Responses to clarification questions: Prostate cancer (hormone relapsed, metastatic) - enzalutamide (after docetaxel)

All replies are in dark blue. In addition, Tables and Figures which have been added to support our replies are labelled with an R (e.g., Table R1 or Figure R1) or A1, A2, A3 (e.g. Table A1.1 or Table A2.1 or Table A3.1). Figures and Tables for which the captions do not have the R, A1, A2, or A3 correspond to those already included in our manufacturer submission (MS). For these Figures and Tables the numbering is the same as in the original MS.

Section A: Clarification on effectiveness data

A1. Study selection

a. *According to the flow diagram on page 38, 3235 records have been screened and 3055 records have been excluded, leaving 51 full-text articles to be assessed for eligibility. However, after excluding 3055 from 3235 the remainder is 180. Please provide a corrected flow diagram or a justification for not including all of the 180 records in the flow diagram. Please also explain the difference between the last two boxes in the flow diagram on page 75 (that is, from 131 records included in the qualitative synthesis to 9 records included in the quantitative synthesis).*

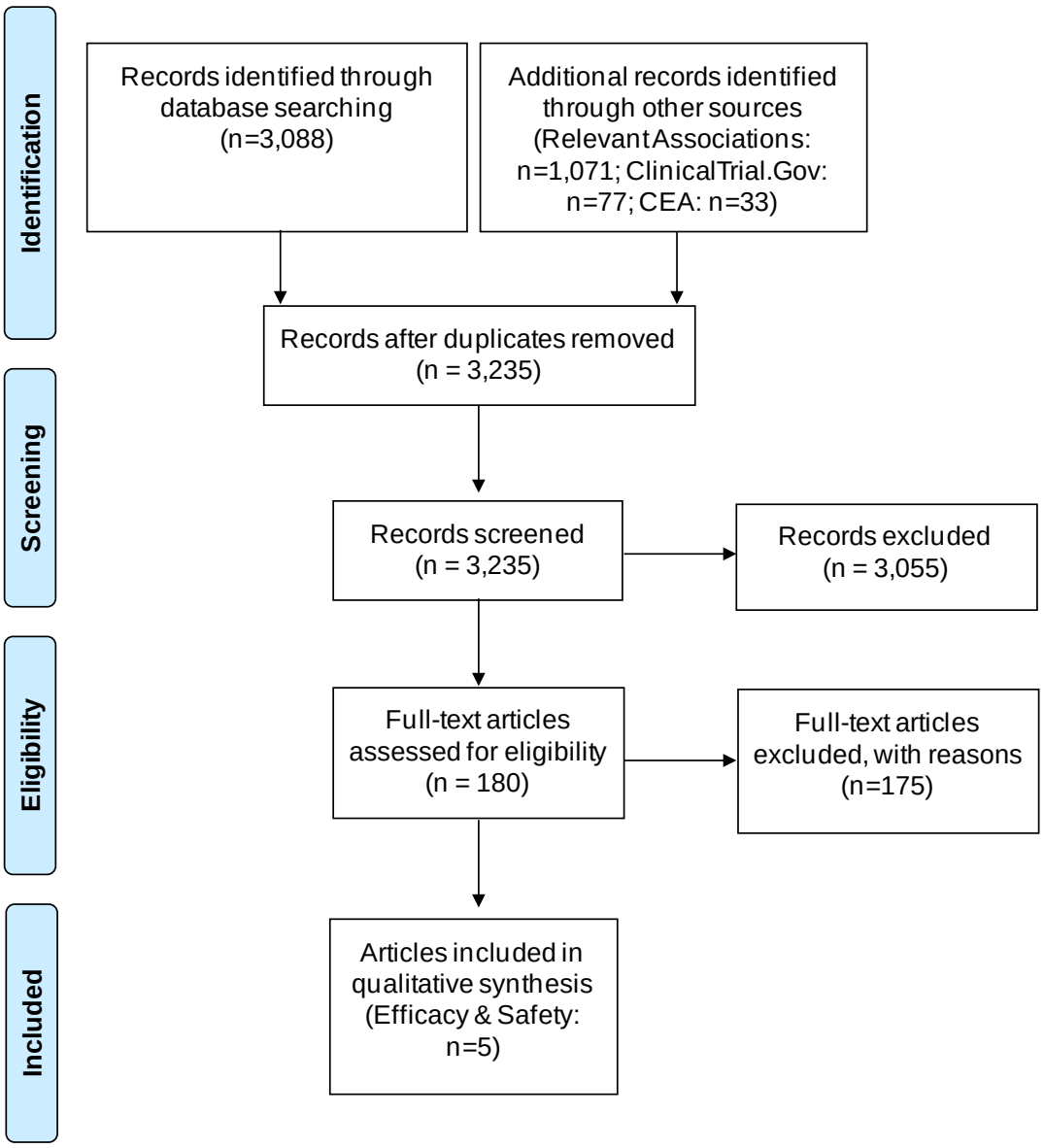
The flow diagram below shows the correct number of studies included in the systematic literature review (SLR) described in section 6.2.2. Overall, 180 articles were assessed for eligibility but only 5 articles were related to studies with enzalutamide. Figure 3 below replaces Figure 3 included in the MS.

