique of manufacturer's overview of current service provision

The MS states that a Single Technology Assessment (STA) for docetaxel in mCRPC was published in 2006 (TA-101[16]) and was subsequently incorporated into the NICE Prostate Cancer guidelines on diagnosis and treatment in 2008 (CG58).[17]

Recommendations from NICE TAG 101 are as follows:

- Docetaxel is recommended, within its licensed indications, as a treatment option for men

with hormone-refractory metastatic prostate cancer only if their Karnofsky performance-status score is 60% or more.[13]

- It is recommended that treatment with docetaxel should be stopped:
  - at the completion of planned treatment of up to 10 cycles, or
  - if severe adverse events occur, or
  - in the presence of progression of disease as evidenced by clinical or laboratory criteria, or by imaging studies.

- Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy.[17]

Recommendation from the NICE Prostate Cancer guidelines (CG58)[17] relating to metastatic disease are as follows:

- When men with prostate cancer develop biochemical evidence of hormone-refractory disease, their treatment options should be discussed by the urological cancer multidisciplinary team (MDT) with a view to seeking an oncological and/or specialist palliative care opinion as appropriate.[17]

Section 2.4 in the manufacturer's submission states:

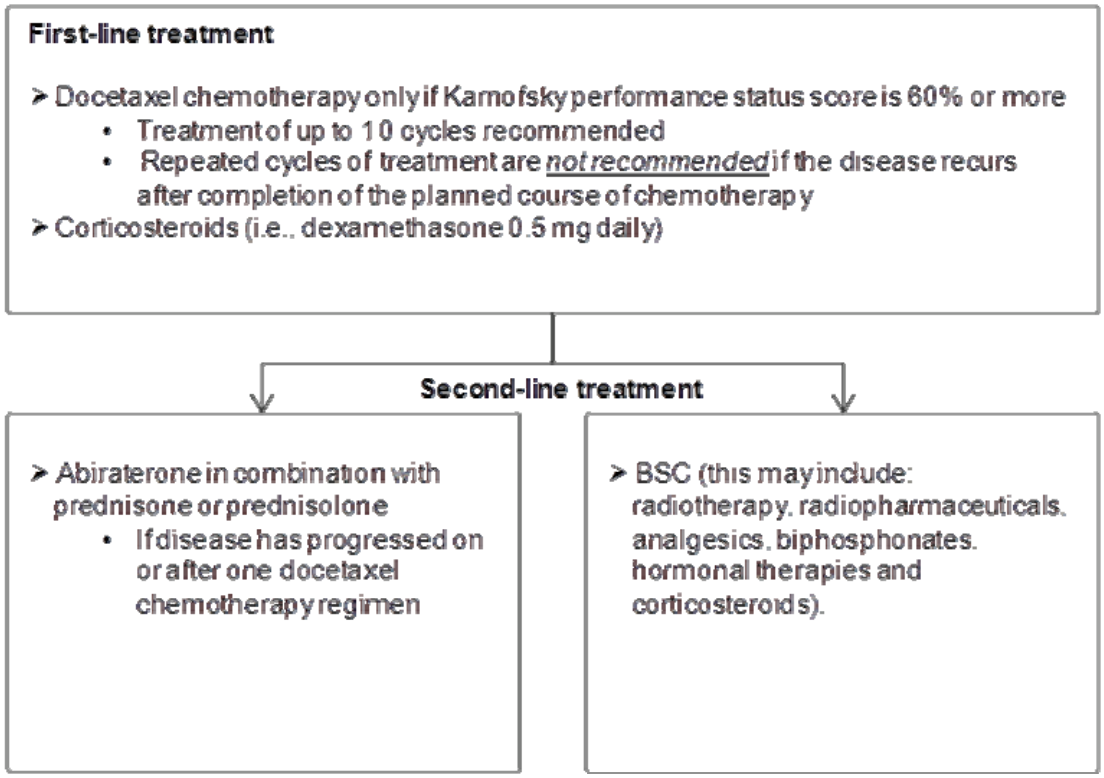
"Following the publication of the 2008 clinical guideline; two other Technology Appraisals for the treatment of mCRPC in the post-chemotherapy setting were published by NICE: cabazitaxel and abiraterone.

- *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."*

Currently, abiraterone is the only available treatment recommended by NICE for mCRPC as a second-line therapy. The MS states that this recommendation is not reflected in the current CG58 clinical guideline on prostate cancer. However, NICE are currently in the process of updating these guidelines with a revised version expected to be published in January 2014.

Section 2.5 in the manufacturer's submission presents a treatment pathway based on several NICE guidance documents and validated by expert opinion which represents current pathway for mCRPC (Figure 2.1).[13]

Figure 2.1: Treatment algorithm of mCRPC in UK clinical practice *(Source: MS, Section 2.5, P26-27)*



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.
Abbreviation: BSC: best supportive care; mCRPC: metastatic castrate-resistant prostate cancer.

The MS suggests the use of enzalutamide instead of abiraterone in the current treatment algorithm of mCRPC in UK clinical practice. The MS states that enzalutamide has demonstrated a small non-significant benefit in overall survival (OS), and statistically significant benefits in rPFS, PSA response rate and QoL over abiraterone.[13]

The MS also notes that enzalutamide has regulatory approval in the US (FDA approval was granted on 29 August 2012) for the treatment of patients with mCRPC who have previously received docetaxel.[13] Enzalutamide (XTANDI™) was also approved by the European Medicine Agency (EMA) in the same population on 21 June 2013.[13]

According to the final scope the main comparators for this submission are: abiraterone (combination with prednisone or prednisolone), mitoxantrone (alone or in combination with prednisolone) and best supportive care (BSC).[1] However, the comparators considered to be relevant by the manufacturer in this submission were abiraterone and BSC. The MS states that mitoxantrone is not considered a relevant comparator to the decision problem as it is not licensed for use in mCRPC and is not included in the NICE 2008 clinical guidelines.[13]

The ERG notes that the cabazitaxel submission states: "Mitoxantrone is used and was licensed in the first-line setting principally for its palliative benefits, including its impact on pain, illustrating the importance of effective symptom control in mHRPC.".[18] The abiraterone submission states that the use of mitoxantrone after taxane failure is likely to be minimal as there is no evidence of a survival advantage. In addition the abiraterone MS states: "Due to the lack of RCT evidence comparing mitoxantrone + prednisolone (MP) with BSC in this patient population coupled with the low use of MP post-docetaxel in the UK, MP is not considered to be a relevant comparator for abiraterone acetate, but is included as a comparator to comply with the scope."[12]

The ERG agrees that the main comparators in this submission are abiraterone (in combination with prednisone or prednisolone) and BSC (which includes radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, hormonal therapies, and corticosteroids), and that there is a lack of evidence for having mitoxantrone as a comparator in this population. However, mitoxantrone should have been included in this submission to comply with the final scope.

3. Critique of manufacturer's definition of decision problem

Table 3.1: Statement of the decision problem (as presented by the manufacturer)

	Final scope issued by NICE	Decision problem addressed in the submission	Comments/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 (See MS, 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	

	Final scope issued by NICE	Decision problem addressed in the submission	Comments/rationale if different from the scope
		the two available treatment alternatives: Abiraterone (+ prednisolone + BSC) BSC alone	
Subgroups to be considered	None	None	
Special considerations, including issues related to equity or equality	None	End-of-Life (EOL) criteria: to compare enzalutamide against BSC (MS, section 7.10.4).	

3.1 Population

The patient population described in the final scope is as follows: "Adults with metastatic hormone relapsed prostate cancer which has been previously treated with a docetaxel-containing chemotherapy regimen".[1] This is in line with the patient population included in the manufacturer submission[13] and in the main trial for this submission, the AFFIRM study.[6]

In the manufacturer's submission the population in the AFFIRM study is compared with the population in the COU-AA-301 study (abiraterone plus prednisone versus placebo plus prednisone). The conclusion is that the population in AFFIRM closely matches the population in COU-AA-301. In the NICE guidance for abiraterone (TA-259[3]), "The Committee considered the manufacturer's base-case population of patients who had received one prior chemotherapy in the COU-AA-301 trial. The Committee noted that this subgroup did not match the population for which abiraterone is licensed (the therapeutic indication in the marketing authorisation does not stipulate only one prior chemotherapy) but probably reflected the population in England and Wales for whom abiraterone would be considered." In addition, the "Committee accepted that this population was likely to reflect patients who would be treated with abiraterone in UK practice, and who would have better treatment outcomes because they have less advanced disease."

If the subgroup of patients who had received one prior chemotherapy in the COU-AA-301 study is considered to have better treatment outcomes because they have less advanced disease; then the total population should have more advanced disease and worse treatment outcomes. Therefore, the population in the AFFIRM study is also likely to be have more advanced disease and worse treatment outcomes. The implications of this in terms of effectiveness of the interventions are unknown.

3.2 Intervention

Enzalutamide received marketing authorisation in the UK on 21 June 2013. Enzalutamide is indicated for the treatment of adult men with metastatic castration resistant prostate cancer whose disease has progressed on or after docetaxel therapy.

The following information is based on the EMA Summary of Product Characteristics (SmPC).[19] The recommended dose is 160 mg enzalutamide (four 40 mg capsules) as a single oral daily dose. 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. The concomitant use of strong CYP2C8 inhibitors should be avoided if possible. No dose adjustment is necessary for older people.

Enzalutamide works by blocking the action of the male hormone testosterone and other male hormones known as androgens. Enzalutamide does this by blocking the receptors on the surface of cells to which these hormones attach and preventing them from responding. Because prostate cancer needs testosterone and other male hormones to survive and grow, by blocking these hormones, enzalutamide slows down the growth of the prostate cancer.

The most common side effects with enzalutamide (which may affect more than 1 in 10 people) are headache and hot flushes. Seizures (fits) occurred in eight patients in 1,000.

3.3 Comparators

The NICE final scope specifies the following comparators:

- Abiraterone in combination with prednisone or prednisolone
- Mitoxantrone alone or in combination with prednisolone
- Best supportive care (this may include radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies, and corticosteroids).

The manufacturer views abiraterone and best supportive care (BSC) as the main comparators. BSC comprises 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 Skeletal-Related Event (SRE).

According to the manufacturer, patients in both treatment arms of the AFFIRM study "received BSC in addition to the study treatment. Therefore, the placebo arm can be considered the equivalent to BSC" (MS, Ch 6.2.3, page 38)[13]. In the trial, patients in the control arm received placebo and additional supportive care, in both treatment groups additional use of prednisone or other glucocorticoids was permitted but not required.

The third comparator specified by NICE, mitoxantrone alone or in combination with prednisolone, was not considered to be relevant by the manufacturer. According to the MS, "mitoxantrone is not licensed for use in mCRPC and is not included in the NICE 2008 CG.[17]

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." (MS, Ch 2.7, page 28)[13]. In addition, the MS states: "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." (MS, Ch 5, page 34)[13].

However, NICE could not confirm that this was agreed and having a license in the UK or being included in NICE guidelines is not a reason to in- or exclude a treatment as a comparator. Moreover, in the comments on the scope (appendix D of the scoping documents), it is stated that "During the scoping workshop, the attendees agreed that mitoxantrone should be included as a comparator, as the most recent available evidence suggests that it is still prescribed for this indication in the NHS." Therefore the ERG asked for a full justification for excluding mitoxantrone as a comparator in the Clarification Letter.[2]

In the response to the clarification letter, the manufacturer provided the following additional justification for excluding mitoxantrone as a comparator (See Response to Clarification letter, Question A4[2]):

"Having reviewed the 2013 NICE methods guide (sections 6.2.1 to 6.2.4), Astellas maintains that mitoxantrone is an irrelevant comparator based on the guide's five criteria.

1. *Mitoxantrone has a very small and diminishing place in NHS practice in England;*
2. *Several new alternative treatments are available which have displaced a vast majority of historic mitoxantrone use;*
3. *Existing NICE guidance does not support mitoxantrone in mCRPC;*
4. *Clinical evidence for mitoxantrone in the post-docetaxel setting does not support any survival benefit for mCRPC patients and therefore it cannot be considered a cost-effective choice;*
5. *Mitoxantrone is not licensed for mCRPC."*

There are several RCTs of mitoxantrone alone or in combination with prednisone versus other active treatments in patient with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy.[20-30] However, none of these trials include a placebo arm or a prednisone arm. Therefore, there is no network linking these trials to enzalutamide and/or abiraterone. In the abiraterone assessment (TA-259) the committee also concluded that there were no trials to link the evidence for mitoxantrone to the COU-AA-301 trial and enable an indirect comparison of abiraterone and mitoxantrone.[3] In the manufacturer's submission for abiraterone, mitoxantrone was included as a comparator, but the evidence was mainly based on assumptions. The main assumption was that in the absence of evidence for any survival benefit from mitoxantrone in mCRPC, the survival of mCRPC patients given second line mitoxantrone would be assumed to be the same as that from BSC in the COU-AA-301 study.

3.4 Outcomes

The following outcomes are specified in the final scope:

- overall survival
- progression-free survival
- response rate
- prostate-specific antigen (PSA) response
- adverse effects of treatment
- health-related quality of life.

All these outcomes suggested by NICE are also specified by the manufacturer.

Definitions of the main outcomes are as follows:

Overall survival (OS): 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).

Progression Free Survival (PFS): The AFFIRM protocol included Radiographic Progression Free Survival (rPFS) as a measure of progression. A Modified Progression Free Survival (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 (See MS, section 7.3.1.2)[13]. The Time to Treatment Discontinuation (TTD) endpoint was considered a more accurate reflection of clinical practice for modelling purposes, and was used as a proxy for PFS in the economic model. 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.[31]

Time to PSA progression: PSA progression was defined 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 three or more weeks later.

Radiographic progression was defined by:

- Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 for soft tissue disease.[7]
- PCWG2 criteria for bone disease.[32, 33]

Unless warranted sooner, disease progression was first assessed at Week 13 and if deemed present then confirmed at least six weeks later using the following criteria:

Table 3.2: 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[34]
Abbreviations: CT: computed tomography; MRI: magnetic resonance imaging; RECIST: response evaluation criteria in solid tumours.

Time to Treatment Discontinuation (TTD): Time from first dose to treatment discontinuation.

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. 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.

FACT-P response rate: The FACT-P questionnaire is a 39-item questionnaire consisting of five 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). Each item can be answered on a scale of 0–4. The sum of the score on the first four domains is the Functional Assessment of Cancer Therapy – General (FACT-G) score. The sum of scores on all five domains constitutes the FACT-P. The higher the score, the better a person's quality of life (QoL) is. 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 two consecutive measurements obtained at least three weeks apart. QoL, as measured by FACT-P, was assessed at baseline and then at every regular study visit beginning at Week 13.

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 three 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.[35]

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 seven 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.

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 three or more weeks later.

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 one post-baseline assessment.

3.5 Other relevant factors

According to the MS, "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" (See MS, Executive Summary, page 7).[13]

In addition the manufacturer also states that "enzalutamide meets the criteria for appraisal of end of life medicines versus BSC" (see MS, section 7.10.4, page 193).[13]

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

An evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS), developed by McGowan et al. was used to inform this critique.[36] The submission was checked against the STA specification for manufacturer/sponsor submission of evidence.[37] The ERG has presented only the major limitations of each search strategy in the main report. Further criticisms of each search strategy can be found in Appendix 1.

Clinical effectiveness: Searches were reported for the majority of databases required by NICE, except Medline in Process (MS 6.1 & 10.2). The ERG queried this omission in their clarification letter and asked if this resource was included in the Embase/Medline search. In the response to the clarification letter, the manufacturer indicated that Medline in Process has been included in PubMed.[2] This has been checked on the website of the National Library of Medicine (NLM) and identified as correct.[38]

The MS included a simultaneous search of multiple databases (Embase and Medline searched at the same time) using a single host and search strategy. This type of search has limitations which could affect recall of results, such as reliance on the use of MeSH terms only.

The ERG noted the following significant errors in the manufacturer's searches:

- The ERG noted that the Emtree terms for enzalutamide and cabazitaxel were not included in the Embase search. As a result, relevant results may have been missed (Table 96[13]).

- The search in Table 96 was confused and inadequate. The intentions of the searcher were unclear. The line combinations were muddled and the use of subheadings excessively restrictive.

The ERG noted errors in the documentation for the following search strategies in this section (MS 10.2):

- The search of the Cochrane Library appeared to use PubMed syntax, which would have failed to retrieve relevant references correctly from the Cochrane Library via the Wiley interface. This was queried by the ERG in the clarification letter. In the response to clarification, the manufacturer stated that Cochrane had been searched via Wiley.[2] The ERG tried to replicate the manufacturer's search strategy in the Cochrane Library (via Wiley) using the syntax provided by the manufacturer; however the strategy resulted in errors and failed to run.

The manufacturer reported that additional searches were undertaken in Google and for conference abstracts, however search strategies were not provided for these resources. The

ERG requested these strategies in the clarification letter, and full strategies were subsequently supplied by the MS in their response.[2] Due to the transitory nature of the content retrieved by Google searches, the ERG did not attempt to replicate these searches.

Indirect and mixed treatment comparisons: The manufacturer stated that the clinical effectiveness searches in section 6.1.1 would be used to inform the mixed treatment comparison.[13] Therefore additional strategies were not included in this section.

Non-RCT evidence: The MS reported that no relevant non-RCTs were identified during a systematic literature review (SLR) conducted by Quintiles (MS 6.8).[8, 13] The SLR was published in June 2013 but included exactly the same search strategies and errors as the industry submission. It appears that minor changes were unintentionally introduced by auto-correction changes made by MS WORD in the NICE submission. The manufacturer decided not to include strategies for non-RCTs in the submission, due to lack of results in the SLR. The search strategy used in the SLR (table 14.1)[8] used ineffective and confused filters and this may have resulted in missing relevant studies.

Adverse events: The manufacturer stated that searches for adverse events were already covered by the clinical effectiveness search.[13] CRD guidance recommends that if searches have been limited by an RCT filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed.[39] Despite the addition of a systematic review filter, the ERG considered that it was possible that some relevant evidence may not have been identified as a consequence of the restrictive study design limit.

Cost effectiveness: Searches were reported for the majority of databases required by NICE, except Medline in Process (MS 10.10.4). The manufacturer stated that the Database of Abstracts of Reviews of Effects (DARE) and the National Health Service Economic Evaluation Database (NHS EED) were searched through the Cochrane Library. However, it was not stated if the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL) were also included. The ERG requested this information in the clarification letter. The manufacturer replied in their clarification response that Medline in Process was included in the PubMed search and that CENTRAL and CDSR were included in the Cochrane library search.[2]

The ERG noted errors in the documentation for the following search strategies in this section (MS 10.10):

- The ERG noted that the lines in table 103 were incorrectly numbered and queried this in the clarification letter. The manufacturer responded with an amended search strategy with corrected line numbers.[2]

- The economics search of the Cochrane Library appeared to use PubMed syntax, which would have failed to retrieve relevant references correctly from the Cochrane Library via the Wiley interface. This was queried by the ERG in the clarification letter. In the

response to clarification, the manufacturer stated that Cochrane had been searched via Wiley.[2] The ERG tried to replicate the manufacturer's search strategy in the Cochrane Library (via Wiley) using the syntax provided by the manufacturer; however the search resulted in an error message and failed to run.

- The strategy included an unused "orphan" line (#6) which was not combined for the final search results. This may have resulted in missing important references.

Measurement and valuation of health effects: The MS reported that the measurement and valuation of health effects analysis (MS 7.4.5, 10.12) was informed by the search for cost effectiveness.[13] Therefore no additional strategies were included in this section.

The ERG noted errors in the documentation for the following search strategies in this section (MS 10.12):

- In the Embase/Medline search strategy in Table 103[13] the lines after #15 were confused, attempting to erroneously combine lines which were not present in the strategy. The ERG asked for a corrected version in the clarification letter, which was provided in the manufacturer's response.[2] The manufacturer's response also included a change in the final line of this search strategy. This change resulted in 20 new results which might not have been included in the manufacturer's review process.

- As discussed in the previous section, the Cochrane Library strategy appeared to employ PubMed syntax rather than the appropriate Wiley Cochrane Library syntax. The ERG attempted to re-run this search however the strategy resulted in an error message and failed to run or retrieve references. Furthermore, line 6 was a redundant orphan line and was not included in the final result. This may have resulted in the omission of results.

Resource identification, measurement and valuation: The MS reported that the resource identification, measurement and valuation section (MS 7.5.3, 10.13) was informed by the search for cost effectiveness.[13] No additional strategies were included in this section.

Summary of searching

The searches documented in the initial manufacturer's submission contained several areas of weakness, only those relating to reproducibility were included in the clarification letter forwarded to the manufacturer by NICE. The manufacturer addressed all the points of concern raised by the ERG in their response to the clarification letter.

4.1.2 Inclusion criteria

The eligibility criteria used in the search strategy are described in Table 5, page 36 of the MS (*see MS, Section 6.2.1, page 36*[13]; and the Table below).

Table 4.1: Eligibility criteria used 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.

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.

The eligibility criteria used in the search strategy are in line with the NICE scope.

4.1.3 Critique of data extraction

One RCT was included for enzalutamide, the AFFIRM trial. The data from this trial were extracted from five publications: the published journal article by Scher et al, 2012,[6] the full clinical study report for the AFFIRM trial,[34] two ASCO abstracts,[40, 41] and a report from Quintiles describing patient reported outcomes in the AFFIRM trial.[35]

In addition, one trial was included for abiraterone, the COU-AA-301 trial. The data from this trial were extracted from five publications: two published journal articles by De Bono et al. 2011[15] and Fazizi et al. 2012,[4] and three ASCO abstracts.[42-44]

4.1.4 Quality assessment

The quality assessments of both the AFFIRM and COU-AA-301 studies can be found in appendix 3, section 10.3 and appendix 5, section 10.5 of the MS, respectively and in the table below.

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.

ERG Comment:

The ERG agrees with the manufacturer's assessment that neither of the two studies used in the indirect comparison were at a high risk of bias.

Table 4.2: Quality assessment results for the AFFIRM and COU-AA-301 studies

	AFFIRM		COU-AA-301	
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	AFFIRM was an international, randomised, double-blind, placebo-controlled, global multicentre phase III study	Y	COU-AA-301 is a phase III, multinational, randomised, double blind, placebo-controlled study.	Y
Was the concealment of treatment allocation adequate?	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.	Y	Patients were randomised in a 2:1 ratio, to receive: • Oral abiraterone: 1g (4x250 mg tablets) oral twice daily + Prednisolone: 5mg oral twice daily • Placebo: 4 tablets, oral twice daily + Prednisolone: 5mg oral twice daily	Y
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?		Y		Y
Were the care providers, participants and outcome assessors blind to treatment allocation?	All patients, investigators, and the sponsor's staff involved in the conduct of the study were blinded to treatment assignment.	Y	All patients, investigators, and the sponsor's staff involved in the conduct of the study were blinded to treatment assignment.	Y
Were there any unexpected imbalances in drop-outs between groups?		N		N
Is there any evidence to suggest that the authors measured more outcomes than they reported?		N		N
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No imputations of missing efficacy data were performed. For all time-to-event analyses, patients that dropped out of the study or had missing data were censored at the last assessment for that endpoint.	Y Y		Y Y

	AFFIRM		COU-AA-301	
	Death dates with missing day of the month were imputed as the earliest possible date that incorporates the available death date information that does not contradict the date last known alive in the database.			

Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination[39]

4.1.5 Evidence synthesis

The same search and inclusion criteria (see Table 4.1) were used for the SLR for the indirect and mixed treatment comparison as for the SLR for the intervention. Based on the searches, 11 relevant studies were identified. These trials are described in Table 19 of the MS (MS, page 76-77)[13] which is reproduced below.

Table 4.3: List of RCTs identified by the systematic literature review

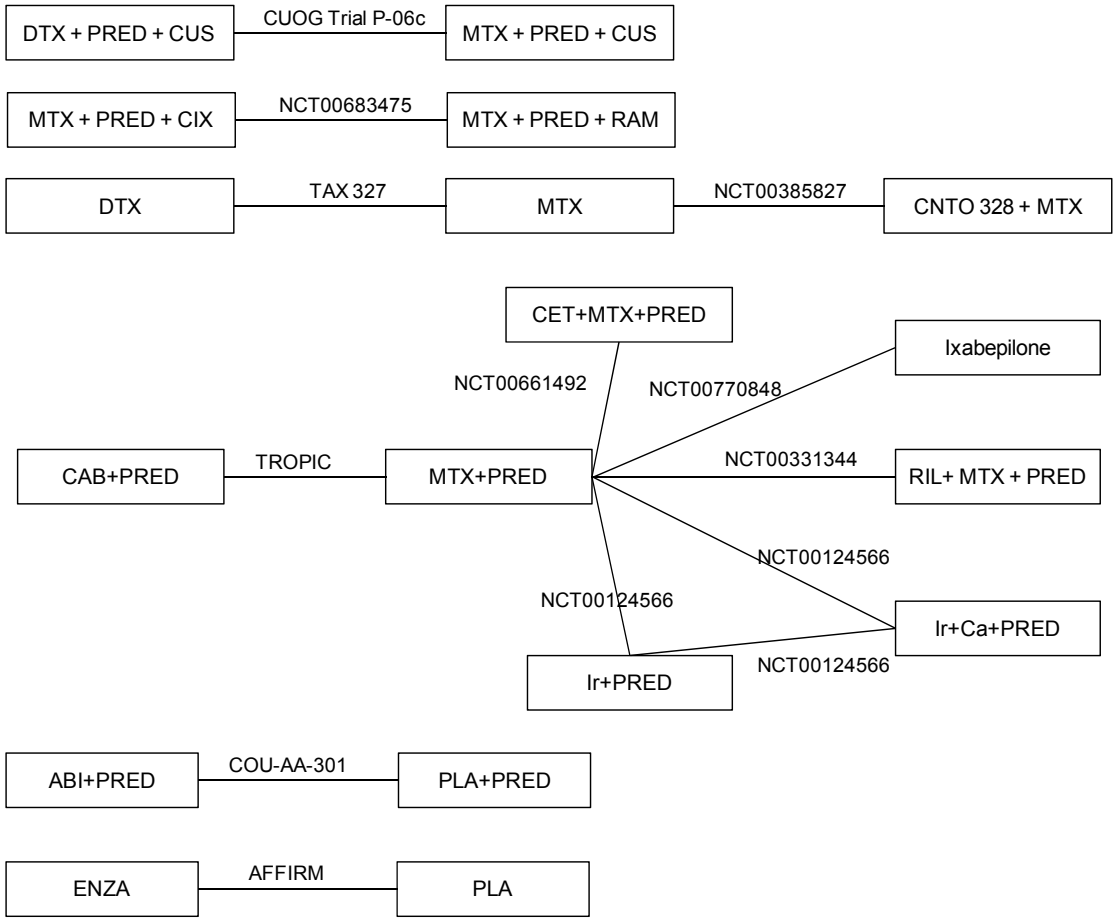
	Study (design)	Intervention	Comparator	References
Studies included in the ITC	AFFIRM (RCT, phase III, DB, PLA-controlled)	ENZA (n=800): •ENZA 160 mg PO OD Use of corticoids was allowed but not required	PLA (n=399) •PLA PO OD Use of corticoids was allowed but not required	Scher 2012a[6] De Bono 2012[41] Scher 2012b[40] AFFIRM CSR (April 24, 2012)[34] PRO 2012[35]
	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[15] Fizazi2012[4] Goodman 2012[43] Scher 2011[42] Efstathiou 2012[44]
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[20] Berger 2007[21]
	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[22]
	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-	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[23]

	Study (design)	Intervention	Comparator	References
		days, followed by x1wk administration		
	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[24] Oudard 2011[25] Sartor 2011[26]
	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[45]
	NCT00661492	CET + MTZ +PRED	MTZ + PRED	Fleming 2010[27] Fleming 2012[28]
	NCT00770848 (RCT, phase Ib/II, DB)	RIL15 mg/kg + MTZ +PRED	RIL 7.5 mg/kg + MTZ +PRED PLA + MTZ	Ryan 2012[29]
	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[30]
	NCT00385827 (non randomised, phase II)	CNTO 328+ MTZ	MTZ	De Bono 2010b[46]

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.

The network of RCT evidence identified by the SLR is described in Figure 15 of the MS (MS, page 78)[13], and reproduced below.

Figure 4.1: 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; MTX: mitoxantrone; PLA: placebo; PRED: prednisone; RCT: randomised clinical trial; RIL: rilotumumab.

Only two of the 11 studies identified were considered relevant for the decision problem in this STA: the AFFIRM trial and the COU-AA-301 trial. The other nine studies were excluded as they were not linked to the intervention of interest: enzalutamide. The COU-AA-301 trial was included because an indirect comparison was deemed feasible when the comparator arms in AFFIRM and COU-AA-301 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 versus 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.

The MS does not present effectiveness results for mitoxantrone which was identified as one of the comparators in the NICE final scope. All trials including mitoxantrone were excluded from the MS. In the economic model for the abiraterone STA (TA-259), evidence for the effectiveness of mitoxantrone was either based on the PP arm of the COU-AA-301 trial or on data from the TROPIC study:[24]

- The OS under mitoxantrone was taken to be equal to the PP arm of the COU-AA-301 trial.
- Progression free survival (PFS) was modelled on treatment discontinuation of the PP arm
- Treatment discontinuation was based on an analysis of the TROPIC study.

An overview of the TROPIC study is presented in section 4.5 of this report.

ERG Comment:
The MS does not provide details of what constituted best supportive care in the two trials (AFFIRM and COU-AA-301). Therefore, the ERG asked the manufacturer to define BSC in both trials. According to the manufacturer "Best supportive care (BSC) in AFFIRM and COU-AA-301 studies encompassed the following:

- In AFFIRM: radiopharmaceuticals, analgesics, bisphosphonates, hormonal therapies and corticosteroids. Radiotherapy was also considered as BSC however, in AFFIRM when radiotherapy was given this was reported as a skeletal related event (SRE) event.
- In COU-AA-301: radiotherapy, bisphosphonates, analgesics and LHRH agonists as needed. In this study, all patients received corticosteroids as part of the study medication. Similarly to AFFIRM, radiotherapy was considered as BSC but when administered, this was reported as a SRE event." (see Response to Clarification Letter, Question A2, page 5-6[2]).

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

In this section we will present the results from the AFFIRM trial. The study characteristics are presented in Table 4.4, a summary of the methodology in Table 4.5 and the eligibility criteria in Table 4.6.

4.2.1 Study characteristics

Table 4.4: Overview of the AFFIRM trial

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	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)	100% prior DTX ENZA •1 course: 72.4% •2 courses: 24.5% •≥2 courses: 3.1%	Scher 2012a[6] De Bono 2012[41] Scher 2012b[40] AFFIRM CSR (April 24, 2012)[34] PRO 2012[35]
	PLA (n=399) •PLA PO OD Use of glucocorticoids was allowed but not required	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)	PLA •1 course: 74.2% •2 courses: 23.8% ≥2 courses: 2.0%	

Source: MS, Table 6, page 39.[13]
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

Table 4.5: 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: MS, Table 7, page 43.[13]
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 the MS, unless otherwise specified were based on the IA dataset.

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.

A stratified log-rank test was used as the primary analysis to compare the enzalutamide and placebo arms, with a two-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,[47] 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).

Table 4.6: 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.	• 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,

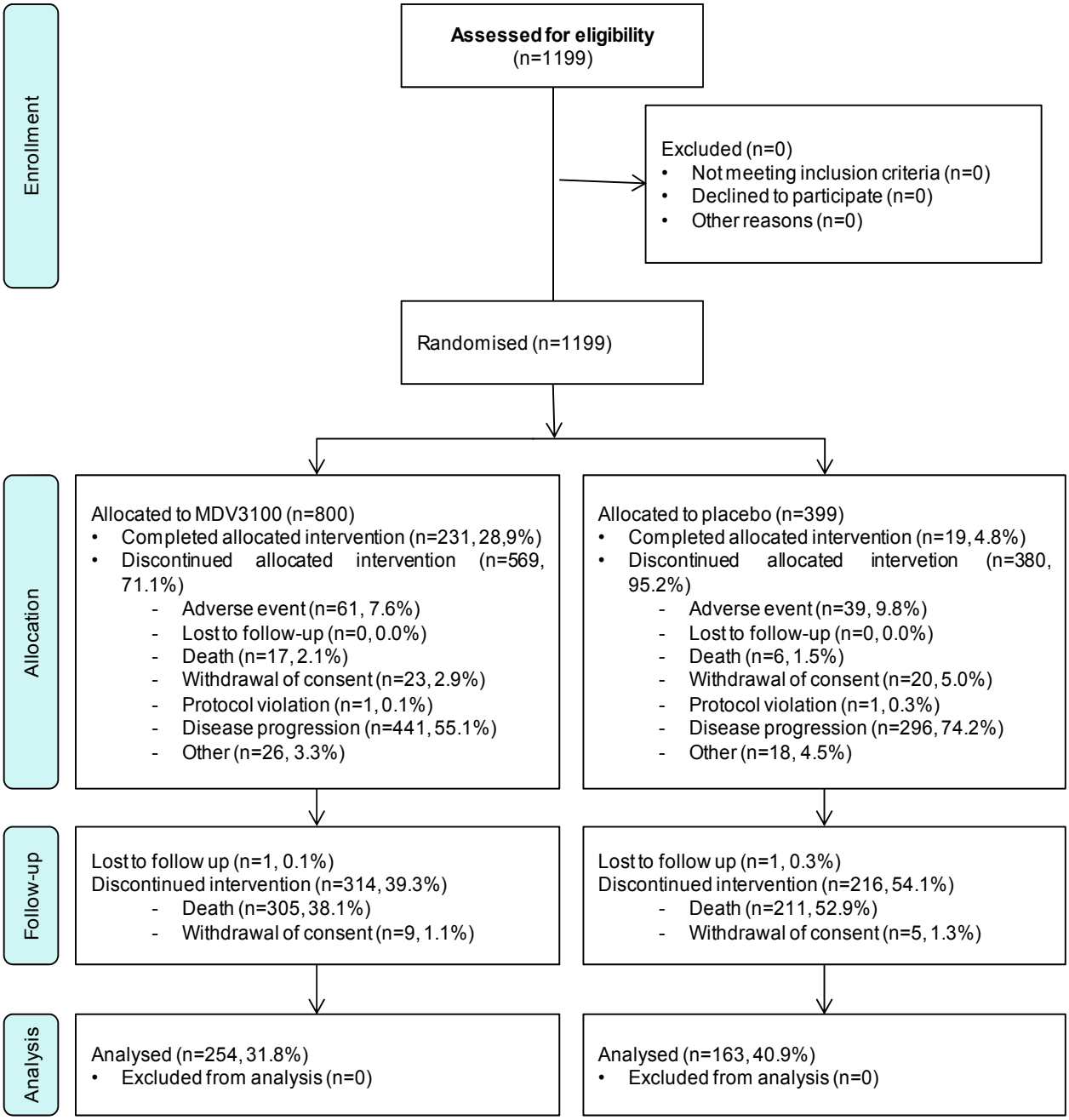
• ≤2 prior chemotherapy regimens with ≥1 regimen containing docetaxel • ECOG performance status of 0–2; • Estimated life expectancy of ≥6 months • Able to swallow the study drug and comply with study requirements • Willing and able to give informed consent.	ketoconazole, an investigational agent or Major 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: MS, Table 8, page 46.[13]
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.

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 flow of patients through the study is presented in Figure 4.2.

Figure 4.2: Patient disposition flow chart as of 25 September 2011 (ITT)



Source: MS, Figure 5, page 58[13]
Note: *Ongoing treatment at data cut-off
Abbreviations: AE, adverse events; ENZA, enzalutamide; PLA, placebo.

The demographics, baseline disease characteristics and medical history of patients in both treatment arms are presented in Table 4.7. Overall, both treatment arms were well balanced.

Table 4.7: 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		
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%)

	enzalutamide(N = 800)	placebo (N = 399)
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: MS, Table 9, page 48.[13]
Abbreviations: ECOG: eastern cooperative oncology group; PSA: prostate specific antigen; SD: standard deviation.

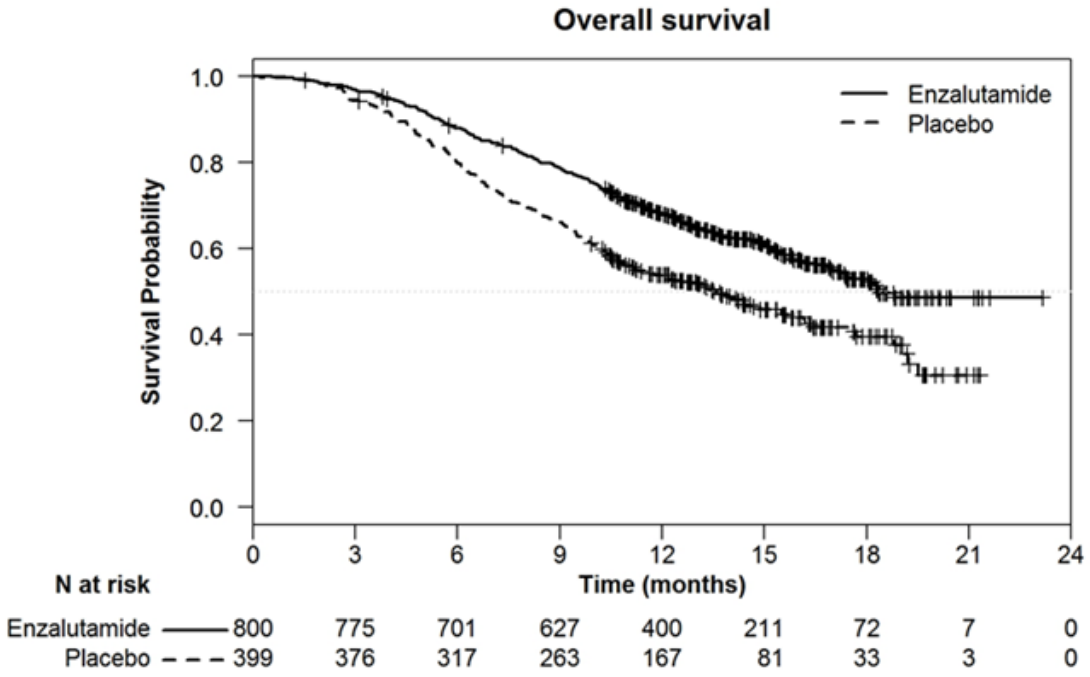
4.2.2 Results

Overall Survival

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 4.3). 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 4.2) (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).[6] 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 4.3: Kaplan-Meier curve for OS (ITT)

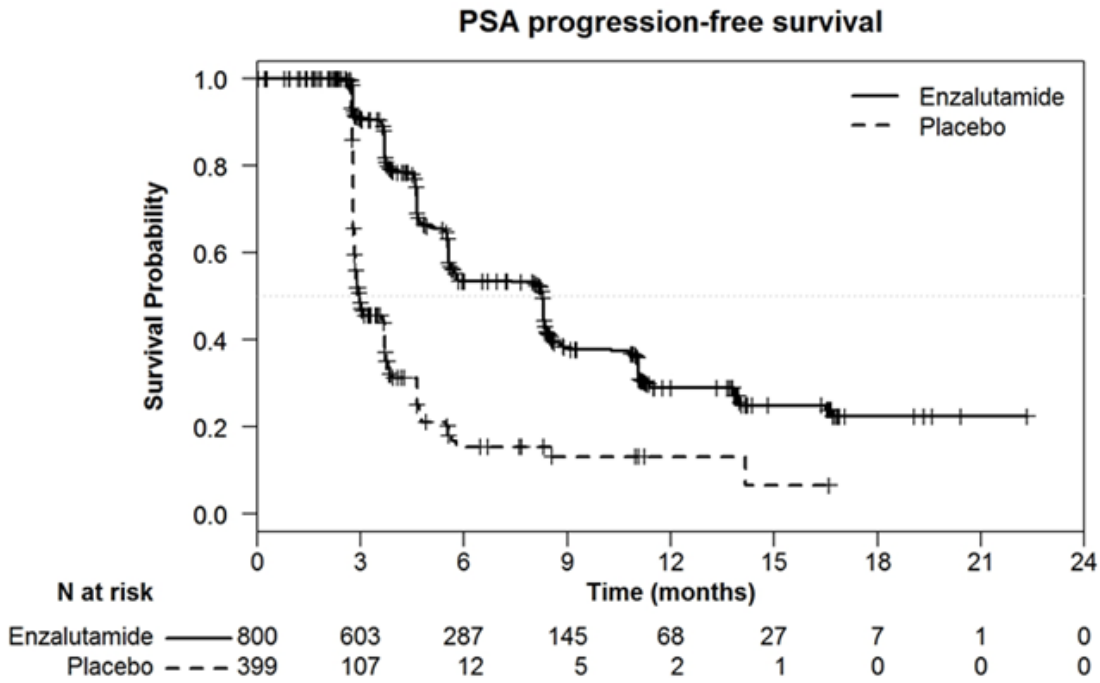


Source: MS, Figure 6, page 61.[13]
Abbreviation: CI: confidence interval; ITT: intention to treat; HR: hazard ration; OS: overall survival.

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 4.4).

Figure 4.4: Time to PSA progression (ITT)



Source: MS, Figure 7, page 63.[13]
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 4.8). Enzalutamide decreased the risk of disease progression by 60% (HR: 0.40, 95% CI [0.35; 0.47]; p<0.001).[6]

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 4.8: 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% Cl)	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% Cl)	0.404 (0.350, 0.466)	
P-value (log-rank)	<0.0001	

Source: Scher 2012a.[6]
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 4.9). 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 4.9: 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% Cl)	16.7 (14.4, 19.1)	13.3 (9.9, not reached)
Stratified Analysis		
Hazard ration (95% Cl)	0.688 (0.566; 0.835)	
P-value (log-rank)	<0.0001	

Source: MS, Table 15, page 64.[13]
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

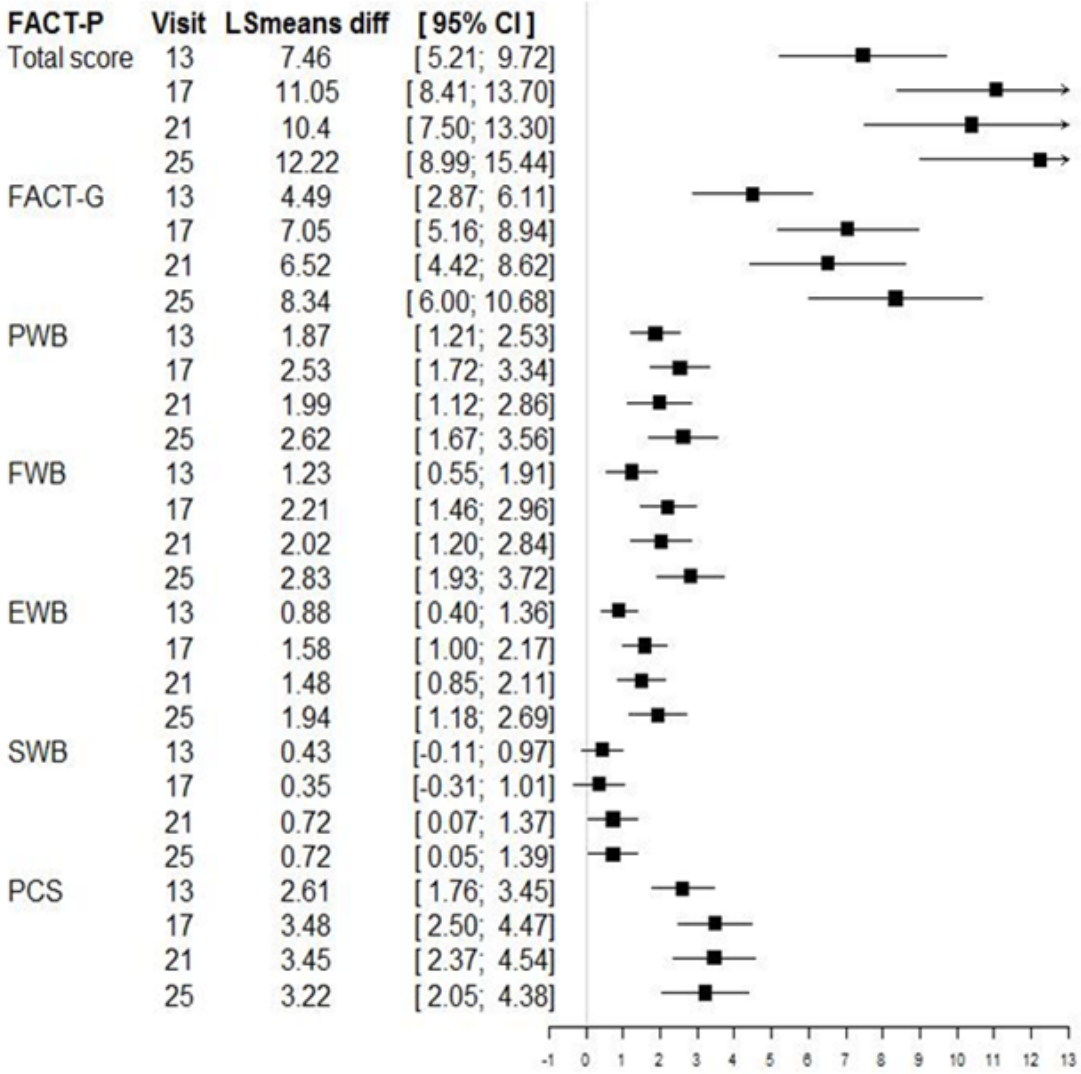
Both secondary and exploratory FACT-P outcomes are presented below.