Regarding the number of records provided in Figure 14, page 75 of the MS: this should have been:

- 23 records for the qualitative analysis
- 9 records for the quantitative analysis.

Figure 14, page 75 of the MS should be replaced with Figure R1 of this document. Details of the 23 and 9 records stated in this figure are provided in Section 1d and Table R1 of this document.

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



b. *The flow diagram on page 38 indicates that 5 studies were included in the qualitative synthesis. Please clarify if this refers to 5 studies or 5 publications describing 1 study? On page 39 (first two bullet points), 5 publications are listed; please clarify if this should be 5 'studies'?*

The SLR identified five articles all related to the same enzalutamide study, i.e., AFFIRM. The flow in the submission should have stated 5 articles. This has been amended in the figure above.

c. *Reference 36 (De Bono, 2012) is described in the submission as a published article but provided in the reference pack as an ASCO abstract. Please clarify*

whether it is a published article or an abstract, and if the former, please provide the article.

De Bono 2012 should have been referred to as an abstract in the text. The submitted reference number 36 is correct.

d. *According to the eligibility criteria in table 5 (page 36), studies of enzalutamide, abiraterone (plus prednisone or prednisolone) and mitoxantrone (plus prednisone or prednisolone) were eligible for inclusion in the systematic review. However, only studies of enzalutamide were included. Please justify why studies of other interventions were excluded.*

The objective of the SLR was to identify studies that included a treatment arm with enzalutamide, abiraterone or mitoxantrone. The PRISMA flow in Figure 3 of the MS gives the number of articles included for the qualitative analysis for section 6.2.4. The PRISMA flow with all the studies included in the qualitative analysis of the original SLR is given below (Figure R1). Overall, 23 articles covering 11 studies were identified.

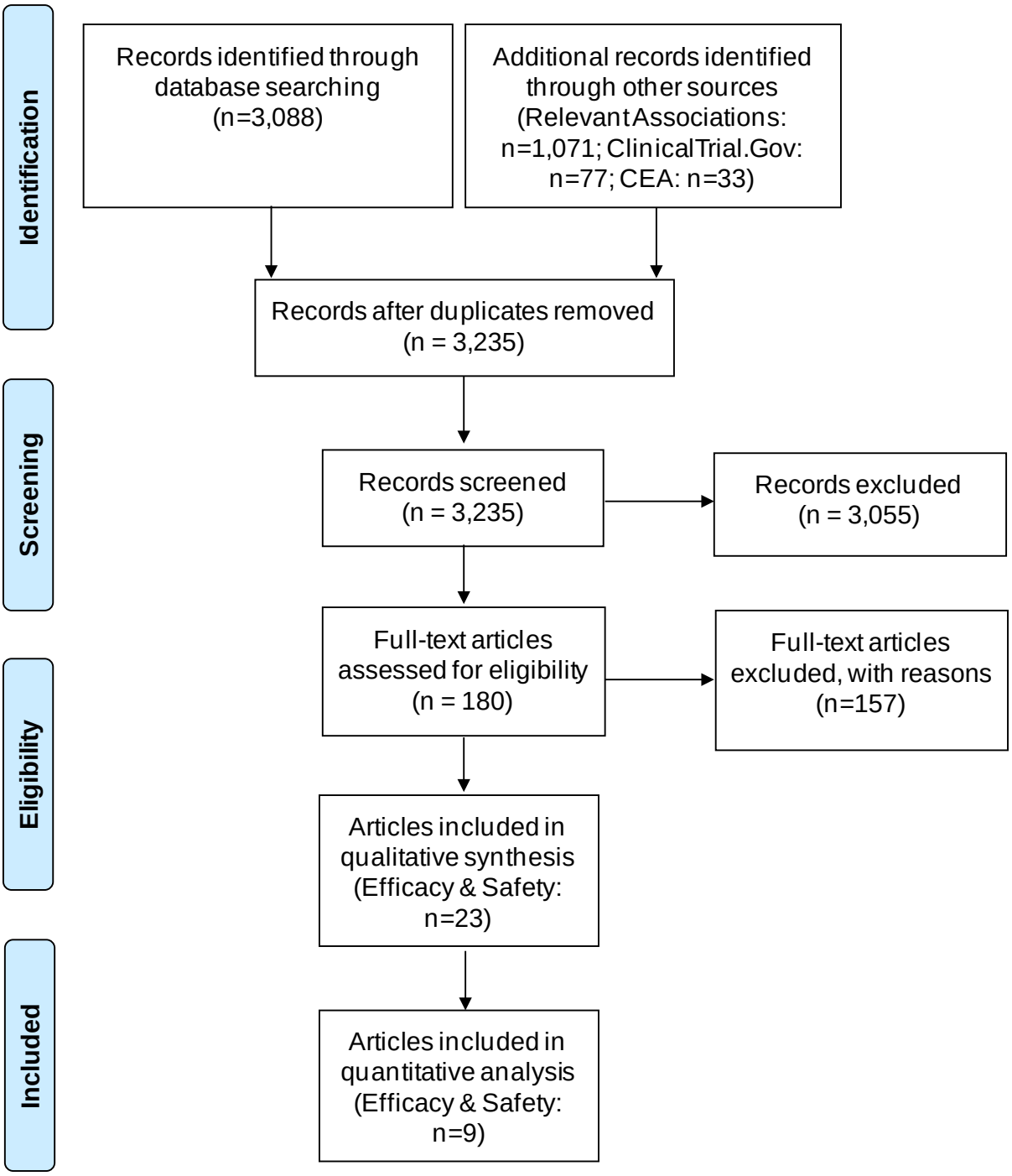
The studies and relevant references included in the SLR qualitative analysis for post-chemotherapy are listed in Table R1. Of these, studies AFFIRM and COU-AA-301 were included in the quantitative analysis. All publications related to these studies except for the AFFIRM Patient Reported Outcomes (PRO) report were used for the quantitative analysis.

Table R1 List of relevant randomised clinical trials selected for this review

Study (design)	Interventions	Reference
AFFIRM (Phase 3, DB, prospective, multinational, PLA-controlled trial)	Two arms: • Enzalutamide 160 mg (n=800) • Placebo (n=399(Use of corticoids was allowed but not required	Scher 2012a[1]
		De Bono 2012[2]
		Scher 2012b[3]
		AFFIRM CSR (April 24, 2012)[4]
		AFFIRM PRO report[5]
COU-AA-301 (Phase 3, multinational, randomized, DB, PLA-controlled study)	Two arms • Abiraterone 1g + prednisone (n=797) • Placebo plus prednisone (n=398)	De Bono 2011[6]
		Fizazi2012[7]
		Goodman 2012[8]
		Scher 2011[9]
		Efstathiou 2012[10]
NCT00124566 (RCT, phase II)	Three arms: • Irofulven plus prednisone • Irofulven plus capecitabine plus prednisone • Mitoxantrone plus prednisone	Hart 2006[11]
		Berger 2007[12]
NCT00331344 (A multicenter, RCT, OL, non comparative, phase 2 study)	Two arms • Ixabepilone (n=41) • Mitoxantrone plus prednisone (n=41)	Rosenberg 2007[13]
CUOG Trial P-06c (OL, non-comparative, multicenter,	Two arms • Docetaxel plus prednisone plus	Saad 2011[14]