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 time point ranged 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 mixed model with repeated measures (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 4.5).

Figure 4.5: 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[35, 48]
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.

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 five domain items correctly answered) throughout the study decreased more rapidly in the placebo arm (Table 4.10). Incidentally, the EQ-5D numbers presented in chapter 6.5.3.3 of the MS (MS, Table 17, page 68)[13] are not consistent with the data reported in chapter 7.4.6 of the MS (MS, page 146)[13].

Table 4.10: 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.[35]
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 showed no statistically significant differences between treatment arms at weeks 13 and 25 (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 (See MS, section 7.4.4).[13, 49]

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).

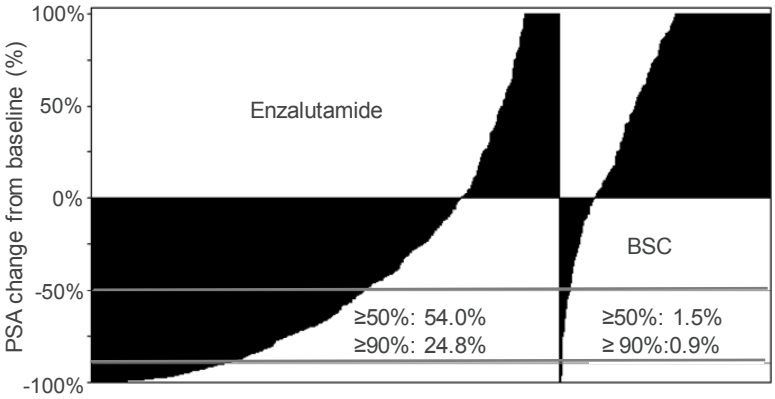
Pain palliation was also defined as ≥30% reduction in average pain score at Week 13 without a ≥30% increase in analgesic use. However, only 6.1% and 3.8% of patients in the enzalutamide and placebo arms, respectively, could be assessed using this definition. Among these patients, significantly more patients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

PSA response rate

Enzalutamide led to a greater PSA response defined as ≥50% decrease confirmed three or four 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 4.6).

Figure 4.6: Waterfall plot of PSA response



Source: MS, Figure 10, page 67[13]
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.

Modified progression-free survival

Median mPFS was [redacted] months (95% CI [[redacted]]) for enzalutamide vs. [redacted] months (95% CI [[redacted]]) for placebo (

Figure 4.7: Kaplan-Meier curves for modified PFS (ITT)). The HR for mPFS favoured enzalutamide significantly (HR: [redacted], 95% CI: [[redacted]]; p <[redacted]).

Figure 4.7: Kaplan-Meier curves for modified PFS (ITT)

Source: MS, Figure 12, page 71.[13]
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 4.8).

Figure 4.8: Kaplan-Meier curves for time to treatment discontinuation (ITT)

Source: MS, Figure 13, page 72.[13]
Abbreviations: ENZA: enzalutamide; ITT: intention-to-treat; PLA: placebo

Adverse Events in AFFIRM

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 4.11: 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]
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]

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)
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: MS, Table 29, page 91-92.[13]

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.

Nearly all enzalutamide-treated and placebo-treated patients experienced at least 1 AE in AFFIRM (Table 4.12).

Table 4.12: 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: MS, Table 30, page 93[13]
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.

Table 4.12 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 4.13). 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 4.13. 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 4.13: 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: MS, Table 31, page 94[13]
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 4.14). 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 4.14: 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: MS, Table 32, page 95[13]
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 4.15: Study drug-related adverse events occurring at a ≥1% frequency in either enzalutamide or placebo terms by preferred term

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)
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]
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]

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)
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: MS, Table 33, page 96-97.[13]
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 (See MS, Section 6.9.2.1, pages 98-100)[13].

ERG Comment:
Although derived from only a single RCT there is compelling evidence that enzalutamide significantly prolongs OS and extends time to progression. Similarly as for abiraterone, the intervention is convenient for the patient and the NHS, in that it is orally self-administered.

Regarding adverse events, the EMA considers enzalutamide to be generally safe;[19, 50] the ERG found no contradictory evidence. In the CHMP assessment report, the safety of enzalutamide is summarised as follows:

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

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

However, the main concerns are about psychiatric and nervous system disorder, paying special attention to seizure. As it is an oral medicinal product, seizures are expected to occur

out of hospital in the majority of cases. In order to prevent or minimise this risk, an effort to further characterise patients at risk should be done. In this sense, the measures implemented to minimise the risk of seizures are considered acceptable (as reflected in section 4.4 and 4.8 of the SmPC and in the RMP). The post-authorisation safety study as detailed in the RMP will provide further information to update risk mitigation recommendations. The submitted draft protocol synopsis of this study was reviewed (see RMP for further information)".[50]

It is important to note that enzalutamide is not associated with some of the more debilitating toxicities that are often seen with cytotoxic drugs such as mitoxantrone such as myelosuppression, diarrhoea, asthenia, alopecia and others. Enzalutamide seems generally safe and the toxicities associated with it are relatively mild in the context of the disease and easily manageable.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

In this section we will compare the study characteristics and results from the AFFIRM trial with the COU-AA-301 trial. The study methodologies are presented in Table 4.16.

Table 4.16: 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,

	AFFIRM	COU-AA-301
		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[4]: 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 • 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[6]; Clinical study report[34]	Fizazi et al 2012[4]; Logothetis et al.[5]; NICE submission 2012[3]

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 manufacturer's ITC were OS, rPFS, modified PFS, time to first SRE, time to treatment discontinuation, all grade and grade 3+ AEs and tolerability (Table 4.17).

Table 4.17: Endpoints assessed and data sources for the indirect treatment comparison

	References used for enzalutamide	**References used for abiraterone**
OS	MS-Data on file	Fizazi et al[4]
rPFS	Scher et al[6]	Fizazi et al[4]
Modified PFS	MS-Data on file	NICE submission[3]
Time to first SRE	Scher et al[6]	Logothetis et al[5]
ORR	Scher et al[6]	Fizazi et al[4]
PSA response	Scher et al[6]	Fizazi et al[4]
AEs	Clinical Study report[34]	Fizazi et al[4]
Tolerability	Scher et al[6]	Fizazi et al[4]
Time to treatment discontinuation	MS-Data on file	NICE submission[3]

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 4.18.

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.

Table 4.18: 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		

	AFFIRM	COU-AA-301
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[40]; Scher 2011[42]; Fizazi 2011[4]
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 4.19).

Table 4.19: 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.[6] 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+.[34]	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.[6] The CSR provides information on those AEs with a ≥1%	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.

	AFFIRM	COU-AA-301
	frequency in either arm for grade 3+.[34]	
Tolerability	Study drug discontinuation due to AEs.	Same as in AFFIRM.

Source: Scher 2012[6]; Fizazi 2012[4]
Abbreviations: AEs: adverse events; CSR: clinical study report.

4.3.1 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 4.20). 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 4.20: 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)

	AFFIRM		COU-AA-301	
	ENZA (n=800)	PLA (n=399)	ABI + PRED (n=797)	PLA + PRED (n=398)
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	442 (55.8%)	219 (55.0%)	361/797 (45%)	164/397 (41%)
Liver	92 (11.6%)	34 (8.5%)	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[6]; Scher 2011[42]; Fizazi 2012[4]
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).

4.3.2 Results

The ITC was performed for the following outcomes: OS, rPFS, mPFS, time to SRE, ORR, PSA response, all grade and grade 3+ specific AEs. An ITC for TTD was not possible because data for TTD was marked as confidential in the COU-AA-301 trial.

The ITC was performed using the "adjusted" indirect comparison methodology described by Bucher.[9] 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[51] 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.

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 4.21 and Table 4.22. All abiraterone-related data including OS correspond to the final analysis as reported in Fizazi 2012[4], Logothetis et al.[5] and the NICE submission[3].

The data cut-off used for the AFFIRM study is the IA analysis (25 September 2011) for all outcome measures [Scher 2012a[6]] with the exception of OS, where the database lock was used (16 December 2011).

Table 4.21: OS, rPFS and time to first SRE data included in the ITC with results (HR, 95%CI)

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

Source: SLR 2013[8]
Abbreviations: HR: hazard ratio; OS: overall survival; rPFS: radiographic progression-free survival; SRE: skeletal-related events; TTD: Time to treatment discontinuation.

Enzalutamide was associated with a significantly higher likelihood of attaining radiographic and modified PFS than abiraterone. In contrast, no significant differences were observed for OS or time to first SRE.

Table 4.22: ORR and PSA response data included in the ITC with results

Outcome		AFFIRM		COU-AA-301		Treatment comparison: ENZA vs. ABI
		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]		[redacted]
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]		[redacted]

Source: SLR 2013[8]
Abbreviations: ABI: abiraterone; ENZA: enzalutamide; HR: hazard ratio; OR: odds ratio; ORR: objective response rate; PLA: placebo; PRED: prednisone; PSA: prostate specific antigen.
In bold: statistically significant outcomes
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.

Enzalutamide was associated with a significantly higher likelihood to achieve a PSA response (defined as ≥50% decrease confirmed three or four weeks later) than abiraterone. However, no significant differences were observed between enzalutamide and abiraterone for ORR.

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.[6] 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+.

- For COU-AA-301, de Bono et al.[15] and Fizazi et al.[4] 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.[4]).

All grade AEs

The incidence of all grades AEs included in the ITC is provided in Table 4.23. 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.

Table 4.23: Summary of all grades AEs included in the ITC with results

AE	AFFIRM			COU-AA-301			ENZA vs. ABI OR [95% CI]
	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]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	25.03%	27.92%	0.86 [0.66; 1.13]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	30.21%	24.11%	**1.36 [1.03; 1.80]**	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	15.42%	13.71%	1.15 [0.81; 1.62]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	33.12%	35.79%	0.89 [0.69; 1.15]	[redacted]
Bone pain	[redacted]	[redacted]	[redacted]	15.93%	29.70%	**0.45 [0.34; 0.60]**	[redacted]
Dehydration	[redacted]	[redacted]	[redacted]	NA	NA	NA	
Diarrhoea	[redacted]	[redacted]	[redacted]	19.72%	14.72%	**1.42 [1.02; 1.98]**	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	14.66%	12.44%	1.21[0.85; 1.73]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	47.03%	44.16%	1.12 [0.88; 1.43]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	0.38%	0.00%	NA	
Hypertension	[redacted]	[redacted]	[redacted]	11.13%	8.12%	1.42 [0.93; 2.16]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	18.08%	9.14%	**2.19 [1.49; 3.23]**	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	NA	NA	NA	
Nausea	[redacted]	[redacted]	[redacted]	32.62%	32.99%	0.98 [0.76; 1.27]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	1.01%	0.51%	2.00 [0.42; 9.48]	[redacted]
Oedema Peripheral/ Fluid retention	[redacted]	[redacted]	[redacted]	33.00%	23.86%	**1.57 [1.19; 2.07]**	[redacted]
Pain	[redacted]	[redacted]	[redacted]	4.80%	5.33%	0.90 [0.52; 1.55]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	19.72%	20.81%	0.93 [0.69; 1.26]	[redacted]
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]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	24.15%	25.63%	0.92 [0.70; 1.22]	[redacted]

Source: Summary of Clinical Safety[52] and SLR[8]

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.

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]]).

Grade 3 or more 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 4.24.

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.

SRE

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

Table 4.24: Summary of grade 3 or more AEs included in the selected studies with results

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

Source: SLR 2013[8] Abbreviation: ABI: abiraterone; 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.

Tolerability assessed as discontinuation due to AEs
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 lower with study intervention (enzalutamide and abiraterone) than the comparator. The ITC showed no significant differences in the rate of treatment discontinuation (tolerability) (OR: [redacted], 95% CI [redacted]) (Table 4.25).

Table 4.25: Summary of tolerability data included in the ITC with results

	AFFIRM (Scher 2012a)		COU-AA-301 (Fizazi 2012)		Comparison
	ENZA	PLA	ABI + PRED	PLA + PRED	ENZA vs. ABI
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]		[redacted]

Source: Scher 2012[6]; Fizazi 2012[4] and SLR 2013[8]
Abbreviations: ABI: abiraterone; ENZA: enzalutamide; OR: odds ratio; PLA: placebo; PRED: prednisone.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The manufacturer examined possible sources of heterogeneity which could arise from (MS, Section 6.7.7, page 87-88):

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

4.4.1 Comparability of the control arm in both studies

Abiraterone needs to be taken with steroids which is not the case for enzalutamide. Therefore a different percentage of patients in the control arm of AFFIRM and the COU-AA-301 study received steroids (n=182/399, 45.6% vs. n=398/398, 100%). According to the manufacturer, 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 (MS, section 6.7.7, page 87)[13].

The ERG asked the manufacturer to justify why steroids have no impact on patient reported outcomes such as pain, quality of life and adverse events (See Clarification Letter, Question A6[2]). The manufacturer's response was as follows:

> *"The impact of steroid use on patient reported outcomes such as pain, quality of life (QoL) and adverse events is likely to be driven by three factors: 1) the potential direct effect of corticosteroids on disease progression, 2) the beneficial effect on symptoms due to anti-inflammatory and other adrenocortical effects, and 3) the implications of adverse events associated with corticosteroid use.*

There is no evidence to suggest that steroids may impact PFS or OS at this late stage of treatment, with experts noting that many patients would have already received steroids earlier in their treatment and subsequently progressed, indicating that they may have become corticosteroid resistant (reference 4 in MS: 'Advisory Board Meeting. London; April 2013'). The benefits to QoL driven by physiological disease improvement associated with steroids are therefore assumed negligible.

The beneficial effect of steroid use on symptoms due to anti-inflammatory and other adrenocortical effects in this population may improve QoL by helping to mitigate metastatic bone pain, improve appetite and reduce weight loss. As such, some patients in the BSC arm of the COU-AA-301 trial may be considered to have had a higher baseline QoL than patients in the BSC arm of AFFIRM.

Conversely, corticosteroid use (particularly chronic use), is associated with adverse effects such as osteoporosis, hyperglycaemia, loss of muscle mass, immune suppression, oedema and hypertension. As such, some patients in the BSC arm of the COU-AA-301 trial may be considered to have had a lower baseline QoL than patients in the BSC arm of AFFIRM.

No controlled study has evaluated the treatment effect of corticosteroids prescribed alone to this patient group. The paucity of controlled data to quantify the steroid effect, coupled with the added complexity that patients in the control arms of AFFIRM and COU-AA-301 were prescribed different types of corticosteroids at different doses for different durations and for different indications led Astellas to take the view that attempting to adjust for the effect of steroids was likely to add substantial unnecessary uncertainty to the indirect comparison. Experts confirmed that the effect of steroids on QoL would be very difficult to quantify and could be highly variable between patients. Therefore the positive and negative effects of steroids were assumed to result in a negligible net benefit to the overall population and it is assumed that the control arms of the AFFIRM and COU-AA-301 trials should be compared without any steroid adjustment." (See Response to Clarification Letter, Question A6, page 9-10[2])

4.4.2 Comparability of the patient population

According to the manufacturer: "when comparing baseline characteristics it seems there is no difference between the populations. Time since PC diagnosis was comparable in both studies (MS, Table 24)" (MS, section 6.7.7, page 87)[13].

Baseline characteristics of patients in the AFFIRM and COU-AA-301 trials are presented in Table 4.20 of this report. From this table it can be seen that:

- The COU-AA-301 trial has slightly more patients aged over 75 years,
- The COU-AA-301 trial has slightly more patients with ECOG classification 2.
- There are small differences in the number of previous cytotoxic chemotherapy regimens, in that the AFFIRM trial has slightly more patients with one or three

previous regimens, while the COU-AA-301 trial has slightly more patients with two previous regimens.

- The AFFIRM trial has slightly more patients who had previous cancer surgery.

In the manufacturer submission the population in the AFFIRM study is compared with the population in the COU-AA-301 study for the comparison with abiraterone. According to the manufacturer, the population in AFFIRM closely matches the population in COU-AA-301. In the NICE guidance for abiraterone (TA-259[3]), "The Committee considered the manufacturer's base-case population of patients who had received one prior chemotherapy (OPC) in the COU-AA-301 trial. The Committee noted that this subgroup did not match the population for which abiraterone is licensed (the therapeutic indication in the marketing authorisation does not stipulate only one prior chemotherapy) but probably reflected the population in England and Wales for whom abiraterone would be considered." In addition, the "Committee accepted that this population was likely to reflect patients who would be treated with abiraterone in UK practice, and who would have better treatment outcomes because they have less advanced disease." In the COU-AA-301 study the OPC sub-population was pre-specified and contributed ~70% of the total; amongst the remaining 30% who received two different chemotherapy regimens one regimen was docetaxel.

If the subgroup of patients who had received one prior chemotherapy in the COU-AA-301 study is considered to have better treatment outcomes because they have less advanced disease; then the total population should have more advanced disease and worse treatment outcomes. Therefore, the population in the AFFIRM study is also likely to be have more advanced disease and worse treatment outcomes. The implications of this in terms of effectiveness of the interventions are unknown.

4.4.3 Definition used for mPFS

The definition of mPFS differs between the two studies (MS, Table 22)[13]. According to the manufacturer, several clinicians indicated that these differences were small.[31] In addition, the manufacturer states that, when looking at the individual components of mPFS (rPFS, time to first SRE and PSA progression) the ITC results show a consistent trend. (MS, section 6.7.7, page 87-88)[13]

The ERG agrees that the baseline population characteristics of individuals in the studies were comparable in terms of demographics and disease status, and that the two trials were similar enough to allow an indirect comparison of enzalutamide versus abiraterone.

The indirect comparison was performed using the "adjusted" indirect comparison methodology described by Bucher.[9] The ERG agrees that this is an appropriate method, and it was performed correctly.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The MS does not present effectiveness results for mitoxantrone which was identified as one of the comparators in the NICE final scope.

In the economic model for the abiraterone submission, OS under mitoxantrone was taken to be equal to the PP arm of the COU-AA-301 trial; progression free survival (PFS) was modelled on treatment discontinuation of the PP arm while treatment discontinuation was based on an analysis of the TROPIC study.[24] Therefore, the TROPIC study is probably most informative for the clinical effectiveness of mitoxantrone. Although the ERG agrees that the available evidence does not allow for an indirect comparison of enzalutamide versus mitoxantrone, we have added the main characteristics and results for the TROPIC-study, as was done in the abiraterone ERG report.

TROPIC study: This was an open label randomised phase III trial that compared efficacy and safety of cabazitaxel plus prednisone against mitoxantrone plus prednisone in patients with mCRPC whose disease has progressed during or after docetaxel therapy. The trial was carried out in 146 centres in 26 countries and recruited 755 patients – 377 to mitoxantrone and 378 to cabazitaxel. The baseline characteristics between the two groups were well-balanced. Please see the table below (Table 4.26).

Table 4.26: Baseline characteristics of patients in the TROPIC study[24]

	Mitoxantrone (n=377)	**Cabazitaxel (n=378)**
Age, median (years)	67	68
Ethnic origin: White	83%	84%
ECOG status 0 or 1	91%	93%
Metastasis to bone	87%	80%
Metastasis to viscera	25%	25%
Pain at baseline	45%	46%
Previous therapy Hormonal 1 chemotherapy regimen 2 chemotherapy regimens >2 prior chemotherapy regimens Radiation Surgery Biological agent	 99% 71% 21% 8% 59% 54% 10%	 99% 69% 25% 6% 61% 52% 7%
Number of previous docetaxel regimens 1 2 >2	 87% 11% 2%	 84% 14% 2%
Total previous docetaxel dose (mg/m2)	529.2 (380.9 to 787.2)	576.6 (408.4 to 761.2)
Disease progression relative to docetaxel administration During treatment <3 months from last dose ≥3 months from last dose Unknown	 28% 48% 24% 1%	 30% 42% 27% 1%
Median time from last docetaxel dose to disease progression (months)	0.7 (0.0 to 2.9)	0.8 (0.0 to 3.1)

The patients were allowed to take bisphosphonates if they had been taking these at a stable dose for 12 weeks prior to the study. Patients received either cabazitaxel at a dose of 25 kg/m^2 intravenously over one hour or mitoxantrone 12 mg/m2 intravenously over 15 to 30 minutes every three weeks. The treatment was given for a maximum of 10 cycles to reduce risk of mitoxantrone related cardiac toxicity. All patients also received oral prednisolone at a dose of 10 mg/day. A single intravenous dose of an antihistamine, corticosteroid and histamine H2-antagonist was given 30 minutes or more before administering cabazitaxel.

In the absence of direct and indirect evidence Table 4.27 below compares data reported in the cabazitaxel submission and TROPIC study against the PP arm of the COU-AA-301 study and the placebo arm of the AFFIRM study.

Table 4.27: Comparison of mitoxantrone against PP and PLA arms

	Mitoxantrone (cabazitaxel submission and TROPIC study)[24, 53]	**PP arm (COU-AA-301)**	**PLA arm (AFFIRM)**
Median OS	12.7 months	11.7 months*	13.6 months
Treatment discontinuation	-	3.7 months	3.0 months
Composite PFS	1.4 months	-	-
Tumour progression	5.4 months	-	-
Time to PSA progression	3.1 months	6.6 months	3.0 months

*) Based on ERG report for abiraterone.[54]

Median times for OS were similar. PFS in the cabazitaxel submission was a composite outcome in which progression corresponded to the first event of any of the following: death, tumour progression, PSA progression, pain progression, or symptom deterioration. The median PFS was 1.4 months. The PFS events were made up of: PSA progression (49.3%), death (7.7%), tumour progression (18%), pain progression (18.6%) and symptom deterioration (3.7%).

In the abiraterone STA, the ERG (Warwick Evidence) considered that the manufacturer's assumption that OS with mitoxantrone is the same as that of the PP arm of the COU-AA-301 trial was reasonable (11.7 months PP, and 12.7 months for mitoxantrone in the TROPIC trial). They considered that "the difficulties of estimating progression in mCRPC mean that the assumption that progression on mitoxantrone approximates to treatment discontinuation in the PP arm of COU-AA-301 is associated with considerable uncertainty but may represent a defendable compromise".[54]

4.6 Conclusions of the clinical effectiveness section

Although derived from only a single RCT there is compelling evidence that enzalutamide significantly prolongs OS and extends time to progression. Similarly as for abiraterone, the intervention is convenient for the patient and the NHS, in that it is orally self-administered.

The results of the indirect comparison showed that enzalutamide was associated with a significantly higher likelihood of attaining radiographic and modified PFS than abiraterone.

In contrast, no significant differences were observed for OS or time to first SRE. Enzalutamide is associated with a significantly higher likelihood to achieve a PSA response (defined as ≥50% decrease confirmed three or four weeks later) than abiraterone. However, no significant differences were observed between enzalutamide and abiraterone for ORR.

The indirect comparison shows that enzalutamide has a similar likelihood to be associated with all specific AEs (all grades) of interest to abiraterone except for bone pain (more likely with enzalutamide) and hypokalemia (less likely with enzalutamide). The likelihood of enzalutamide to be associated with any of the grade 3+ AEs assessed is not statistically different from that of abiraterone, while the rate of treatment discontinuation (tolerability) showed no statistically significant difference either. Therefore, the side effect profile for enzalutamide is similar to that of abiraterone, but of less concern than that of other comparators, such as mitoxantrone; furthermore, although mitoxantrone may have a palliative effect, there is no convincing evidence that it prolongs survival when used as first or second line therapy in this population.

Given that survival is similar between enzalutamide and abiraterone, the main decision problem hinges on whether the quality of the extended survival experienced by patients treated with enzalutamide compared to BSC is worth the extra cost incurred with its use. Therefore, it is evident that estimations of the quality of life for patients in the non-progressed and progressed states under enzalutamide, abiraterone, mitoxantrone and BSC therapies are the most critical issues for the decision problem.

The AFFIRM trial used the EQ-5D questionnaire 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 (enzalutamide: n=126/800; placebo: n=53/399 at baseline). The number of subjects with evaluable forms (i.e., with the five domain items correctly answered) throughout the study decreased more rapidly in the placebo arm with only six patients responding after 37 weeks. 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 (See MS, section 7.4.4).[49]

The QoL data evidence is consistent with benefit from enzalutamide in terms of delayed deterioration in QoL and superior QoL during treatment with enzalutamide than during treatment with placebo. The trial provided no evidence that could be of use in estimating QoL following treatment cessation (i.e. of the progressed state).

5. COST EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost effectiveness evidence

A full systematic review was carried out by the manufacturer to identify relevant cost-effectiveness studies. The quality of the search strategy is discussed in chapter 4.1.1 of this report.

5.1.1 Objective of cost effectiveness review

The main objective of the cost effectiveness review was to retrieve relevant data from published literature regarding the cost effectiveness of enzalutamide and relevant comparators as outlined in the scope. The search strategy for relevant economic studies was detailed in appendix 10, section 10.10 of the MS. 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). All searches were conducted on 2 January 2013 and covered the period between 1 January 1993 and 1 January 2013. The search was limited to the year 2012 for conference abstracts. A description of the search strategies is given in appendix 10 (section 10.10) of the MS.

ERG Comment:

The ERG believes that the objective of the cost effectiveness review was appropriate. The quality of the search strategy is discussed in chapter 4.1.1 of this report.

5.1.2 Inclusion/exclusion criteria used in the study selection

The inclusion criteria were according to the PICOS criteria reported in Table 106 of the MS (section 10.10.6). Exclusion criteria were: any studies not meeting the PICOS criteria.

Table 5.1: PICOS strategy for studies on cost-effectiveness

PICOS	
Population	Adults with metastatic castration-resistant prostate cancer which has been previously treated with a docetaxel-containing chemotherapy regimen.
Intervention*	Enzalutamide, abiraterone in combination with prednisone or prednisolone, mitoxantrone alone or in combination with prednisolone
Comparator*	• Abiraterone in combination with prednisone or prednisolone • Mitoxantrone alone or in combination with prednisolone • Cabazitaxel alone or in combination with prednisolone • Best supportive care (this may include radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies, and corticosteroids).
Outcomes	• Quality-adjusted life-years (QALYs); Life-years gained (LYG) • Incremental cost-effectiveness ratios (ICERs) such as cost per QALY
Study design	• Full economic evaluations, i.e., comparative analyses including enzalutamide and/or any of the other interventions in terms of both costs (resource use) and consequences (outcomes) that use cost-effectiveness analyses, cost-utility analyses or cost-benefit analyses (Shemilt I, Mugford

PICOS	
	M, Byford S, Drummond M, Eisenstein E, Knapp M, et al. on behalf of the Campbell and Cochrane Economics Methods Group. Incorporating economics evidence. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0.) (Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ 1996;313:275-83.). • Partial economic evaluations, i.e., cost analyses, cost comparison studies or cost-outcome descriptions of any intervention against any comparator.

Source: MS, Table 106 pg. 227.[13]
*No specific search for these interventions or comparators was conducted, but only those studies including these agents in the economic comparisons were reviewed.

ERG Comment:
The ERG views that the inclusion and exclusion criteria used in the study selection are appropriate.

5.1.3 Included/excluded studies in the cost effectiveness review

The systematic literature review identified six economic evaluations directly related to the decision problem. Table 5.2 below gives an overview of these six economic evaluations, namely Chopra et al. (2012),[55] Pereira et al. (2012),[56] Efstathiou et al. (2012),[57] Persson et al. (2012),[58] Maran et al. (2012),[59] and Wilson et al. (2012)[60]. Details of the analyses conducted are summarised in Table 5.2 (see also Table 42 of the MS [MS, pg. 114-115]).[13] However, none of these studies included enzalutamide as a comparator.

Table 5.2: Summary list of relevant cost-effectiveness evaluations in mCRPC

Study	Country(ies) where study was performed	Comparators	Summary of model	Patient population
Chopra 2012[55]	US	Abiraterone (ABI) + prednisone (P) vs placebo + P	-CEA (decision-analytical model) -Payer perspective	That of COU-AA-301
Pereira 2012[56]	Not reported	ABI + P vs placebo + P	CEA Brazilian Private Health System perspective	Not reported
Efstathiou 2012[57]	Greece	ABI + P vs placebo + P	CEA (costs per incremental month) Greek health care perspective	Pts in COU-AA-301 and TROPIC
Persson 2012 [58]	Sweden	ABI + P vs placebo + P	CEA Societal perspective	Not reported
Maran 2012[59]	Italy (Veneto region)	Cabazitaxel vs mitoxantrone	CEA Italian RHS perspective	Not reported
Wilson 2012[60]	Not reported	ABI and cabazitaxel vs mitoxantrone and placebo	CEA Societal perspective	Not reported

Source: Adapted from MS, Table 42, pg. 114-115.[13]

The manufacturer has also reported an additional 21 economic evaluations which were associated with health technology assessment (HTA) appraisals reporting any economic outcomes in mCRPC. Details of the reported economic outcomes were given in Table 43 of the MS (MS, pg. 115-119). Again, none of these studies included enzalutamide as a comparator.

ERG comment:
The ERG considers the six studies displayed in Table 5.2 as the more relevant ones from the search performed. However, none of these studies included enzalutamide as a comparator and therefore their findings are less relevant to the current submission.

5.1.4 Conclusions of the cost effectiveness review

No specific conclusions from the economic review were provided in the submission.

ERG comment:
None of the studies in the economic review included enzalutamide as a comparator. For this reason the manufacturer has provided a de novo analysis. The ERG agrees that this is the appropriate approach.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

An overall summary of the *de novo* economic model developed by the manufacturer is given in Table 5.3.

Table 5.3: Summary of the manufacturer's economic evaluation (with signposts to MS)

	Approach	Source / Justification	Signpost (location in MS)
Model	Cohort model with population defined according to AFFIRM study. Time horizon was 10 yrs (in effect lifetime) in the base case.		Pg. 121
States and events	Health states: stable disease (SDis), progressive disease (PDis) and dead. Metastatic CRPC patients enter the model in the SDis health state (after a docetaxel therapy). Patients who progress move to the PDis health state and patients who die move to the dead health state. Transition from PDis to SDis is not possible. Transition probabilities are defined by OS and PFS curves for each treatment. The model also includes adverse events and skeletal-related events.	Inputs on OS, PFS, adverse events, and skeletal-related events for enzalutamide and BSC were derived from AFFIRM trial. Abiraterone data was derived from the COU-AA-301 study, and indirectly compared using the control arms in both studies.	Pg. 122 Pg. 125
Comparators	The comparators are enzalutamide (once daily 160 mg as four 40 mg capsules), abiraterone (in combination with prednisone or prednisolone) and BSC	Mitoxantrone alone or in combination with prednisolone was not included on the MS	Pg. 34

	Approach	Source / Justification	Signpost (location in MS)
	(this may include radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies, and corticosteroids).	based on the reasoning that: *"(it) is not licensed for mCRPC nor is it listed in NICE clinical guidelines as a treatment option for mCRPC."*	
Natural History	Overall survival (HRs applied to the placebo reference curve): For enzalutamide a HR of 0.618 (95% CI: [0.52; 0.73]). For abiraterone OS was assumed time dependent with HR = exp(-0.65128+0.03923*Time). Beyond 25 months, a HR of 1.39 is used for all subsequent cycles in the model. Progression free survival (HRs applied to the placebo reference curve): For enzalutamide HR of [redacted] (95% CI: [redacted]). For abiraterone HR of 0.52 (95% CI: [0.44; 0.60])	OS and PFS for enzalutamide come from AFFIRM study. Placebo arm from AFFIRM was assumed to represent BSC. OS for abiraterone comes from COU-AA-301, derived from Fizazi 2012[4] and PFS for abiraterone comes from COU-AA-301 derived from the abiraterone manufacturer submission[12]	Pg. 125-128
Treatment effectiveness	Overall survival and progression free survival state	AFFIRM and ITC of AFFIRM and COU-AA-301 trials	Pg. 74-88
Adverse events	Single estimate for all comparators.		Pg. 89-106
Health related QoL	EQ-5D values were preferred for the health economic model. FACT-P mapped values were only used for analyses where the number of EQ-5D responses was insufficient. The baseline mean utility value in AFFIRM was [redacted] using the EQ-5D values (N = 209, SE = [redacted]).	AFFIRM trial, FACT-P mapping algorithm, and literature.	Pg. 146-147
Resource utilisation and costs	Categories were: medication costs, health care resource utilisation costs and costs of adverse events and skeletal-related events.		Pg. 157-169
Discount rates	3.5 % for utilities and costs	According to NICE reference case	Pg. 137
Sub groups	No sub-group analysis was undertaken.	The subgroup in which abiraterone is accepted – the one prior chemo population - was not considered a relevant subgroup.	Pg. 191
Sensitivity analysis	Numerous scenario analyses were run investigating the effect of changing the		Pg. 169-171 Pg. 172

	Approach	Source / Justification	Signpost (location in MS)
	base case assumptions. Probabilistic sensitivity analysis was undertaken using 10,000 Monte Carlo simulations.		

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.4: NICE reference case checklist

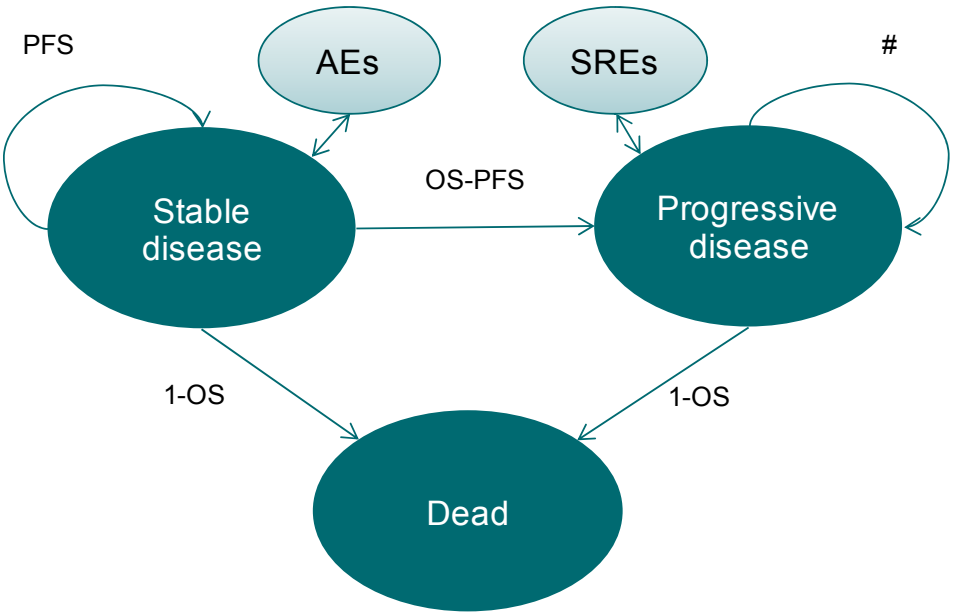
Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes (partially). The NICE scope specifies abiraterone (in combination with prednisone or prednisolone), mitoxantrone (alone or in combination with prednisolone) and BSC (which may include corticosteroids, etc). The comparators in the post-docetaxel setting considered in the submission are: abiraterone and BSC. The rationale for excluding mitoxantrone from the decision problem is given on page 34 of the MS as: *"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."*
Patient group	As per NICE scope	Yes (partially). The patient group in the submission refers to the same group of patients as in AFFIRM trial (i.e. patients with mCRPC who received at least one prior chemotherapy). However, the patient group used to derive the HR for TTD for abiraterone vs placebo is different from the total population (as described in the scope). This HR was based on a subgroup consisting of patients who received only one prior chemotherapy (OPC) and is used by the manufacturer to calculate TTD for abiraterone.
Perspective costs	NHS and Personal Social Services (PSS)	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	10 years, which given the patient group and simulated survivals is assumed to be sufficient to capture the remaining lifetime of mCRPC patients. The modelled life years show that the probability of dying at 10 years

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
		is 1.00 for all arms.
Synthesis of evidence on outcomes	Systematic review	The main comparison with BSC relies upon the pivotal head to head AFFIRM trial. For the clinical effectiveness an indirect treatment comparison with abiraterone is performed using AFFIRM and COU-AA-301 trials
Outcome measure	Quality adjusted life years (QALYs)	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes (partially). Health-related quality of life (HRQoL) data were collected during the pivotal trial (AFFIRM study) through FACT-P and EQ-5D questionnaires. FACT-P questionnaires were collected from all (1,199) AFFIRM patients while EQ-5D from only 331 AFFIRM patients (resulting in only 209 patients with valid EQ-5D forms at baseline). As a result FACT-P responses were mapped to EQ-5D values using an internal mapping algorithm However, due to uncertainty from mapping utility values, the EQ-5D values were preferred for the health economic model, and the mapped values were only used for analyses where the number of EQ-5D responses was insufficient. The baseline utility value in AFFIRM was [redacted] using the EQ-5D values (N = 209, SE = [redacted]). As it was not possible to calculate the utility values for survival with progression and AEs from the pivotal trial, this was based on the literature.
Benefit valuation	Time-trade off or standard gamble	Yes. The EQ-5D utility scores were calculated using the UK time trade-off (TTO) value set.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Probabilistic modelling	Probabilistic modelling	Yes
Sensitivity analysis		Yes. A range of sensitivity analyses were performed.

5.2.2 Model structure

The structure of the Markov state transition model follows the structures used in numerous NICE STAs and multiple technology assessments (MTA) in metastatic cancer. It includes three health states: Stable Disease (SDis), Progressive Disease (PDis) and Dead (see Figure 5.1). The assumed cycle length is three weeks (mainly chosen based on previous models in the same indication) and the time horizon is 10 years (assumed to be sufficient to capture the remaining lifetime of mCRPC patients). Metastatic CRPC patients enter the model in the SDis state after their disease has progressed on or after chemotherapy. 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. The number of people remaining in each health state after each cycle in the BSC strategy was calculated from the OS and time to treatment discontinuation (TTD; as a proxy for PFS) curves from the placebo arm in the AFFIRM trial. Time in the post-progression state was calculated as the difference between OS and PFS. The enzalutamide and abiraterone strategies were modelled by applying HRs to the survival curves. The analysis took an NHS and personal social services perspective and discounted costs and benefits at 3.5%.

Figure 5.1: Model structure of the enzalutamide economic model



Source: MS, Figure 17 pg. 121. [13]
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.

The major structural assumptions were as follows:

- All patients are assumed to be stable upon starting treatment, and receive enzalutamide, BSC or abiraterone (SDis).

- Patients can experience AEs only in the SDis health state and only grade ≥3 AEs are taken into account.
- An on treatment utility benefit is applied for enzalutamide and abiraterone.
- Once patients progress to the PDis health state they no longer experience any on treatment utility benefit.
- Transition to the PDis health state is determined using treatment discontinuation as the best proxy.
- Patients in the PDis health state receive BSC, irrespective of the prior treatment, and do not receive another active treatment.
- Patients in the PDis health state can only experience SREs; no other complications are taken into account.
- AE and SREs result in an additional decrement in utility and additional costs.
- Post study treatment in the AFFIRM trial is assumed to have had no impact on OS.

ERG comments:
The structure of the model follows the structures used in other NICE STAs in metastatic cancer and is appropriate in the view of the ERG.

5.2.3 Population
The population used in MS represents the overall patient population in the AFFIRM study which is: "*adult men with mCRPC whose disease has progressed on or after docetaxel therapy*" (MS, pg. 120, section 7.2.1). This is the same population as the licensed indication for enzalutamide (MS, pg. 18) and is in line with the NICE scope.

ERG Comments:
The manufacturer argues that the patient group in the AFFIRM study (i.e. patients with mCRPC who received at least one prior chemotherapy) is comparable to the one used in the COU-AA-301 study. This is because "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" (MS, pg.82).

However, the patient group used to derive the HR for TTD for abiraterone versus placebo is different from the total population (as described in the scope). This HR was based on a subgroup consisting of patients who received only one prior chemotherapy (OPC) and was calculated from the treatment discontinuation curve used in the abiraterone manufacturer submission (COU-AA-301 study). The manufacturer used this HR to estimate TTD (i.e. PFS) for abiraterone. The ERG considers using two different populations for different outcomes in the model as inconsistent and suggests correcting for this.

5.2.4 Interventions and comparators
The comparators are enzalutamide (once daily 160 mg as four 40 mg capsules), abiraterone (in combination with prednisone or prednisolone) and BSC (this may include radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies, and corticosteroids). A comparison to mitoxantrone (alone or in combination with prednisolone)

is excluded based on the reasons given on section 2.7 of the MS (MS, pg.28) stating that: "*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*." In addition, the MS states: "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." (MS, pg. 34).[13]

ERG Comments:
NICE could not confirm that this was agreed and having a license in the UK or being included in NICE guidelines is not a reason to in- or exclude a treatment as a comparator. Moreover, in the comments on the scope (appendix D of the scoping documents), it is stated that "During the scoping workshop, the attendees agreed that mitoxantrone should be included as a comparator, as the most recent available evidence suggests that it is still prescribed for this indication in the NHS." Therefore, the ERG asked for a full justification for excluding mitoxantrone as a comparator in the Clarification Letter.

In the response to the Clarification Letter, the manufacturer provided the following additional justification for excluding mitoxantrone as a comparator (See Response to Clarification Letter, Question A4):[2]

"Having reviewed the 2013 NICE methods guide (sections 6.2.1 to 6.2.4), Astellas maintains that mitoxantrone is an irrelevant comparator based on the guide's five criteria.

1. *Mitoxantrone has a very small and diminishing place in NHS practice in England;*
2. *Several new alternative treatments are available which have displaced a vast majority of historic mitoxantrone use;*
3. *Existing NICE guidance does not support mitoxantrone in mCRPC;*
4. *Clinical evidence for mitoxantrone in the post-docetaxel setting does not support any survival benefit for mCRPC patients and therefore it cannot be considered a cost-effective choice;*
5. *Mitoxantrone is not licensed for mCRPC."*

There are several RCTs of mitoxantrone alone or in combination with prednisone versus other active treatments in patient with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy.[20-30] However, none of these trials include a placebo arm or a prednisone arm. Therefore, there is no network linking these trials to enzalutamide and/or abiraterone. In the abiraterone assessment (TA-259) the committee also concluded that there were no trials to link the evidence for mitoxantrone to the COU-AA-301 trial and enable an indirect comparison of abiraterone and mitoxantrone.[3] In the manufacturer submission for abiraterone, mitoxantrone was included as a comparator, but the evidence was mainly based on assumptions. The main assumption was that in the absence of evidence for any survival benefit from mitoxantrone in mCRPC, the survival of mCRPC patients given second line mitoxantrone would be assumed to be the same as that from BSC

in the COU-AA-301 study. The ERG recognizes the fact that evidence for including mitoxantrone alone or in combination with prednisone as a comparator remains scarce. However, the inclusion of this comparator should be considered in order to comply with the scope of the submission.

5.2.5 Perspective, time horizon and discounting

The perspective is that of the patient for benefits and the NHS and PSS for costs. A 10 year time horizon is adopted with a discount rate of 3.5%. In the scenario analysis the time horizon has been varied to four, six and eight years. Costs are considered from an NHS and Personal Social Services perspective (MS, pg. 34).

ERG comments:

The perspective and discount rates are in line with the NICE reference case. The time horizon of 10 years, assumed in the base case, is in effect lifetime.

5.2.6 Treatment effectiveness and extrapolation

The economic evaluation uses OS and PFS as the primary short-term clinical outcomes and responses.

Overall survival and progression free survival - BSC

Patient-level data on duration of OS based on all deaths at database lock for the placebo arm of AFFIRM study were used to fit different accelerated failure time (AFT) parametric models. Five distributions were considered: Exponential, Weibull, Log-Logistic, Log-Normal and Generalized Gamma. (MS, pg.125). Goodness of fit checks included statistical fit using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). The examination of the statistical goodness of fit showed that the AIC and BIC of all distributions were similar, except for the exponential distribution. The Log-Logistic distribution was judged to fit the underlying data best (see Table 5.5). Figure 5.2 gives the predicted estimates for the placebo arm.