Study (design)	Interventions	Reference
monocountry, RCT, phase II)	custirsen (n=20) • Mitoxantrone plus prednisone plus custirsen (n=22)	
TROPIC (Randomised, multinational. OL, phase III)	Two arms • Mitoxantrone plus prednisone (n=377) • Cabazitaxel plus prednisone (n=378)	De Bono 2010a[15] Oudard 2011[16] Sartor 2011[17]
TAX 327 (RCT, cross-over phase III)	Three arms: • Docetaxel (x3 wk) to mitoxantrone (n=89) • Docetaxel (x1wk) to mitoxantrone (n=76) • Mitoxantrone to docetaxel (n=67)	Berthold 2008[18]
NCT00661492	Two arms • Cetuximab + mitoxantrone + prednisone • Mitoxantrone plus prednsione	Fleming 2010[19] Fleming 2012[20]
NCT00770848 (RCT, double blind, phase Ib/II)	Three arms • Rilotumumab 15 mg/kg + mitoxantrone +prednisone • Rilotumumab 7.5 mg/kg + mitoxantrone +prednisone • Placebo+ mitoxantrone +prednisone	Ryan 2012[21]
NCT00683475 (phase II, RCT)	Two arms: • Mitoxantrone plus prednisone plus cixutumumab (n=66) • Mitoxantrone plus prednisone plus ramucirumab (n=66)	Hussain 2012[22]
NCT00385827 (non-randomized, single arm, phase II)	Two arms: • CNTO 328 plus mitoxantrone plus prednisone • Mitoxantrone plus prednisone	De Bono 2010b[23]

Figure R1 PRISMA flow diagram with the efficacy and safety RCTs identified through the predefined search strategy



A2. ***Priority Question:*** *Table 20 (page 79) does not provide details on best supportive care. Please provide details on what constituted best supportive care for both trials.*

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.

A3. ***Priority Question:*** *The clinical study report does not provide UK-specific data. Please provide UK data for the AFFIRM study.*

Overall, 132 patients (Enzalutamide: n=82; placebo: n=50) were recruited in the UK. The key demographics and baseline characteristics of these patients are provided in Table R2.

UK patients had similar demographics to the overall population.

Table R2 Demographics and baseline characteristics of patients recruited in the United Kingdom

	Overall population		UK patients	
	Enzalutamide (N = 800)	Placebo (N = 399)	Enzalutamide (N = 82)	Placebo (N = 50)
Age (years)				
Median	69	69	[redacted]	[redacted]
Range	41-92	49-89	[redacted]	[redacted]
Race				
White	745 (93.1%)	366 (91.7%)	[redacted]	[redacted]
Black or African American	27 (3.4%)	20 (5.0%)	[redacted]	[redacted]
Asian	5 (0.6%)	8 (2.0%)	[redacted]	[redacted]
Indian/Alaskan	1 (0.1%)	1 (0.3%)	[redacted]	[redacted]
Other	21 (2.6%)	4 (1.0%)	[redacted]	[redacted]
Baseline ECOG performance				
0	298 (37.3%)	156 (39.1%)	[redacted]	[redacted]
1	432 (54.0%)	211 (52.9%)	[redacted]	[redacted]
2	70 (8.8%)	32 (8.0%)	[redacted]	[redacted]
PSA (ng/ml)				
Median	107.7	128.7	[redacted]	[redacted]
Range	0.2-11,794	0-19,000	[redacted]	[redacted]
Time (months) from Initial Diagnosis of Prostate Cancer to Randomisation				
Mean (SD)	86.1 (54.83)	81.9 (50.89)	[redacted]	[redacted]
Median	70.9	71.6	[redacted]	[redacted]
Gleason Score at Diagnosis				
2–4	10 (1.4%)	8 (2.2%)	[redacted]	[redacted]
5–7	349 (48.1%)	167 (45.5%)	[redacted]	[redacted]
8–10	366 (50.4%)	193 (52.4%)	[redacted]	[redacted]
Missing	74	31	[redacted]	[redacted]
Disease Localisation at Screening				
Bone only	225 (28.1%)	123 (30.8%)	[redacted]	[redacted]
Soft tissue only	62 (7.8%)	34 (8.5%)	[redacted]	[redacted]
Both bone and soft tissue	505 (63.1%)	241 (60.4%)	[redacted]	[redacted]
None	8 (1.0%)	1 (0.3%)		
Type of Disease Progression at Study Entry				
PSA progression only	326 (41.0%)	164 (41.2%)	[redacted]	[redacted]
Radiographic progression	470 (59.0%)	234 (58.8%)	[redacted]	[redacted]