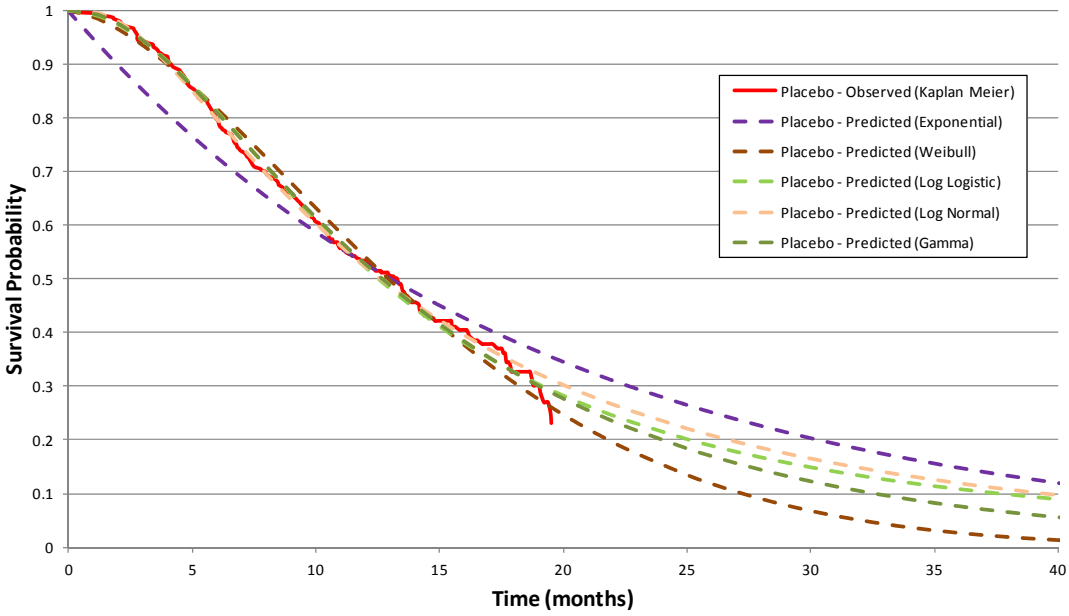
Table 5.5: Goodness of fit for AFFIRM placebo overall survival

	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

Source: MS, Table 45 pg. 126.[13]

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

Figure 5.2: Comparison of OS K-M estimates with OS parametric models for placebo



Source: MS Figure 18 p. 126.[13]

The Manufacturer argues that although all curves had approximately the same median (Table 5.5), there are considerable differences in the mean OS between the curves. The Manufacturer has chosen the Weibull distribution over the Log-Logistic distribution to model OS based on face validity and validity checks by clinical experts.[61] This choice was justified by "the more realistic shape of the 'tail'" (MS, pg.126). The proportion remaining alive with the Log-Logistic distribution (also illustrated by the five months longer mean OS) was considered unrealistic. The OS Weibull intercept and the OS Weibull scale were [redacted] (SE = [redacted]) and [redacted] ([redacted]), respectively (corresponding to λ=[redacted] and γ=[redacted]).

PFS was modelled based on time to treatment discontinuation TTD. Both modified PFS and radiographic PFS were disregarded in the modelling. The Manufacturer argues that this choice was based on two main reasons: (1) radiographic progression was measured only at three months intervals, and (2) UK experts have indicated that neither modified or radiographic PFS accurately reflect how disease progression (and treatment discontinuation) would be defined in UK clinical practice since the decision to discontinue treatment would not be made on a single measure of disease progression.[12, 31] In contrast, treatment discontinuation in AFFIRM was a continuous process. 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) and the patient was scheduled to initiate another systemic antineoplastic therapy (MS, pg. 128).[13]

Similarly to the OS case, the K-M curve of the placebo arm of the AFFIRM study was assumed to represent BSC and consequently used as the reference curve. Again, the five

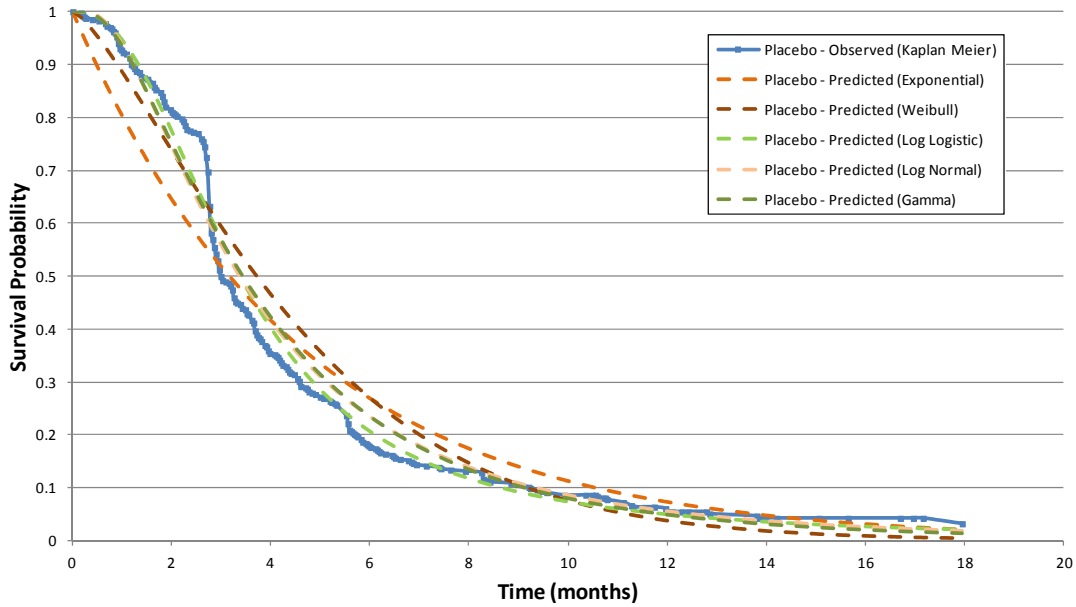
distributions were used to fit different AFT parametric models. Table 5.6 gives the goodness of fit statistics while Figure 5.3 gives KM estimates with parametric models for placebo. Goodness of fit statistics showed that the Log-Logistic model had the best statistical fit according to AIC and BIC criteria. Yet, the Weibull model was selected after validation by clinical experts due to the more realistic shape of the tail (see Figure 5.3).[61] The PFS Weibull intercept and the PFS Weibull scale were [redacted] (SE = [redacted]) and [redacted], respectively (corresponding to λ=[redacted] and γ=[redacted]).

Table 5.6: 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

Source: MS, Table 48, pg. 129. [13]
Abbreviation: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; LL: Log Likelihood; Numbers in bold indicate the lowest information criterion.

Figure 5.3: Comparison of Treatment Discontinuation K-M estimates with parametric models for placebo



Source: MS, Figure 20, pg. 130.[13]

ERG comments:

The ERG asked for clarifications from the manufacturer as to why for OS and PFS (i.e. TTD) the tails of the BSC Weibull curves were considered more realistic than the Log-Logistic curves (which fit the data best according to the AIC and BIC statistical checks). The manufacturer has argued in the response to the clarification requests that:

"Using log-logistic distribution as the reference curve, the model resulted in a much higher percentage of patients alive at 5 and 10-years than using the Weibull distribution (Table 5.7).

These percentages were considered clinically implausible by the experts consulted in the advisory boards who indicated that no treatment effect is expected after 5-years and for 5-years survival values between 0-5% were expected.[61]"

Table 5.7: Five and 10 year survival rates using log-logistic and Weibull distributions (model results)

	BSC		**Enzalutamide**	
Distribution used for reference curve	5-year	10-year	5-year	10-year
Log-Logistic	4.20%	1.10%	14.10%	6.10%
Weibull	0.00%	0.00%	0.60%	0.00%

Source: Response to the Clarification Letter, Table R5, pg. 13.[2]

Taking the above into account, the Weibull distribution was selected to be used in the base case analysis despite the higher AIC and BIC fit statistics for the Log-Logistic model. However, the Log-Logistic distribution is used in a scenario analyses.

The ERG agrees that the choice of the Weibull distribution seems reasonable given the high percentages of patients alive at five and 10 years when the Log-Logistic model was considered.

Overall survival and progression free survival - enzalutamide

OS for enzalutamide was based on the OS Weibull model described above for BSC combined with a HR of 0.618 (95%CI 0.523; 0.730). This HR was calculated by using a stratified Cox proportional hazards model based on data from the AFFIRM trial. Given that the assumption of proportional of hazards was met (MS, pg. 127), a constant HR was used.

Similar as for OS, PFS for enzalutamide was based on the TTD Weibull model described above for BSC combined with a HR of [redacted] (95% CI [redacted]). This HR was also obtained by using a stratified Cox proportional hazards model based on data from the AFFIRM trial and the proportional hazards assumption was met.

ERG comments:

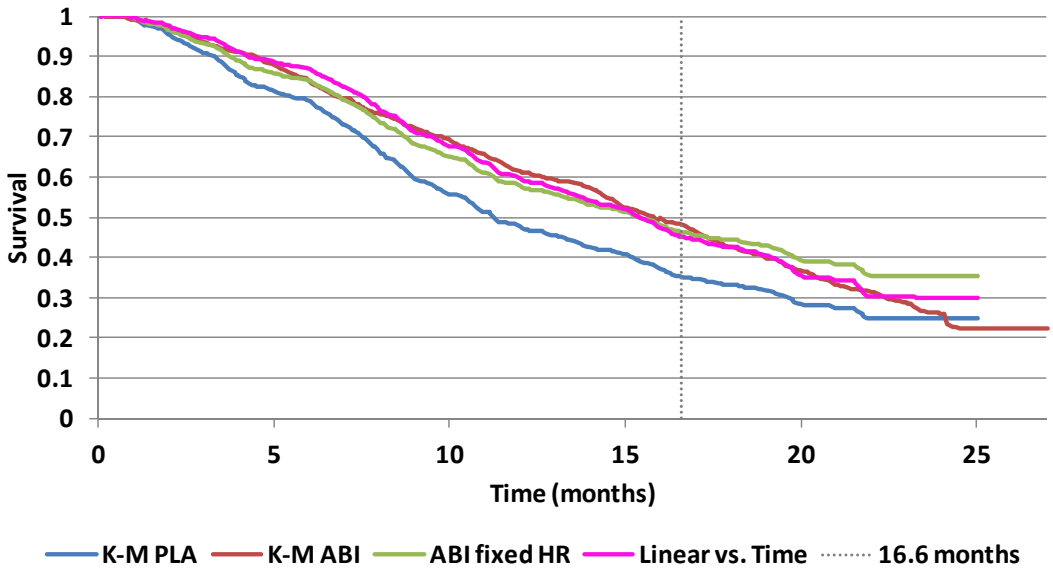
The ERG agrees with the approaches followed for modelling OS and PFS for enzalutamide.

Overall survival and progression free survival - Abiraterone

The results from the COU-AA-301 study reported in Fizazi et al. (2012)[4] were used by the manufacturer to estimate OS and PFS for abiraterone. Fizazi et al. (2012)[4] reported a HR for OS, and mentioned that the proportional hazards requirement was not met. In order to model OS for abiraterone, the Manufacturer took a three step approach. Firstly, the reported KM curves for OS in the Fizazi et al. (2012) paper[4] were digitised using Engauge digitizer v4.1 software.[62] Secondly, Individual Patient Data (IPD) were reconstructed from the KM curves and the reported number at risk using the method published by Guyot, (2012).[63] Thirdly, 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 (MS, appendix 15, section 10.15). After expert

consultation, the model with a time dependent covariate was preferred over the piecewise model, as the latter required arbitrary selection of the time intervals. Using visual inspection of the resulting survival curves, the curve based on the HR with a linear time function (linear versus time) was selected as providing the best fit (Figure 5.4).

Figure 5.4 COU-AA-301 OS curves and predictions of abiraterone curve based on a fixed HR (green line), and the time dependent HR (pink line)



Source: MS, Figure 19, pg. 128. [13]
Abbreviations: ABI; abiraterone; K-M: Kaplan-Meier; PLA: placebo

All coefficients in the model were significant. The HR in the model is calculated by HR = exp (-0.65128+0.03923*Time). This function resulted in a HR ranging from 0.52 at the start of model, to 1.0 at 16.6 months, and finally a HR of 1.39 at 25 months which is kept constant afterwards as no data were reported beyond 25 months.[4] In the health economic model, the time dependent HR is combined with the OS Weibull model for BSC (AFFIRM placebo arm) to estimate OS for abiraterone.

Due to the lack of the data on HR for the TTD of abiraterone in the total post-chemotherapy mCRPC setting, the Manufacturer proposes two approaches:

1. Using an approximation from the ratio of medians of treatment duration for abiraterone (7.4 months) and placebo arms (3.6 months) as published by Fizazi 2012[4] and assuming a constant hazard in each trial arm (i.e., exponential distribution). This would result in a HR of 0.49 (95% CI 0.37; 0.63).
2. Using the treatment discontinuation curve used in the abiraterone manufacturer submission (MS) for the one prior chemo (OPC) subgroup (Figure 16, abiraterone MS[12]) and fitting a Cox Proportional Hazards model to the data, resulting in a HR of 0.52 (95% CI 0.44; 0.60) for abiraterone vs. prednisone in the OPC population.

Furthermore the test of proportional hazard ratios for this HR was met making it possible to apply to the model.

The Manufacturer has decided to use the HR of 0.52 (95% CI 0.44; 0.60) for abiraterone vs. prednisone and directly apply that to the reference curve (AFFIRM placebo, Figure 5.2). The justification for this was that this was "assumed to be conservative compared to the HR calculated from medians (0.49), as it estimates lower costs for the comparator" (MS, pg. 131). However, the Manufacturer recognizes that such HR of 0.52 refers to the subgroup of patients with only one prior chemotherapy. The Manufacturer argues this to be a fair assumption as in the AFFIRM study, the OPC population had a similar HR for TTD as the entire (ITT) population (MS, pg. 131).

ERG comments:
One of the assumptions that the ERG has noted was the increase of the time-dependent HR for OS for abiraterone versus placebo to 1.39 at 25 months (indicating a worse survival probability per cycle for abiraterone compared with BSC) (MS, pg. 243-244). This HR was then kept constant in the model at 1.39 after 25 months. The ERG has asked for further clarifications and justifications on the use of such HR over the constant HR of 0.74 from COU-AA-301 trial).[4] The manufacturer (Response to Clarification Letter, pg.15)[2] has justified this choice by arguing that:

> *"Although very few patients were in the study at 25 months, the HR of 1.39 is derived using the linear function, which includes all events and not only those in the end of the study."*

In the ERGs opinion, the use of the HR of 1.39 after 25 months for abiraterone versus BSC is not justified given the very low number of observations after 25 months. Instead, the ERG argues that a conservative approach should be adopted here by adopting a HR of 1.00 for OS of abiraterone after 25 months, i.e., the time-dependent probability of dying is equal for both abiraterone and BSC after 25 months.

The ERG also questions the use of the HR of 0.52 for PFS (TTD) of abiraterone versus BSC based on the subgroup from the COU-AA-301 trial with **only one** prior chemotherapy, as this does not comply with the NICE reference case for the patient group (i.e. patients with mCRPC who received **at least one** prior chemotherapy). The ERG prefers the use of the HR based on the ratio of median TTD in the whole population (0.49; 95% CI 0.37; 0.63).

<u>*Adverse events*</u>
The base case includes all adverse events (AEs) with a grade ≥3 and incidence above 1.0% in the enzalutamide or placebo arm as extracted from the AFFIRM trial. Seizures were also added to the list of AEs, as they were classified as important based on expert opinion. A complete list of AEs is included in Table 50 of the MS (MS, pg. 132).

As mentioned earlier, AEs are modelled only in the SDis health state using a cycle probability for AEs. Such probability is retrieved from the AE rates based on 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). For abiraterone, the incidences for AEs were taken from the Fizazi publication[4] and the abiraterone NICE submission[12] while the number of patients with each AE and the treatment emergent period (patient years) by Logothetis [MS, 67]. The rates included in the model were calculated as the rate difference for abiraterone versus prednisone, and this difference was added to the AFFIRM placebo AE rates.

ERG Comments:
The AE probabilities for abiraterone were calculated by taking the rate difference versus BSC for abiraterone as reported in COU-AA-301,[4] and adding this to the AE rates of the placebo group in the AFFIRM study. The ERG questions why the rate ratio in the COU-AA-310 was not used instead. Also, the ERG questions the formula used to convert rates to probabilities, which is the annual rate per year multiplied by the cycle length in years (i.e. 21/365=0.057). This is actually the formula for the rate per cycle and not a probability. However, it can be shown that for rates this small (about one per year (0.057 per cycle) the rate per cycle is approximately equal to the cycle probability. Also, a scenario analysis shows that omitting consequences in terms of disutilities for AEs does not impact the ICER (MS, Table 88, p. 187).

The ERG also explored the impact of removing all consequences of AEs (on costs and QoL) in one of the additional analyses.

Skeletal Related Events
The SREs considered in the model were: spinal cord compression, pathologic bone fractures (non-vertebral), radiation to bone, surgery to bone (MS, pg.133). As all SREs are considered typically a result of progression of metastatic bone disease, they were applied to the PDis health state as cycle probabilities. The number of events and the treatment emergent period (in patient years) for enzalutamide and BSC were taken from AFFIRM study. SRE rates were calculated similarly as for AE rates. SRE rates for abiraterone were calculated from the number of events and the treatment emergent period as reported by Logothetis et al.[5] The rate difference versus prednisone was calculated for abiraterone, and applied to the rates of the AFFIRM placebo arm, (assuming that both control arms were similar).

ERG Comments:
For SREs a similar approach was taken as for AEs; the same ERG comment applies.

5.2.7 Health related quality of life
Quality of life data were collected in the AFFIRM study through FACT-P and EQ-5D questionnaires. The FACT-P questionnaire was collected in all 1,199 AFFIRM patients, while the collection of EQ-5D questionnaire was only instituted at all sites in France, Germany, Italy, Spain, and the UK. As a result the number of patients with evaluable EQ-5D

forms (i.e., with the five domain items correctly answered) at baseline was 209 (67 [60.4% of those asked] in the placebo arm and 142 [64.5% of those asked] in the enzalutamide arm). FACT-P responses were mapped to EQ-5D values using an internal mapping algorithm. However, due to uncertainty from mapping utility values, the EQ-5D values were preferred for the health economic model, and the mapped values were only used for analyses where the number of EQ-5D responses was insufficient. The baseline utility value using the actual EQ-5D in the AFFIRM study was [redacted] (N = 209, SE = [redacted]).

ERG comments:
The ERG agrees that using the EQ-5D utility value of [redacted] (N = 209, SE = [redacted]) from the AFFIRM study is the preferred approach given the uncertainty of the mapped utility values based on FACT-P responses. However, the ERG does regard the EQ-5D utility value as uncertain for the following reasons. Only a very small proportion of the patients in the AFFIRM trial completed/were asked to complete the EQ-5D: At baseline 142 of 800 (18%) patients in the enzalutamide arm and 67 of 399 (17%) patients in the placebo arm completed the EQ-5D (MS, pg. 146).. In addition, the proportion of patients with missing items among those asked is considerable (response 60-64%). Together with the fact that the population in the AFFIRM trial could have been fitter than generally seen in clinical practice, the utility value of [redacted] could be an overestimation of the quality of life of the patient population.

Incidentally, the EQ-5D numbers presented in chapter 6.5.3.3 of the MS (MS, Table 17, page 68) are not fully consistent with the data reported in chapter 7.4.6 of the MS (MS, page 146).

On treatment utility gain
In order to derive the treatment arm effect for patients in the SDis health state, the FACT-P responses were mapped to EQ-5D values using an internal mapping algorithm as from Skaltsa et al.[49] Patient changes from baseline utility as implied by the FACT-P mapping function were then 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).

The least squared (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 5.5).

Figure 5.5: Adjusted mean change from baseline in mapped EQ-5D utility index score

[redacted]

Source: MS, Figure 21, pg.148.[13]
Note(s): ** p-value<0.005, results for within group comparison

On treatment benefit for the abiraterone arm was taken from the Abiraterone Dutch CVZ submission[64] and was reported to be [redacted] (95% CI: [[redacted]]).

ERG comments:
The ERG has asked the manufacturer to provide the internal mapping algorithm and further details used to calculate the utility increments. In the response to the clarification letter (Response to the Clarification Letter, pg. 18) the manufacturer has repeated the same arguments and information as stated in the MS and did not provide the details on the calculation of the utility increments for on treatment benefits.

The ERG also asked for further clarifications and original references for the on treatment utility increment for abiraterone of [redacted] (95% CI: [[redacted]]). In the response to clarification letter (Response to the Clarification Letter, pg. 18) the manufacturer has provided three references; de Bono et al. (2011),[15] Wu et al., (2012)[65] and Anderson et al. (2012).[66] In addition, on page 21 of the response to clarification letter the manufacturer stated that:

"These references do not provide the actual value. The abiraterone CVZ submission was used for reference for the abiraterone on-treatment benefit as, to our knowledge, this is the only published source for the 0.04 value."

The CVZ submission does not give any details on the calculation of this on treatment utility increment. The ERG views the on treatment utility increment for abiraterone versus BSC as highly uncertain as it is not supported by evidence. The difference in the on treatment utility gain for enzalutamide and abiraterone is important for determining the QALY gain from using enzalutamide over its direct active treatment comparator (i.e. abiraterone). In the

opinion of the ERG there is no strong evidence to assume different on treatment utility increments for enzalutamide and abiraterone.

The ERG further argues that incorporating the on treatment utility increments for enzalutamide and abiraterone versus BSC in the health economic model is likely to be an overestimation of the real on treatment utility gain. This is mainly because part of this utility benefit is already captured by the utility decrements used for AEs in the SDis health state. This creates potential for double counting (since utility benefits of enzalutamide and abiraterone has been included in the model). The ERG has asked further clarifications as to why the 'on-treatment benefit' for enzalutamide (expressed as a utility increment) was considered in addition to the disutility associated with AEs in the SDis health state. In its response (Response to the Clarification Letter, pg. 19) the manufacturer has stated that:

"To be noted, we do not agree with ERG that scenario 13 (excluding the on-treatment utility gain) should be the one to look at in order to prevent double counting, because the model only included grade 3+ AEs and may thus not capture the full impact of all AEs on QoL and any other effects on QoL."

The ERG keeps the opinion that in scenario 13 the risk of double counting is excluded, but agrees with the manufacturer that this scenario may underestimate the total impact of AEs and other effects on quality of life. However, in the absence of details on the calculation of the utility increments for the on treatment utility increment for enzalutamide versus BSC, together with the weak evidence on the on treatment utility increment for abiraterone versus BSC, the ERG prefers taking a conservative approach and disregarding the on treatment utility increments in the base case scenario.

Utility decrements for progression

For the purpose of the economic model the utility decrement derived from Sandblom et al.[67] (-0.085) was considered the most appropriate value, as the time intervals (16-8 and 8-0 months before death) in which data were collected approximately match the time in stable and progressive disease for patients in the AFFIRM study.

ERG comments:

The ERG argues that the time intervals (16-8 and 8-0 months before death) should match the time in stable and progressive disease states for patients in Sandblom et al.[67] as it is assumed that patients for whom the utility values are measured have progressive disease 8-0 months before death and are stable 16-8 months before death. It is unclear whether this is the case in Sandblom et al.[67] But, it is likely that some patients will still be progression free 8-0 months before death while others may have already progressed 16-8 months before death. Further clarifications were asked from the manufacturer.

In the response to the clarification letter (Response to the Clarification Letter, pg. 20-21) the manufacturer states that several methods to calculate the utility decrement for disease progression were considered:

1. Derived from the AFFIRM study by estimating the impact of progression according to mPFS criteria (radiographic progression, first SRE or death) (MS, pg 147):
    a. using the mapped values – decrement estimated as [redacted]
    b. using the collected EQ-5D values – decrement estimated as [redacted].
2. Using literature data (MS, pg 152):
    a. derived from the Sullivan et al.[68] as described in the cabazitaxel NICE submission[18] – decrement estimated as 0.070.
    b. derived from Sandblom et al.[67] as described in the cabazitaxel NICE submission[18] – decrement estimated as 0.085 using the decrease in utility from 16-8 months before death to 8-0 months before death (estimated from the graph).
    c. derived from Sandblom et al.[67] as described in the abiraterone NICE submission[12] - post-progression utility value of 0.5 using the average of the utilities 8-4 months and 4-0 months before death.