	Overall population		UK patients	
	Enzalutamide (N = 800)	**Placebo (N = 399)**	**Enzalutamide (N = 82)**	**Placebo (N = 50)**
Bone only	205 (25.6%)	117 (29.3%)	[redacted]	[redacted]
Soft tissue only	127 (15.9%)	59 (14.8%)	[redacted]	[redacted]
Both bone and soft tissue	138 (17.3%)	58 (14.5%)	[redacted]	[redacted]
Missing	4	1	[redacted]	[redacted]
Measurable Soft Tissue Disease at Screening				
Yes	446 (55.8%)	208 (52.1%)	[redacted]	[redacted]
No	354 (44.3%)	191 (47.9%)	[redacted]	[redacted]
Distribution of Disease at Screening				
Bone	730 (92.2%)	364 (91.5%)	[redacted]	[redacted]
Lymph node	442 (55.8%)	219 (55.0%)	[redacted]	[redacted]
Visceral liver	92 (11.6%)	34 (8.5%)	[redacted]	[redacted]
Visceral lung	122 (15.4%)	59 (14.8%)	[redacted]	[redacted]
Other soft tissue	147 (18.6%)	70 (17.6%)	[redacted]	[redacted]
Missing	8	1	[redacted]	[redacted]
Number of Bone Metastases at Screening				
0	70 (8.8%)	35 (8.8%)	[redacted]	[redacted]
1	28 (3.5%)	21 (5.3%)	[redacted]	[redacted]
2–4	112 (14.0%)	45 (11.3%)	[redacted]	[redacted]
5–9	121 (15.1%)	68 (17.0%)	[redacted]	[redacted]
10–20	167 (20.9%)	79 (19.8%)	[redacted]	[redacted]
> 20	302 (37.8%)	151 (37.8%)	[redacted]	[redacted]

The outcomes of the key efficacy endpoints of OS and rPFS have been analysed for the cohort of patients recruited in the UK. These results are presented in Table R3 and can be summarised as follows.

- Similar to the overall study population, enzalutamide was associated with a significantly longer rPFS than placebo in the UK cohort of AFFIRM patients ([redacted] vs. [redacted]months; HR [redacted], 95% CI [[redacted], [redacted]] p=[redacted]). Despite the study not being powered to demonstrate superiority of enzalutamide over placebo for any of the endpoints in the UK cohort of patients, the treatment effect on median rPFS in these patients reached statistical significance.

- Similar to the overall study population, enzalutamide was associated with a benefit in median OS, however the UK sample size prevented demonstration of statistical significance. Median OS had not been reached for enzalutamide-treated UK patients, but the HR is favourable to enzalutamide (HR: [redacted], 95% CI [[redacted], [redacted]]) (p=[redacted]).

Table R3 Key efficacy-related outcomes for AFFIRM patients recruited in the United Kingdom

	All patients		UK only	
	Enzalutamide (n=800)	**Placebo (n=399)**	**Enzalutamide (n=82)**	**Placebo (n=50)**
Overall survival				
Number of deaths	308 (38.5%)	212 (53.1%)	[redacted]	[redacted]
Median (m)	18.4	13.6	[redacted]	[redacted]
Hazard ratio	0.631		[redacted]	
95% CI	(0.529, 0.752)		[redacted]	
p-value	<0.0001		[redacted]	
rPFS				
Number of progression events	524 (65.5%)	337 (84.5%)	[redacted]	[redacted]
Median (m)	8.3	2.9	[redacted]	[redacted]
Hazard ratio	0.404		[redacted]	
95% CI	(0.350, 0.466)		[redacted]	
p-value	<0.0001		[redacted]	

A4. ***Priority Question:*** *The rationale for excluding mitoxantrone from the decision problem is given on page 34 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.'

According to NICE, at the Decision Problem meeting 'The manufacturer laid out the reasons for why they do not consider mitoxantrone a comparator, and we said that this was not unreasonable, and that they have to provide this justification including information from use in clinical practice in the submission.'

Please provide a justification for excluding mitoxantrone as a comparator (with references wherever possible), taking into account that the absence of a UK licence or the fact that it is not in NICE guidance is not a sufficient reason to exclude a treatment as a comparator if it is routinely used in UK clinical practice. Please see the 2013 NICE methods guide, sections 6.2.1 to 6.2.4 on selecting comparator technologies for further information.

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.

A study which includes the current use of mitoxantrone for mCRPC treatment in the UK has been conducted by Dr Heather Payne. The results have not yet been published however, the author has agreed to be contacted by the ERG to discuss her findings given the relevance to this appraisal.

We believe that this study will confirm the irrelevance of mitoxantrone to this appraisal given the very small and decreasing number of patients likely to receive any second line chemotherapy in the UK – in particular mitoxantrone.

A5. Please present estimates of mean overall survival, by treatment group, with the analysis truncated at 5 years for each parametric distribution used (exponential, Weibull, log-logisitc, log-normal and gamma).

In our understanding, this question refers to the extrapolation of the trial data. An overview of the mean OS up to the first five years is provided in Table R4.

Table R4 Mean OS (months, undiscounted), truncated at 5 years.

	Mean OS	
Distribution	**Enzalutamide**	**Placebo**
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

A6. The placebo arms in the COU-AA-301 (in which all patients received prednisone) and AFFIRM trials were assumed to have the same treatment outcomes for the purpose of the indirect comparison on the basis that 'there is no evidence to suggest that steroids have an impact on PFS or OS' (section 6.7.7, page 87). Please justify why steroids have no impact on patient reported outcomes such as pain, quality of life and adverse events.

Baseline demographics are similar between patients in the AFFIRM and COU-AA-301 trials, however, while abiraterone must be taken with steroids, enzalutamide can be prescribed with or without steroids. Although a high proportion of patients in the AFFIRM trial were prescribed steroids, there is a difference in use within the control arms of AFFIRM and COU-AA-301 (n=182/399, 45.6% vs. n=398/398, 100% respectively).

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)[24]. 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.

A7. In table 24, page 83, the two studies show significant differences for disease location: 'Node' (enzalutamide 11.6%, placebo 8.5%; abiraterone 45%, placebo: 41%), and 'Liver' (enzalutamide 55.8%, placebo 55%; abiraterone 11%, placebo 8%). However, in the Supplementary Appendix from Scher 2012 (NEJM), page 15, the data for the AFFIRM study are the other way round. Please clarify which of these are the correct data.

The numbers provided in Table 24 regarding disease location have been reversed for node and liver. The correct values are those stated in the Supplementary Appendix of Scher 2012. The values have now been corrected in the table below which replaces Table 24 from the MS.

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

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

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).

Section B: Clarification on cost-effectiveness data

B1. ***Priority Question:*** *On page 126 it is stated that: 'Experts (70) evaluated the plausibility of the slope and the curves' tail, and the proportion alive at 2 and 3 years. The Weibull distribution was chosen over the Log-Logistic distribution to model OS due to the more realistic shape of the 'tail''. A similar justification is provided for choosing the Weibull function over other parametric functions to model progression-free survival; on page 129 it is stated that: 'Log-Logistic model has the best statistical fit according to AIC and BIC criteria. However, the Weibull model was selected after validation by clinical experts due to the more realistic shape of the tail'.*

a. *Please provide a more detailed justification as to why, for OS and PFS, the tails of the Weibull curves were considered more realistic than the log-logistic curves (pages 126 and 129) which fit the data best according to the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).*

To determine the best model fit in line with the recommendations in the NICE DSU technical support document 14 (Reference 113 in MS[25]), the following criteria were considered, with the most appropriate model identified based on a combination of these:

AIC/BIC - Model fits were evaluated using Akaike's information Criteria (AIC) and Bayesian Information Criteria (BIC) statistics. Lower AIC/BIC figures are indicative of a better statistical fit of the survival function of the Kaplan-Meier data.