Given that mCRPC patients are likely to spend their last eight months of life in the progressed health state, the manufacturer argues that Sandblom et al.[67] provides the most appropriate data to be used in the model.

The ERG agrees that in light of the available evidence multiple approaches to the estimation of a utility decrement for disease progression could be considered. According to the ERG none of these approaches is clearly superior. In the abiraterone STA the ERG favoured the 0.07 value from Sullivan et al .[68] The ERG explored the impact of using this value.

Overall the ERG agrees that the 0.085 utility decrement, based on the average of the utilities 8-4 months and 4-0 months before death as reported in Sandblom et al., is a reasonable estimate.[67]

Utility decrements for adverse events

The utility decrements for experiencing AEs were based on the 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.[54] The disutilities and durations used were further validated by experts,[61] and are reported in Table 58 of the MS (MS, pg. 152-153).

ERG Comments:

The ERG agrees with the estimation of the utility decrements for experiencing AEs. Moreover, a scenario analysis shows that omitting disutilities for AEs does not impact the ICER (MS, Table 88, p. 187).

Utility decrements for Skeletal Related Events

Similar to the calculation of the disutility for progression, disutilities were calculated for 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]]).

ERG Comments:

The ERG agrees with the estimation of the utility decrements for experiencing SREs. Moreover, a scenario analysis shows that omitting disutilities for SREs does not impact the ICER (MS, Table 88, p. 187).

5.2.8 Resources and costs

Categories considered for resource utilisation and costs were: technology costs, health resource utilisation costs and costs of adverse events and SREs. As no resource utilisation was collected in the AFFIRM trial, data were retrieved from the literature which was modified based on the input from UK clinical experts. A systematic search of health resource utilisation (HRU) data identified four studies.[69-72] In addition to these studies, two NICE STAs, cabazitaxel[10] and abiraterone[3], were identified estimating resource utilisation in men with mCRPC whose disease has progressed on or after docetaxel therapy.

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]

Resource use and costs of monitoring

The manufacturer based monitoring requirements and frequency on the abiraterone MS (MS abiraterone, Table 38, pg. 119[12]), and has modified these based on the experience of UK clinical experts. Medical Resource Utilisation for monitoring of mCRPC patients on treatment and unit costs for routine monitoring are shown in Table 61 and Table 62 of the MS (MS, Table 61-62, pg. 161-163). It is assumed that all monitoring is performed by a clinical oncologist. The manufacturer argues that as enzalutamide does not require the additional monitoring required for abiraterone, the monitoring frequency was estimated at once every four weeks in the first three months, and once every eight weeks thereafter. The total costs for each comparator are shown in Table 5.9.

Resource use and costs of concomitant medication

The Manufacturer has based the concomitant medication on the results of the AFFIRM trial. Six concomitant medications have been included in the economic model: anti-histamines, H2-antagonists, anti-emetic drugs, corticosteroids, granulocyte colongy-stimulating factors (G-CSFs) and bisphosphonates (Table 5.8). Concomitant medication use in the abiraterone arm was assumed equal to concomitant use in the enzalutamide arm (as per AFFIRM) (except from the use of prednisolone for all abiraterone patients). The manufacturer reports dosing to have been taken from the British National Formulary (BNF 65) and costs taken from eMit and BNF 65 (MS, Table 64, pg. 164)[69].

Table 5.8: Use of concomitant medications

Concomitant medications	**% 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 (£)	**41.42**	**41.62**	**41.42**

Source: As applied in the Manufacturer's Enzalutamide Health Economic Model.
Abbreviations: ABI: abiraterone; BSC: best supportive care; G-CSF: Granulocyte colony-stimulating factor; ENZ: enzalutamide; MIT- Mitoxantrone

A summary of the total treatment costs is shown in Table 5.9.

Table 5.9: Costs (£) per three week cycle in SDis

Items	**ENZ (£)**	**ABI (£)**	**BSC (£)**
Technology cost per 3 week cycle	[redacted]	[redacted]	0
Administration cost	0	0	0
Monitoring cost	142* 71**	245* 127**	71
Concomitant medication	41	42	41
Total	[redacted]	[redacted]	**112**

Source: MS, Table 65, pg. 165. [13]
Abbreviations: ENZ: enzalutamide; BSC: best supportive care; ABI: abiraterone; * First three months; ** Subsequent months.

Medication in the PDis health state

The economic model includes costs for routine monitoring and medication in the PDis state. Medication in the PDis state is assumed to consist only of the concomitant medication of the BSC arm (MS, Table 66, pg. 166). The manufacturer justifies this with the fact that no active treatment is currently recommended in the UK for post-chemotherapy mCRPC patients after progression. Post study treatment was allowed in the AFFIRM study (MS, Table 66, pg. 166) but no reliable data were available on the duration of post study treatment. Furthermore, no reliable data were available on post study treatment in the COU-AA-301 study. The

manufacturer provides a scenario analysis to show the impact of including the costs for post study treatment.

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 of the MS (MS, Table 61-62, pg. 161-163). The average monitoring cost per cycle is £70.90.

Terminal treatment costs

Terminal care cost for a patient's last months has also been considered in the model. The terminal treatment cost of £3,133 per patient, was applied in the model as a transition cost to the death state.

Hospitalisations costs

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.

Costs of adverse-events and skeletal related events

The manufacturer has used the same assumptions regarding HRU costs associated with AEs as in the cabazitaxel STA.[10] The cost of these AEs was calculated based on this HRU, applying the updated NHS prices. For the AEs that were not reported in the cabazitaxel submission, costs were taken from the abiraterone ERG report.[54]

Costs for SREs were also included in the health economic model. The costing was derived from Botteman 2011,[11] and recalculated using the 2011-2012 NHS Reference costs (MS, pg.168).

ERG Comments:

The ERG viewed the resource use and unit costs used as reasonable. The ERG notes that the totals in Table 63 in the MS (pg. 164) are incorrect (corrected in Table 5.8 in this report). However, the numbers in Table 65 (MS, pg. 165) and in the economic model are correct.

5.2.9 Cost effectiveness results

The probabilistic base case results were reported by the manufacturer in the Response to the Clarification Letter (see Table 5.10). Enzalutamide was both more costly and more effective compared to abiraterone resulting in an ICER of £14,576 (taking into account the PAS). Similarly, enzalutamide was both more costly and more effective compared to BSC resulting in an ICER of £43,239.

Table 5.10: Base case results

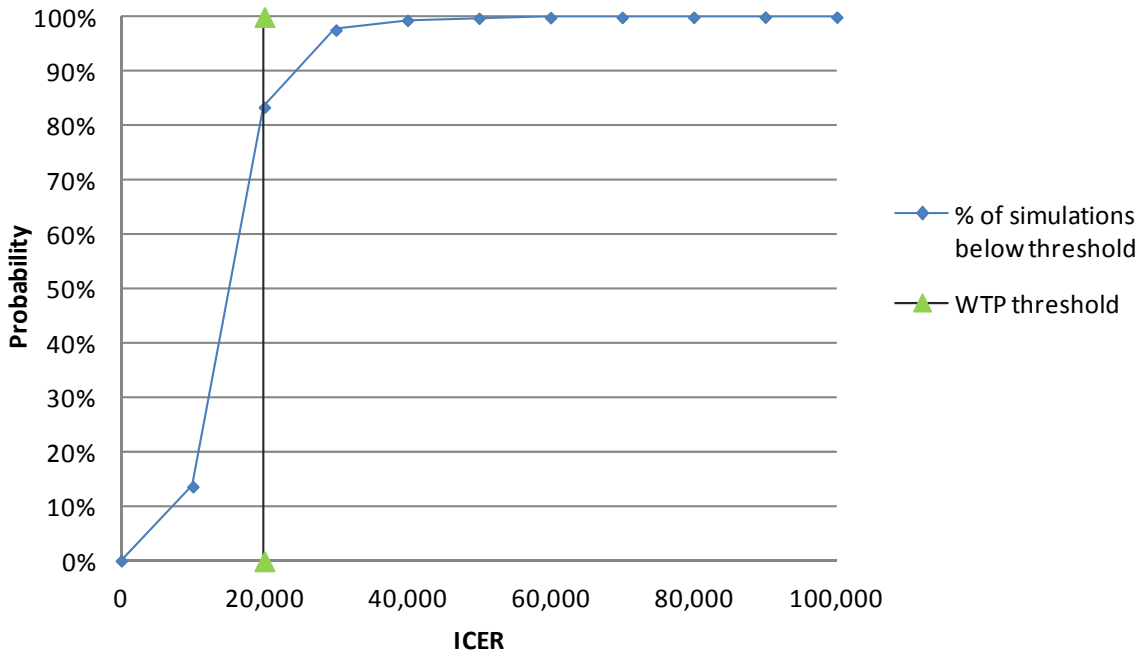
Treatment	Expected outcomes		Enzalutamide compared to abiraterone / BSC		
	Costs	QALYs	Δ Costs	Δ QALYs	ICER
Enzalutamide	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	14,576*
BSC	[redacted]	[redacted]	[redacted]	[redacted]	43,239

Source: MS, Tables 86- 87, pg. 186.[13]
Abbreviations: BSC: best supportive care.
* Extended dominated (added by ERG).

In addition to the base case results, the deterministic outcomes of multiple scenario analysis were presented.

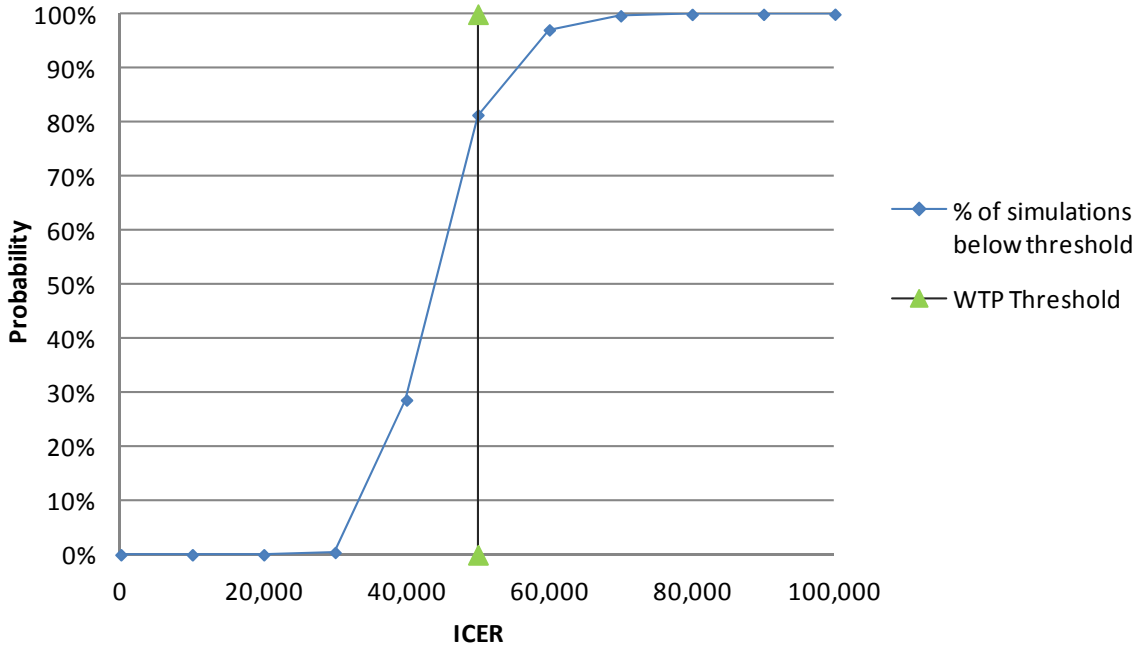
The manufacturer presented two cost-effectiveness acceptability curves, the first one comparing enzalutamide and abiraterone (Figure 5.6) and the second on comparing enzalutamide and BSC (Figure 5.7).

Figure 5.6: CEAC enzalutamide versus abiraterone



Source: MS, Figure 31, pg. 184.[13]
Abbreviations: ICER: incremental cost-effectiveness ratio; WTP: willingness to pay.

Figure 5.7: CEAC enzalutamide versus BSC



Source: MS, Figure 33, pg. 185.[13]
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; WTP: willingness to pay.

The probabilities that enzalutamide is cost-effective for different willingness to pay thresholds is shown in Table 5.11.

Table 5.11: 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%

Source: Adapted from MS Table 85, pg. 186.[13]
Abbreviations: ABI: abiraterone; BSC: Best Supportive Care; WTP: Willingness to pay.

ERG Comments:

The base case results show that abiraterone is extended dominated by BSC, which implies that for decision making the comparison of enzalutamide against BSC is relevant. Two CEAC figures were used by the manufacturer to present the probabilistic base case results (enzalutamide versus BSC and enzalutamide versus abiraterone). According to the ERG, all comparators should be included in one CEAC figure to appropriately evaluate the probability of cost-effectiveness.

It should be noted that the cost effectiveness of abiraterone versus BSC in the manufacturer's base case is estimated to be £102,751. This seems to be a less favourable ICER than the one

reported in the abiraterone STA.[12] Of course, the two submissions are not fully comparable, further complicated by the large amount of data on abiraterone that is CIC information. However, in general a higher ICER of abiraterone versus BSC is likely to favour enzalutamide in the comparison against abiraterone.

5.2.10 Sensitivity analyses

Multiple sensitivity analyses were performed, the 10 most influential sensitivity analyses (based on the 95% confidence intervals of the input parameters) for both comparisons are presented in Tables 5.12 and 5.13 (sorted by ICER spread). For enzalutamide compared to abiraterone, the HR used to calculate OS for abiraterone was considered the most influential variable resulting in an ICER spread ranging from £11,843 to £46,022. In addition, for enzalutamide compared to BSC, the HR used to calculate OS for enzalutamide (based on the Weibull model) was considered the most influential variable resulting in an ICER spread ranging from £34,692 to £58,042. As noted by the Manufacturer, the impact of these HRs and other correlated parameters included in the sensitivity analyses is actually smaller than presented in Tables 5.12 and 5.13, as the correlated parameters (e.g. the intercept) are not varied at the same time.

Table 5.12: The 10 most influential sensitivity analyses for enzalutamide compared to abiraterone

Name	Description	Model Input [low;high]	ICER low; high (£/QALY)
Base Case			**14,576**
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]	25,898; 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]	12,336; 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

Name	Description	Model Input [low;high]	ICER low; high (£/QALY)
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

Source: MS, table 83, pg.181.[13]

Abbreviations: BSC; best supportive care; HR: hazard ratio; OS: overall survival; TTD: time to treatment discontinuation.

Table 5.13: Ten most influential sensitivity analyses for enzalutamide compared to BSC

Name	Description	Model Input [low;high]	ICER low; high (£/QALY)
Base Case			**43,239**
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

Source: MS, table 84, pg. 182.[13]

Abbreviations: BSC; best supportive care; HR: hazard ratio; OS: overall survival; TTD: time to treatment discontinuation.

ERG Comments:

Although a large number of sensitivity analyses were undertaken, in the opinion of the ERG the following were particularly missing:

- omitting the impact of SREs and AE on costs (due to uncertainty with regard to the indirect comparison of enzalutamide and abiraterone).
- the disutility of progression.

- the baseline utility over a wide range to explore the impact of a worse baseline utility in clinical practice than observed in a subpopulation of the AFFIRM trial.
- the PFS (TTD) HR of enzalutamide versus BSC over wide range to explore the impact of uncertainty caused by using TTD as a proxy for PFS.

5.2.11 Scenario analyses

The manufacturer performed a large number of scenario analyses. The deterministic results of these analyses were reported in the MS (MS, Table 88, p. 187).[13]

ERG Comment:

In the clarification letter the ERG requested the probabilistic results of the scenario analyses, which were provided by the manufacturer. In Table 5.14 the incremental outcomes of these analyses are presented. For the comparison of enzalutamide versus abiraterone, the results of the scenario analyses varied from £8,881 (Log Logistic model instead of Weibull model for OS reference curve) to £20,932 (use of a Log Logistic model instead of a Weibull model for PFS reference curve). For the comparison of enzalutamide versus BSC, the results of the scenario analyses varied between £25,525 (Log Logistic model instead of Weibull model for OS reference curve) and £51,075 (on treatment utility gain excluded).

Table 5.14: Scenario analyses

	Enzalutamide compared to abiraterone			**Enzalutamide compared to BSC**		
	Δ Costs	**Δ QALYs**	**ICER**	**Δ Costs**	**Δ QALYs**	**ICER**
Base case	[redacted]	[redacted]	14,576	[redacted]	[redacted]	43,239
Time Horizon 4 years	[redacted]	[redacted]	14,711	[redacted]	[redacted]	44,395
Time Horizon 6 years	[redacted]	[redacted]	14,666	[redacted]	[redacted]	43,464
Time Horizon 8 years	[redacted]	[redacted]	14,597	[redacted]	[redacted]	43,300
Discount rate costs and effects – 0%	[redacted]	[redacted]	14,476	[redacted]	[redacted]	42,043
Discount rate costs and effects – 1.5%	[redacted]	[redacted]	14,566	[redacted]	[redacted]	42,608
Discount rate costs and effects – 5%	[redacted]	[redacted]	14,641	[redacted]	[redacted]	43,817
Use a fixed HR for abiraterone OS	[redacted]	[redacted]	19,481	[redacted]	[redacted]	43,337
Apply on ITC on mean OS to the abiraterone arm	[redacted]	[redacted]	17,532	[redacted]	[redacted]	43,255
Use Log Logistic model for OS reference curve (AFFIRM placebo)	[redacted]	[redacted]	8,881	[redacted]	[redacted]	25,525
Use mPFS instead of TTD for PFS	[redacted]	[redacted]	13,234	[redacted]	[redacted]	43,186
Use Log Logistic model for PFS reference curve (AFFIRM placebo)	[redacted]	[redacted]	20,932	[redacted]	[redacted]	47,571
No disutility for AEs	[redacted]	[redacted]	14,531	[redacted]	[redacted]	43,231
No disutility for SREs	[redacted]	[redacted]	14,592	[redacted]	[redacted]	43,435
No disutility for AEs or SREs	[redacted]	[redacted]	14,625	[redacted]	[redacted]	43,462
Utility values for health states	[redacted]	[redacted]	12,728	[redacted]	[redacted]	38,224

	Enzalutamide compared to abiraterone			Enzalutamide compared to BSC		
	Δ Costs	Δ QALYs	ICER	Δ Costs	Δ QALYs	ICER
used in abiraterone CVZ submission						
Pre-progression value of 0.80 post-progression of 0.50	[redacted]	[redacted]	13,555	[redacted]	[redacted]	37,000
Use mapped utility values for baseline ([redacted]) and progressed disease (decrement of [redacted]) utility	[redacted]	[redacted]	14,251	[redacted]	[redacted]	42,628
Exclude on treatment utility gain	[redacted]	[redacted]	16,577	[redacted]	[redacted]	51,075
Same on treatment utility gain for enzalutamide and abiraterone	[redacted]	[redacted]	15,513	[redacted]	[redacted]	43,380
Assume routine visits are alternated between nurse and consultant	[redacted]	[redacted]	15,319	[redacted]	[redacted]	42,780
Include active treatment costs post-progression	[redacted]	[redacted]	12,704	[redacted]	[redacted]	36,715

Source: Response to the Clarification Letter, Tables A2.1- A2.43 and MS, Tables 86 -87.[2 13]
Abbreviations: BSC: best supportive care; 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.

5.2.12 Model validation and face validity check

Face validity

The manufacturer reported that a series of advisory boards were held to validate the health economic model, the underlying assumptions and its inputs. For each advisory board meeting, 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. Clinical parameters validated by the clinical experts included (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.

Internal validity

The manufacturer reported 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.

In addition to the internal model validation by the manufacturer, the ERG performed internal validity checks including (but not limited to): recalculating the time-dependent probabilities

based on the parametric survival models and HRs for PFS and OS, rerunning the PSA, scrutinizing and reproducing the Markov traces, recalculating the expected life-years, randomly checking input parameters and formulas.

Cross-validation

Cross-validation includes examining different models that address the same problem and comparing their results. This was difficult as the manufacturer found no published economic evaluations considering enzalutamide for the treatment of mCRPC in adult men whose disease has progressed on or after docetaxel therapy. The manufacturer's submission of abiraterone to NICE calculated an ICER of £52,851 for abiraterone versus BSC in the one prior chemo population, however, it is difficult to compare this with the ICER calculated in the presented analysis (£102,324; incremental costs [redacted], incremental QALYs [redacted]). Not only was a different subgroup modelled, but also many inputs are different (i.e., utility values) as shown in Table 90 of the MS (MS, pg. 192). In addition, many inputs in the abiraterone submission were CIC, which makes a comparison of the ICERs even more complicated.

External validity

External validity of the model was evaluated as good by the manufacturer: all modelled medians were close to the reported values. The manufacturer notes that the median PFS (in terms of TTD) for BSC is slightly longer in the model compared to the clinical trial results (Table 5.15). This was considered 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] months), thereby confirming the validity of the modelled curve.

Table 5.15: 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

Source: MS, Table 71, pg. 173. [13]

Abbreviations: BSC: best supportive care; CI: confidence interval; TTD: time to treatment discontinuation; OS: overall survival.

ERG Comments:

The model is appropriately simple and transparent. The appropriate validity checks are undertaken by the manufacturer and the results are satisfactory. Re-running the model, the base case deterministic and probabilistic results cross check with those of the manufacturer. The extreme value analyses undertaken by the ERG resulted in outcomes in the expected direction. No programming errors were detected.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

5.3.1 Additional analyses

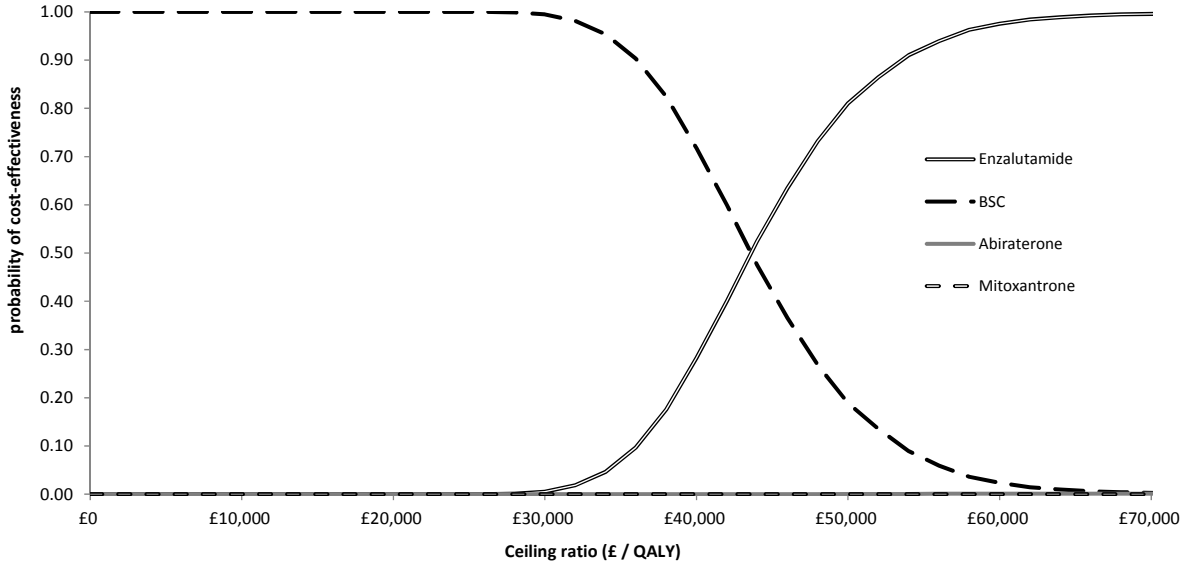
The ERG has added mitoxantrone alone or in combination with prednisone as a comparator to the health economic model (see Appendix 2 for methods used) to comply with the scope. All ERG sensitivity analyses are based on this adapted model with four comparators (enzalutamide, abiraterone, mitoxantrone, BSC). The ICER of enzalutamide versus mitoxantrone amounts to £33,585, but is extended dominated. The results are in Table 5.16 and the acceptability curve in Figure 5.8.

Table 5.16: Manufacturer base case results including mitoxantrone as a comparator

Treatment	Expected outcomes*		Enzalutamide compared to ABI / Mitoxantrone /BSC		
	Costs	QALYs	Δ Costs	Δ QALYs	ICER
Enzalutamide	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	**14,599****
Mitoxantrone	10,722	0.75	[redacted]	[redacted]	**33,585****
BSC	[redacted]	[redacted]	[redacted]	[redacted]	**43,288**

* Differences to the Manufacture's base case are due to PSA. ** Extended dominated
Abbreviations: BSC: best supportive care.

Figure 5.8 Cost-effectiveness acceptability curve including mitoxantrone as a comparator



Abbreviations: BSC: best supportive care.

At a willingness to pay (WTP) threshold of £50,000 the probability that enzalutamide is cost-effective is 81%, while this is 19% for BSC and 0% for abiraterone and mitoxantrone.

The following additional analyses were undertaken:

- Keeping a constant HR of 1.00 for OS of abiraterone versus BSC beyond 25 months,

- Using the whole population to estimate the HR for PFS of abiraterone versus BSC,
- Excluding on treatment utility benefits,
- All of the above (ERG base case).

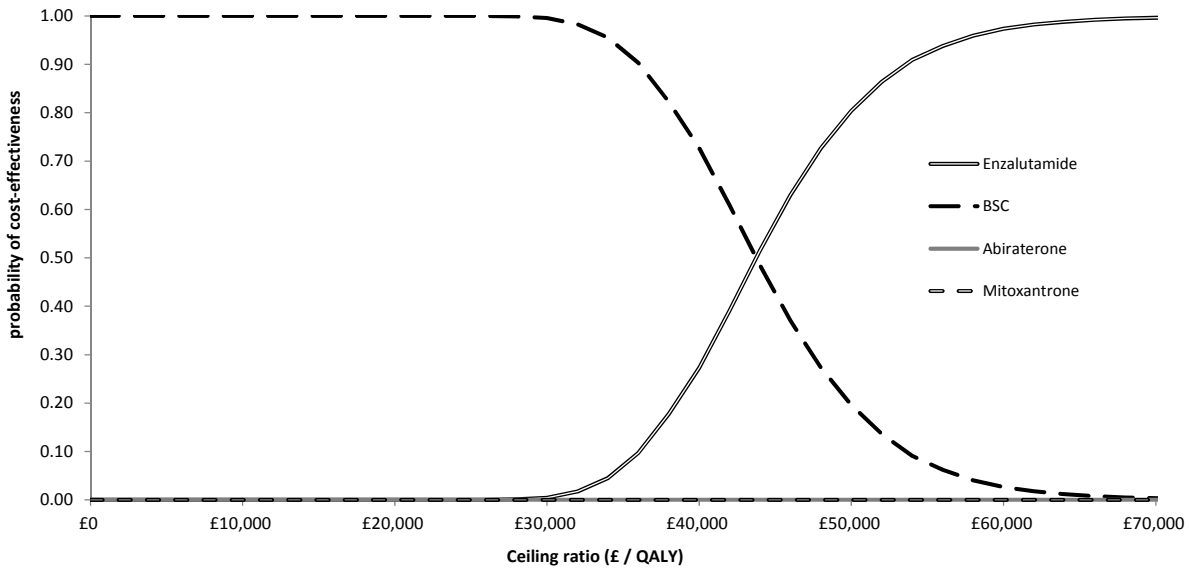
According to the ERG the evidence does not justify the use of the HR of 1.39 after 25 months, for OS for abiraterone versus BSC given the very low number of observations at 25 months and the unlikely linear relation. To adopt a more conservative approach, a constant HR of 1.00 is used for abiraterone versus BSC after 25 months. The acceptability curves are given in Figure 5.9 and the results are given in Table 5.17. The ICER of enzalutamide versus abiraterone increased to £15,020, but is extended dominated.

Table 5.17: Results using a constant HR of 1.00 for OS of abiraterone versus BSC after 25 months

Treatment	**Expected outcomes**		**Enzalutamide compared to ABI / Mitoxan /BSC**		
	Costs	**QALYs**	**Δ Costs**	**Δ QALYs**	**ICER**
Enzalutamide	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	**15,020***
Mitoxantrone	10,761	0.751	[redacted]	[redacted]	**33,582***
BSC	[redacted]	[redacted]	[redacted]	[redacted]	**43,398**

* Extended dominated . Abbreviations: BSC: best supportive care.

Figure 5.9 Cost-effectiveness acceptability using a constant HR of 1.00 for OS of abiraterone versus BSC after 25 months



Abbreviations: BSC: best supportive care.

At a willingness to pay (WTP) threshold of £50,000 the probability that enzalutamide is cost-effective is 80%, while this is 20% for BSC and 0% for abiraterone and mitoxantrone.

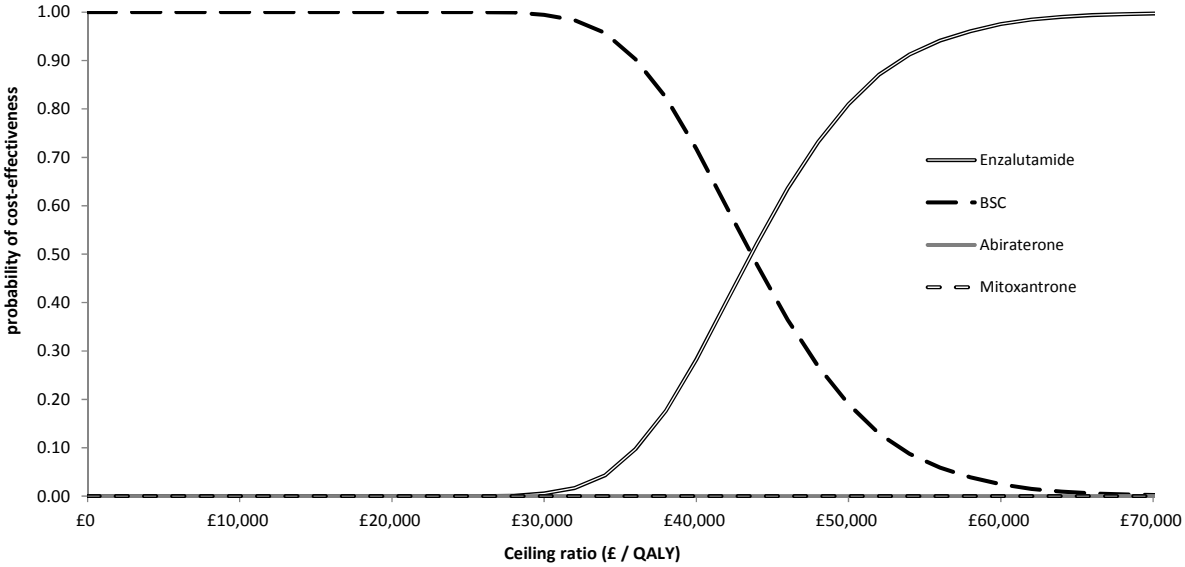
By using an alternative HR for PFS (i.e. TTD), the OS and PFS estimates for abiraterone are now based on the whole population instead of a subgroup from the COU-AA-301 trial. The ICER of enzalutamide versus abiraterone decreased to £12,461, but is extended dominated. The results of this analysis are in Table 5.18 and the acceptability curves in Figure 5.10.

Table 5.18: Results using the whole population HR of 0.49 for abiraterone

Treatment	Expected outcomes		Enzalutamide compared to ABI / Mitoxan /BSC		
	Costs	QALYs	Δ Costs	Δ QALYs	ICER
Enzalutamide	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	**12,461***
Mitoxantrone	10,750	0.752	[redacted]	[redacted]	**33,510***
BSC	[redacted]	[redacted]	[redacted]	[redacted]	**43,285**

** Extended dominated. Abbreviations: BSC: best supportive care.

Figure 5.10 Cost-effectiveness acceptability curve using the whole population HR of 0.49 for abiraterone



Abbreviations: BSC: best supportive care.

At a willingness to pay (WTP) threshold of £50,000 the probability that enzalutamide is cost-effective is 81%, while this is 19% for BSC and 0% for abiraterone and mitoxantrone.

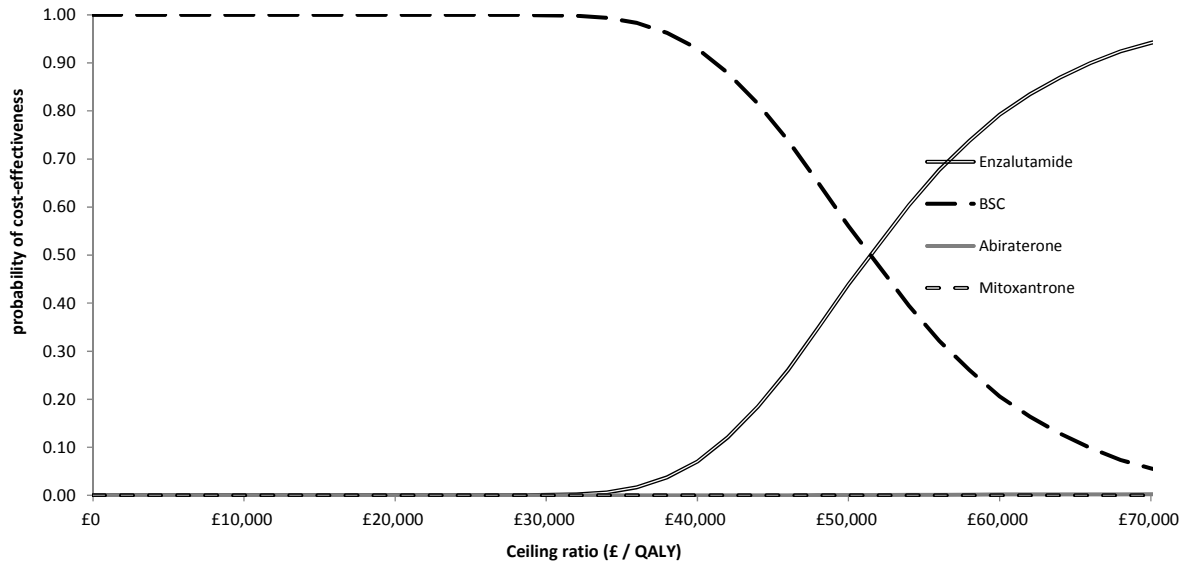
The ERG suggests taking a conservative approach and disregarding the on treatment utility increments in the base case scenario to prevent double counting in the advantage of enzalutamide. The ICER of enzalutamide versus abiraterone increased to £16,464 (extended dominated), and the ICER of enzalutamide versus BSC increased to £51,014. The results of this analysis are in Table 5.19 and the acceptability curves in Figure 5.11.

Table 5.19: Exclude on treatment utility gain

Treatment	Expected outcomes		Enzalutamide compared to ABI / Mitoxan /BSC		
	Costs	QALYs	Δ Costs	Δ QALYs	ICER
Enzalutamide	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	**16,464***
Mitoxantrone	10,744	0.737	[redacted]	[redacted]	**37,703***
BSC	[redacted]	[redacted]	[redacted]	[redacted]	**51,014**

* Extended dominated . Abbreviations: BSC: best supportive care.

Figure 5.11 Cost-effectiveness acceptability curve excluding on treatment utility gain



Abbreviations: BSC: best supportive care.

At a willingness to pay (WTP) threshold of £50,000 the probability that enzalutamide is cost-effective is 44%, while this is 56% for BSC and 0% for abiraterone and mitoxantrone.

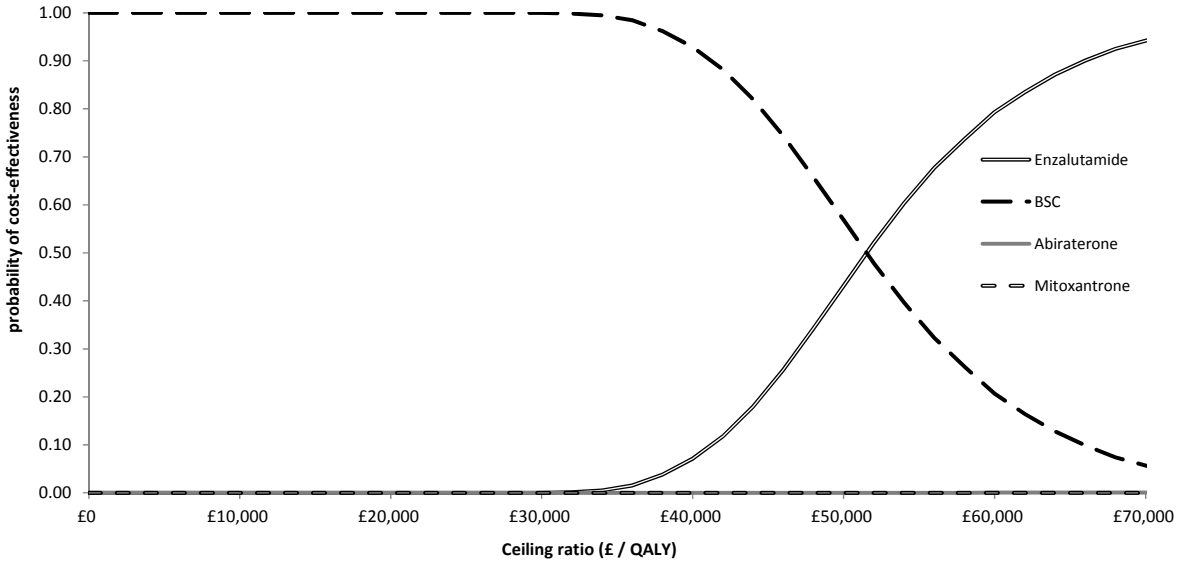
The ERG base case takes into account all the above changes. The ICER of enzalutamide versus abiraterone decreased to £14,488 (extended dominated), and the ICER of enzalutamide versus BSC increased to £51,124. Results are given in Table 5.20 and acceptability curves are depicted in Figure 5.12.

Table 5.20: ERG base case

Treatment	Expected outcomes		Enzalutamide compared to ABI / Mitoxan /BSC		
	Costs	QALYs	Δ Costs	Δ QALYs	ICER
Enzalutamide	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	**14,488***
Mitoxantrone	10,732	0.736	[redacted]	[redacted]	**37,840***
BSC	[redacted]	[redacted]	[redacted]	[redacted]	**51,124**

* Extended dominated . Abbreviations: BSC: best supportive care.

Figure 5.12 Cost-effectiveness acceptability curve ERG base case



Abbreviations: BSC: best supportive care.

At a willingness to pay (WTP) threshold of £50,000 the probability that enzalutamide is cost-effective is 43%, while this is 57% for BSC and 0% for abiraterone and mitoxantrone.

5.3.2 Exploratory analyses

The ERG performed exploratory analyses with regard the impact of SREs and AEs, the disutility for progressive disease, PFS (TTD) HR of enzalutamide versus BSC and the baseline utility.

Omitting the impact of SREs and AEs on costs and QALYs (ignoring any disutility) in the economic model resulted in slightly increases the ICERs of enzalutamide versus BSC (£45,091) and abiraterone (£15,087).

The disutility for progressive disease could be estimated in various ways, of which none was clearly superior. Using the disutility from Sullivan et al (2007)[68] of 0.07 instead of the value of 0.085 from Sandblom (2004)[67] increases the ICER of enzalutamide versus BSC (£43,704) and decreases the ICER versus abiraterone (£14,724).

In the economic model PFS was modelled based on TTD, in absence of more reliable data. The ERG agrees that regarding the available evidence, TTD is the most reasonable measure to estimate PFS. Nonetheless, there is uncertainty around the estimate. To explore the impact of changes in the estimate of the PFS (TTD) HR of enzalutamide versus BSC a threshold analysis was performed. If the HR is 0.23 or lower (base case value [redacted]) the ICER of enzalutamide versus BSC is higher than £50,000 (for the MS base case). It is to be noted that Enzalutamide becomes less costly if it becomes less effective in terms of PFS, while OS remains equal. See figure 5.13.

Figure 5.13: ICER Threshold analysis for the PFS (TTD) HR (enzalutamide versus BSC)

[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; PFS: progression free survival; TTD: time to treatment discontinuation; HR: hazard ratio; BSC: best supportive care.

The ERG regards the EQ-5D baseline utility value as uncertain for the following reasons. Only a very small proportion of the patients in the AFFIRM trial completed/were asked to complete the EQ-5D. At baseline 142 of 800 [18%] patients in the enzalutamide arm and 67 of 399 (17%) patients in the placebo arm completed the EQ-5D (MS, pg. 146). In addition, the proportion of patients with missing items among those asked is considerable (response 60-64%). Together with the fact that the population in the AFFIRM trial could have been fitter than generally seen in clinical practice, the utility value of [redacted] could be an overestimation of the quality of life of the patient population. From the utility values listed in the MS (MS, Table 113, pg. 234) it becomes clear that a large range of utility values for this population have been reported in the literature. The applicability of these values to the decision problem is however questionable due to differences in populations (e.g. country, disease stage), use of other instruments than EQ-5D, and small samples. Therefore, the ERG

performed a threshold analysis for baseline utility. If the baseline utility is 0.58 or lower (in the MS base case), the ICER is higher than £50,000. A value of 0.58 does not seem unrealistic based on the literature summarized in the MS (MS, Table 113, pg. 234), though the values presented in this table of the MS probably represent an average value for PFS and PD patients.

Figure 5.14: ICER Threshold analysis for baseline utility (enzalutamide versus BSC)

[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; BSC: best supportive care.

5.4 Conclusions of the cost effectiveness section

The literature search for relevant cost effectiveness studies was appropriate and did not identify any studies that included enzalutamide as a comparator. Hence, a de novo economic analysis was performed.

The manufacturer presented a comparison of enzalutamide, abiraterone and BSC. Mitoxantrone was not included as a comparator, although it was listed in the scope. Although the ERG agrees that regarding the limited use of mitoxantrone in clinical practice and limited evidence available a comparison would be seen as secondary, the ERG has the opinion that the MS should comply with the scope. Also after request for clarification the manufacturer did not include mitoxantrone as a comparator. Therefore, the ERG modelled mitoxantrone as a comparator in a similar manner as done in the abiraterone STA.[3]

The Markov state transition model follows the structures used in other NICE STAs in metastatic cancer (health states are stable disease, progressive disease and death) and is appropriate in the view of the ERG. The model applied a 10 year time horizon, which was in effect lifetime, coupled with a three weekly cycle. The backbone of the model is made up by

survival curves for PFS and OS. Time in the progressive disease state was calculated as the difference between OS and PFS. In addition to disease progression and survival, AEs (grade ≥3) in stable disease, SREs in progressive disease, and an on treatment utility gain for enzalutamide and abiraterone are taken into account. The manufacturer submission was in line with the NHS reference case, apart from omitting mitoxantrone as a comparator, selecting the subgroup with OPC to estimate the HR for PFS of abiraterone versus BSC, and using mapped EQ-5D utility based on FACT-P data for 'on-treatment utility gain' and disutility of SREs.

The effectiveness estimates in the model are based on the patient level data on OS and TTD of the AFFIRM trial for enzalutamide and BSC and published results of the COU-AA-301 study for the effectiveness of abiraterone versus BSC. The AFFIRM and COU-AA-301 trials are reasonably comparable with regard to population, interventions and outcomes, allowing an indirect comparison. Both modified PFS and radiographic PFS are disregarded in the modelling, instead TTD is used as a proxy for PFS. The manufacturer argues that TTD as measured in the trials best reflected UK practice. The ERG agrees that among the measures for disease progression available TTD is to be preferred, although this estimate remains uncertain. The OS and curves for BSC are based on the AFFIRM trial. Several models were fitted, of which the Log-Logistic models had the best statistical performance. The manufacturer however chose to use the Weibull models based on expert opinion. After further clarification was provided, the ERG agrees that the Weibull models are more realistic. The effectiveness of abiraterone versus BSC was estimated from the COU-AA-301 study. The OS HR of abiraterone versus BSC was appropriately modelled as time-dependent. However, this resulted in a HR of 1.39 at 25 months (end of follow up in the trial), which was then kept constant in the model for the remaining time horizon. The ERG asked for further clarification as this extrapolation is based on very few patients. The manufacturer did not provide additional arguments. In the ERG's opinion a conservative approach is preferred by keeping a HR of 1.00 for OS of abiraterone versus BSC after 25 months, i.e., both abiraterone and BSC produce the same hazard function after month 25.

Utility data was collected using the EQ-5D among a subset of the patients in the AFFIRM study. Response was just above 60% among the patients asked. It should be noted that overall only for a very small proportion of the patients in AFFIRM complete (none of the five items missing) EQ-5D forms were available (at baseline between 13% and 16% for the placebo and enzalutamide arm respectively). The AFFIRM EQ-5D data were used to estimate baseline utility. The 'on treatment utility gain' for enzalutamide was based on AFFIRM data using FACT-P mapping. Utility values for the progressive disease health state, 'on treatment utility gain' for abiraterone, AEs, and SREs could not be estimated from AFFIRM data and were taken from the literature. Given the relatively small number of patients asked and the considerable non-response, the ERG has some concerns regarding the applicability of the baseline utility value [redacted] (SE = [redacted]) for the population in clinical practice. As the population in the AFFIRM trial could have been fitter than generally seen in clinical practice, the utility value of [redacted] could be an overestimation of the quality of life of the patient

population. Furthermore, the ERG questioned the application of the 'on treatment utility gain' for abiraterone ([redacted] (95% CI: [[redacted]]) and enzalutamide ([redacted] (95% CI: [[redacted]]) for the following reasons. Firstly, details on the internal mapping algorithm and further details used to calculate the enzalutamide 'on treatment utility gain' were missing (and not provided after clarification questions). Secondly, the 'on treatment utility gain' for enzalutamide and abiraterone versus BSC are likely to be an overestimation of the real 'on treatment utility gain' as part of this utility benefit is already captured by the utility decrements used for AEs in the stable disease health state. This creates potential for double counting. Thirdly, the evidence base to assume a different 'on treatment utility gain' for enzalutamide and abiraterone is extremely thin as the estimate for abiraterone is taken from a Dutch submission report that does not include any details with regard to the methods used. In response to questions for clarification the manufacturer argues that excluding the 'on treatment utility gain' would underestimate the total impact of AEs as only AEs grade ≥3 are taken into account. The ERG agrees with this. However, in light of the weak evidence on the 'on treatment utility gain' for both enzalutamide and abiraterone and the risk of double counting, the ERG prefers taking a conservative approach and disregarding the 'on treatment utility gain' in the base case scenario.

The list price of enzalutamide is £2,734.67 for each 28 day pack. The manufacturer has agreed a PAS with the Department of Health, which is reflected in the base case analysis. The PAS consists of a [redacted] discount, resulting in a price per pack of enzalutamide of [redacted]. [redacted]. Treatment specific costs further include costs for monitoring and concomitant medication. Monitoring costs are less for enzalutamide as compared to abiraterone as a result of a lower frequency, and in line with the abiraterone STA.[3] Costs of concomitant medication were based on AFFIRM and assumed the same for enzalutamide and abiraterone, apart from the need abiraterone patients to receive prednisolone. Total technology costs per cycle amounted to [redacted] (first three months) and [redacted] (subsequent months) for enzalutamide, to [redacted] (first three months) and [redacted] (subsequent months) for abiraterone, and to £112 for BSC. Post-progression (post-study) treatment costs were not taken into account. The impact of this assumption was tested in univariate (for one comparator at the time) sensitivity analyses showing that this impacted the ICERs (MS: Table 83 & Table 84; p. 183-184). However, when including post-progression treatment costs for all comparators in the model alike, the impact on the ICERs was only modest (MS: Table 88; p.187). Post-progression monitoring costs were assumed to be equal to pre-progression monitoring costs in BSC. Terminal treatment costs of £3,133 per patient were calculated in the same manner as in the abiraterone STA[3] and taken into account as a transition cost to the death state. Costs for AEs were based on resource use reported in the cabazitaxel STA[10] and the abiraterone STA[3] and 2011-2011 NHS reference prices. The resource use associated with SREs was taken from Botteman 2011[11] and recalculated using 2011-2012 NHS reference prices. The ERG viewed the resource use and costs as reasonable.

The base case expected outcome is that, with the PAS, the cost effectiveness of enzalutamide is £14,576 per QALY against abiraterone (extended dominated), and £43,239 against BSC.

For a threshold of £20,000 per QALY the probability that enzalutamide is cost effective is 83% against abiraterone, and 0% against BSC. For a threshold of £50,000 per QALY the probability that enzalutamide is cost-effective against BSC is 80%. The manufacturer presented a large number of sensitivity (using the 95% CI limits as inputs) and scenario analyses. The most influential variable in the sensitivity analyses for the comparison of enzalutamide versus abiraterone is the HR for OS of abiraterone versus BSC (ICER spread £11,843 to £46,022). For enzalutamide compared to BSC, the HR for OS for enzalutamide versus BSC is considered the most influential variable (ICER spread £34,692 to £58,042). In the clarification letter the ERG requested the probabilistic results of the scenario analyses, which were provided by the manufacturer. For the comparison of enzalutamide versus abiraterone, the results of the scenario analyses varied from £8,881 (Log Logistic instead of Weibull model for OS) to £20,932 (Log Logistic instead of Weibull model for PFS). For the comparison of enzalutamide versus BSC, the results of the scenario analyses varied between £25,525 (Log Logistic instead of Weibull model for OS) and £51,075 (on treatment utility gain excluded). It should be noted that the cost effectiveness of abiraterone versus BSC in this analysis is estimated to be £102,751. This seems to be a less favourable result than in the abiraterone STA, although this is difficult to judge due to large amount of data on abiraterone that is CIC information[12]. As a result, it was impossible to exactly pin-point the sources of differences underlying the analyses undertaken for this STA, and the analyses undertaken in the abiraterone STA. In general, a less favourable cost effectiveness of abiraterone against BSC is likely to favour enzalutamide in the comparison against abiraterone.

The ERG has added mitoxantrone alone or in combination with prednisone as a comparator to the health economic model to comply with the scope. With this adapted model, the following additional analyses are undertaken:

- Constant HR of 1.00 for OS of abiraterone versus BSC beyond 25 months (ICER enzalutamide versus abiraterone £15,020),
- Using the whole population to estimate the HR for PFS of abiraterone versus BSC (ICER enzalutamide versus abiraterone £12,461),
- Excluding on treatment utility gain (ICER enzalutamide versus abiraterone £16,464; ICER enzalutamide versus BSC £51,014),
- All the above as ERG base case (ICER enzalutamide versus abiraterone £14,488; ICER enzalutamide versus BSC £51,124).

Adding mitoxantrone did not change the relative cost effectiveness of enzalutamide versus abiraterone and versus BSC. The additional analyses lead to higher ICERs of enzalutamide versus BSC. The ERG base case ICER for enzalutamide versus abiraterone is very similar to the manufacturer's estimate. The additional analysis excluding on treatment utility gain increases the ICER of enzalutamide versus abiraterone with £2,000.

The ERG performed exploratory analyses with regard to the TTD (as a proxy for PFS) HR of enzalutamide versus BSC and the baseline utility. If the HR is 0.23 or lower (base case value

[redacted]) the ICER of enzalutamide versus BSC is higher than £50,000. It is to be noted that in the model Enzalutamide becomes less costly if it becomes less effective in terms of PFS, while OS remains equal. A baseline utility of 0.58 or lower results in an ICER of enzalutamide versus BSC higher than £50,000.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

Table 6.1: Overview of additional and exploratory analyses undertaken by the ERG

Treatment	Expected outcomes		Enzalutamide compared to		
	Costs	QALYs	Δ Costs	Δ QALYs	ICER
MS Base case					
Enzalutamide	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	14,576**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	43,239
Adding mitoxantrone*					
Enzalutamide	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	14,599**
Mitoxantrone	10,722	0.75	[redacted]	[redacted]	33,585**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	43,288
Constant HR of 1.00 for OS of abiraterone versus BSC after 25 months					
Enzalutamide	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	15,020**
Mitoxantrone	10,761	0.751	[redacted]	[redacted]	33,582**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	43,398
Whole population HR of 0.49 for abiraterone instead of OPC subgroup					
Enzalutamide	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	12,461**
Mitoxantrone	10,750	0.752	[redacted]	[redacted]	33,510**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	43,285
Exclude 'on treatment utility gain'					
Enzalutamide	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	16,464**
Mitoxantrone	10,744	0.737	[redacted]	[redacted]	37,703**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	51,014
ERG base case					
Enzalutamide	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	14,488**
Mitoxantrone	10,732	0.736	[redacted]	[redacted]	37,840**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	**51,124**

Abbreviations: BSC: best supportive care. * Differences to the Manufacture's base case are due to PSA. ** Extended dominated

7. END OF LIFE

NICE has issued supplementary advice to the Appraisal Committees for appraising life-extending, end of life treatments. These are treatments which may be life-extending for patients with short life expectancy, and which are licensed for indications affecting small numbers of patients with incurable illnesses.[73]

NICE end of life supplementary advice should be applied in the following circumstances and when all the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and;
- The treatment is licensed or otherwise indicated, for small patient populations.

The end of life criteria used for enzalutamide in the manufacturer's submission and the manufacturer's justification for applying the end of life criteria to enzalutamide are outlined in section 7.10.4 of the manufacturer's submission (MS, page 193; see Table 7.1 below)[13].

Table 7.1: End of life criteria for enzalutamide

Criteria	Justification
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[4] and the AFFIRM study[6], patients currently treated with BSC have a short life expectancy of approximately one year.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to 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 treatment is licensed or otherwise indicated, for small patient populations	As indicated in section 2.2 of the MS, 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.

In the abiraterone assessment(TA-259[3]), the NICE Committee agreed that the first criterion related to life expectancy was fulfilled, because life expectancy from trials including patients randomised to best supportive care was less than 15 months (see NICE guidance TA259, section 4.21, page 31).[3] Data from the control arms of the COU-AA-301 study[4] and the AFFIRM study[6] seem to confirm this.

The second criterion is more difficult to establish as there is no information about the mean increase in survival of enzalutamide compared with best supportive care. However, in the AFFIRM trial: "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)[6]." (see MS, section 6.5.3.1, page 61).[13] This suggests an increase in median OS of 4.8 months for enzalutamide when compared with best supportive care. Although it is possible that the mean survival benefit for enzalutamide over best supportive care is less than three months, it is most likely more. However, based on the economic model, it can be estimated that enzalutamide has 2.88 months survival benefit over best supportive care. The model provides an indication of mean life years ("Life Years cumulative" on the "Calculation..." sheets). Assuming that the duration of the AFFIRM trial was 24 months, the modelled values are as in the table below (the closest approximation is 2.01 years).

Table 7.2: Mean survival years

Enzalutamide		
Years	Life years	Months
2.01	1.40	16.82
BSC		
Years	Life years	Months
2.01	1.16	13.94
		Difference
		2.88

Regarding the third criterion, the NICE Committee stated in the abiraterone assessment (TA-259[3]): "The Committee understood from estimates obtained from the appraisal of cabazitaxel that approximately 3,500 people with hormone-refractory metastatic prostate cancer received docetaxel in England and Wales in 2011, and that, according to estimates provided by the manufacturer, approximately 70% of these (n=25,00) would be able to receive second-line abiraterone treatment in line with the marketing authorisation." (see NICE guidance TA259, section 4.21, page 32) These numbers are similar as the numbers provided by the manufacturer in this appraisal.

Therefore, it is likely that enzalutamide meets the end of life criteria as specified by NICE. However, the mean survival benefit for enzalutamide over best supportive care might be just under three months.

8. OVERALL CONCLUSIONS

In conclusion, the additional analyses showed that changing assumptions and inputs in a way that, according to the ERG, is more appropriate increases the ICER of enzalutamide versus BSC from £43,239 to £51,014 per QALY; abiraterone and mitoxantrone are both extended dominated. In the additional analyses the ICER of enzalutamide versus abiraterone is highest when excluding the treatment specific estimates of 'on treatment utility gain' (£16,464 instead of £14,576 in the MS). Exploratory analyses show that the cost-effectiveness of enzalutamide versus BSC is most sensitive to the baseline utility value and the PFS HR of enzalutamide versus BSC.

8.1 Implications for research

A head-to-head trial of enzalutamide versus abiraterone with respect to PFS, OS, AEs, and SREs would reduce the uncertainty surrounding any differences in clinical effectiveness considerably.

In addition, further research on the utility values in stable disease and progressive disease as well as on treatment utility gain would be valuable.

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Appendix 1: Further critique of manufacturer's searches

Clinical effectiveness

Further limitations

- The ERG noted CAS registry numbers were not included in the search strategies.
- The ERG noted a number of missing synonyms for the main interventions including: cb 7598, mdv 3100, cl 232315, domitrone, elsep, formyxan, misostol.
- Restrictive subheadings were used, e.g. "abiraterone – clinical trials". The ERG was concerned that through these relevant references could have been missed.
- The ERG noted that the more commonly used spelling mitrozantrone has been omitted in the favour of mitroxantrone.
- It was noted that a limit to exclude animal studies was used ineffectively. The ERG was concerned that this limit could also exclude potentially relevant studies in humans.
- The ERG noted inadequate truncations, spelling mistakes and missing alternative spelling variations which might have resulted in missing relevant references.

Indirect and mixed treatment comparisons

The MS reported that the mixed treatment analysis (MS 6.7) was informed by the search for clinical effectiveness.[13] Therefore no additional strategies were included in this section.

Non-RCT Evidence

The MS reported that no relevant non-RCTs were identified during the systematic literature review (SLR) (MS 6.8).[13] Therefore no additional strategies were included in this section. In the SLR, the use of search filters was confused and both filters for RCT and non-RCT were used in the same search strategy simultaneously (table 14-1).[8] This was considered overly restrictive and may have impaired strategy recall. In the Cochrane Handbook of Systematic Reviews (Chapter 13.3.1.1) it is stated that non-RCTs are difficult to categorise and are often not called or indexed as non-RCTs.[74] The search would have been more efficient and comprehensive without a study design filter.

Adverse events

The manufacturer stated that searches for adverse events were already covered by the search for clinical effectiveness.[13] Therefore no additional strategies were included in this section. The ERG did not consider this adequate.

Cost effectiveness
Further limitations

- It was noted that a limit to exclude animal studies was used in effectively. The ERG was concerned that this limit would also exclude relevant studies containing humans.

- The ERG noted inadequate truncations, spelling mistakes and missing spelling variations which could have resulted in missing relevant references.

Measurement and valuation of health effects
Further limitations

- It was noted that a limit to exclude animal studies was used ineffectively. The ERG was concerned that this limit would also exclude relevant studies containing humans.

- The ERG noted inadequate truncations, spelling mistakes and missing alternative spelling variations which could have resulted in missing relevant references.

Resource identification, measurement and valuation
The MS reported that the resource identification, measurement and valuation section (MS 7.5.3, 10.13) was informed by the search for cost effectiveness.[13] Therefore no additional strategies were included for this section.

Appendix 2: Methods used to incorporate mitoxantrone as a comparator in the model

The ERG has considered mitoxantrone and prednisolone (MP) as a valid comparator based on the final scope issued by NICE. However, direct treatment comparisons for MP vs. abiraterone or MP vs. enzalutamide do not exist (Abiraterone MS, pg.28[12]). On the other side, despite the fact that several RCTs exist for mitoxantrone alone or in combination with prednisone versus other active treatments in patients with mCRPC whose disease has progressed on or after docetaxel therapy[20-30] none of these trials include a placebo arm or a prednisone arm. Therefore, there is no network linking these trials to enzalutamide and/or abiraterone. The ERG has added a MP arm to the model consistent with most of the assumption used in a recent STA considering abiraterone (one of the comparators).[3] Hence, the ERG has considered OS and PFS for mitoxantrone similar to BSC. The main assumptions are as in Table A.1 below.

Table A.1: Mitoxantrone plus corticosteroid as comparator

Input	Source/Assumption
PFS	Equal to BSC in the enzalutamide model (consistent with abiraterone STA)
OS	Equal to BSC in the enzalutamide model (consistent with abiraterone STA)
Treatment costs	As in the abiraterone STA. Based on Table 36 of the MS for abiraterone[12] Table A.5.
Follow-up costs	As in the abiraterone STA. Based on Table 38 of the MS for abiraterone[12] Table A.3.
Concomitant medication costs	Based on the enzalutamide model (see A.4)
On treatment utility	Assumed equal to abiraterone in the enzalutamide model (consistent with the abiraterone STA)
AE (and associated AE utilities + costs)	Based on the TROPIC trial if available, otherwise assumed equal as for BSC. The probabilities retrieved from the TROPIC trial (Table A.2) were converted into rates using the median survival as time at risk.

Table A.2 below gives the main data and assumptions regarding the inclusion of AEs rates for the mitoxantrone arm.

Table A.2: Adverse events (all grade or grade 3/4) in patients taking mitoxantrone

	Grade >=3 AE events*			
Types of adverse event	**Events**	**Per number of patients (%) (n=371)**	**Probability**	**Rate*** **
Abdominal pain	0	0%	0.000	0.000
Anaemia	18	5%	0.049	0.047
Arthralgia	4	1%	0.011	0.010
Asthenia	9	2%	0.024	0.023
Back pain	11	3%	0.030	0.028
Bone pain	9	2%	0.024	0.023
Dehydration**				[redacted]
Diarrhoea	1	(<1%)	0.003	0.003
Dyspnoea	3	1%	0.008	0.008
Fatigue	11	3%	0.030	0.028
Febrile neutropenia	5	1%	0.013	0.013
Hypertension**				[redacted]
Leukopenia	157	42%	0.423	0.520
Nausea	1	(<1%)	0.003	0.003
Neutropenia	215	58%	0.580	0.819
Oedema Peripheral/Fluid retention**				[redacted]
Pain	7	2%	0.019	0.018
Pain in extremity	4	1%	0.011	0.010
Pulmonary embolism**				[redacted]
Seizure**				[redacted]
Thrombocytopenia	6	2%	0.016	0.015
Vomiting	0	0%	0.000	0.000

* The data in the table comes from the published paper on the TROPIC study[15] except for **

** Rate assumed the same as in BSC arm of the MS (MS, Table 30, p132).

*** The probabilities retrieved from the TROPIC trial were converted into rates using the median survival as time at risk.

Table A.3: Medical Resource Utilisation for monitoring of mCRPC patients for mitoxantrone

Resource	Mitoxantrone			
	On treatment*		Not on treatment**	
	Frequency (every X weeks)	% of pts	Frequency (every X weeks)	% of pts
Outpatient visit consultant	4	100%	8	100%
CT scan	8	5%	8	5%
Radiographic/MRI scan	8	5%	8	5%
ECG	8	5%	8	5%
Ultrasound	8	5%	8	5%
Bone scan	8	5%	8	5%
Full blood count	4	100%	8	100%
Liver function test	4	100%	8	100%
Kidney function test	4	100%	8	100%
PSA	4	100%	8	100%
Cost (£) per 3 weeks		**128.94**		**70.90**

Abbreviations: CT: computed tomography; ECG: electrocardiogram; MRI: magnetic resonance imaging; PSA: prostate specific antigen
*Patients are on treatment in case of stable disease during the first 10 cycles (30 weeks)
** Resource utilization is equal as for Best Supportive Care

Table A.4: Use of concomitant medications

Concomitant medications	% requiring concomitant treatment
	Mitoxantrone
Antihistamine	10%
H2-antagonist	25%
Anti-emetic	100%
Corticosteroid (prednisolone)	56%
G-CSF	10%
Biphosphonates	47%
Cost per 3 weeks (£)	**47.13**

Abbreviations: G-CSF: Granulocyte colony-stimulating factor

Table A.5: Costs (£) per 3 week cycle in stable disease

Items	Mitoxantrone (£)
Technology cost per 3 week cycle	[redacted]
Administration cost	211
Monitoring cost Table A.3	129* 71**
Concomitant medication Table A.4	47
Total	[redacted]

* On treatment
** Not on treatment.

Appendix 3: Phillips et al. Checklist

Question(s)	*Response (Y, N or NS)*	*Comments*
Is there a clear statement of the decision problem?	Y	
Is the objective of the evaluation and model specified and consistent with the stated decision problem?	N	Partially. The NICE scope specifies abiraterone (in combination with prednisone or prednisolone), mitoxantrone (alone or in combination with prednisolone) and BSC (which may include corticosteroids, etc). The comparators in the post-docetaxel setting considered in the submission are: abiraterone and BSC. The rationale for excluding mitoxantrone from the decision problem is given on page 34 of the MS as: *"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."*
Is the primary decision-maker specified?	Y	NICE
Is the perspective of the model stated clearly?	Y	NHS and Personal Social Services (PSS)
Are the model inputs consistent with the stated perspective?	Y	
Has the scope of the model been stated and justified?	Y	
Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Y	
Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Y	
Are the sources of data used to develop the structure of the model specified?	Y	
Are the causal relationships described by the model structure justified appropriately?	Y	
Are the structural assumptions transparent and justified?	Y	
Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Y	
Is there a clear definition of the options under evaluation?	Y	
Have all feasible and practical options been evaluated?	N	Mitoxantrone alone or in combination with prednisone has not been considered.
Is there justification for the exclusion of feasible options?	Y	"(it) is not licensed for mCRPC nor is it listed in NICE clinical guidelines as a treatment option for mCRPC."

Question(s)	*Response (Y, N or NS)*	*Comments*
Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	Y	
Is the time horizon of the model sufficient to reflect all important differences between options?	Y	10 years is in effect lifetime
Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	Y	
Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Y	
Is the cycle length defined and justified in terms of the natural history of disease?	Y	
Are the data identification methods transparent and appropriate given the objectives of the model?	Y	
Where choices have been made between data sources, are these justified appropriately?	Y	
Has particular attention been paid to identifying data for the important parameters in the model?	Y	
Has the quality of the data been assessed appropriately?	Y	
Where expert opinion has been used, are the methods described and justified?	Y	
Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Y	
Is the choice of baseline data described and justified?	Y	
Are transition probabilities calculated appropriately?	N (partially)	Use of the OPC subpopulation for the abiraterone PFS HR is questionable
Has a half-cycle correction been applied to both cost and outcome?	Y	
If not, has this omission been justified?	-	
If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	-	Only one trial for each active treatment

Question(s)	*Response (Y, N or NS)*	*Comments*
Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Y	
Have alternative extrapolation assumptions been explored through sensitivity analysis?	Y	
Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	Y	
Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	Y	
Are the costs incorporated into the model justified?	Y	
Has the source for all costs been described?	Y	
Have discount rates been described and justified given the target decision-maker?	Y	
Are the utilities incorporated into the model appropriate?	N (partially)	The on treatment utility benefit included is likely to cause double counting. The difference in on treatment utility benefit between enzalutamide and abiraterone is not substantiated with strong evidence.
Is the source for the utility weights referenced?	Y	
Are the methods of derivation for the utility weights justified?	Y	
Have all data incorporated into the model been described and referenced in sufficient detail?	Y	
Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	N (partially)	Use of the OPC subpopulation for the abiraterone PFS HR is questionable
Is the process of data incorporation transparent?	Y	
If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	Y	
If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	Y	
Have the four principal types of uncertainty been addressed?	Y	

Question(s)	***Response (Y, N or NS)***	***Comments***
If not, has the omission of particular forms of uncertainty been justified?	-	
Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	Y	
Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	Y	
Has heterogeneity been dealt with by running the model separately for different subgroups?	N	
Are the methods of assessment of parameter uncertainty appropriate?	Y	
If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Y	
Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	Y	
Are any counterintuitive results from the model explained and justified?	-	
If the model has been calibrated against independent data, have any differences been explained and justified?	-	
Have the results of the model been compared with those of previous models and any differences in results explained?	Y	