Visual Inspection - Visual inspection was carried out by plotting the projected survival curves overlaid with the Kaplan-Meier survival functions.

Clinical Validity - The clinical plausibility of the proportion of patients estimated to be surviving at the tails of the curve was examined. Fits were first assessed by the economic modelling team and validated using expert opinion during a series of advisory boards (as indicated in the MS page 136) with UK clinicians and health economic experts to test and validate all key model inputs. Clinical experts were consultant oncologists specialising in treatment of prostate cancer in the UK setting and had experience with previous HTA appraisals for prostate cancer. The economic experts consulted were chosen based on general academic and professional qualifications as a health economist with experience in economic evaluation of health technologies in a UK setting and experience with previous NICE appraisals in cancer.

Anchoring – Wherever possible, extrapolation estimates were validated through comparison with more mature external data sources.

Based on the AIC and BIC statistics log-logistic distribution appear to offer the best fit for OS and PFS data (see Table 45 and Table 48 of the MS). It is to be noted that log-normal, gamma and Weibull distributions also provide quite similar AIC and BIC values. Visually, they also offer a reasonable fit to the observed KM curves (see Figure 18 and Figure 20 from the MS).

Despite our efforts to identify external data sources to externally validate the extrapolation estimates for OS, we were not able to find any such data for post-chemotherapy mCRPC.

The log-logistic distribution is an accelerated failure time model and has a hazard function which can be monotonic (when 1/scale ≤ 1) or non-monotonic (when 1/scale > 1) with

respect to time. The NICE DSU technical support document 14 recommends that "*when considering the applicability of the log-logistic distribution, the validity of non-monotonic hazards must be considered. Owing to their functional form, log-logistic models often result in long tails in the survivor function, and this must also be considered if they are to be used*". The curve fitting for placebo resulted in a parameter value > 1 for both the OS and PFS data (table 46 and 48 in the MS), indicating initially an increasing hazard, followed by a decreasing hazard, which was not considered plausible. Data from other mCRPC studies[15,26,27,28] support an assumption of a monotonically increasing hazard, such as a Weibull function.

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 R5). 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 (Reference 70 in MS[29]).

Table R5 Five and ten-year survival rates using log-logistic and Weibull distributions (model results)

	Placebo		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%

Taking the above into account, Weibull distribution was selected to be used in the base case analysis despite the higher AIC and BIC fit statistics. However, the log-logistic distribution can be selected in the model, and is used in a scenario analyses. The results of the probabilistic outcomes using log-logistic for PFS and OS are provided in Table R6 and Table R7.

b. *Please provide the probabilistic outcomes (both mean outcomes as well as incremental outcomes) using the Weibull function instead of the log-logistic models for progression free survival (PFS) and overall survival (OS), as suggested by AIC and BIC.*

The manufacturer's base case considers the Weibull function for both PFS and OS. We believe the ERG requests probabilistic outcomes using the log-logistic distribution instead of the Weibull distribution. This is what we report in Table R6 and Table R7 below.

Table R6 Summary of probabilistic sensitivity analysis results – enzalutamide vs. abiraterone

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,765
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,559
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,610
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,783
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,602
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-78,616
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,154

Abbreviations: LCL: lower confidence level; UCL: upper confidence level; PSA: probabilistic sensitivity analysis; QALY: quality adjusted life year.

Table R7 Summary of probabilistic sensitivity analysis results – enzalutamide vs. BSC

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	34,819
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	34,451
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,706
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	42,615
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,878
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	60,465
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,062

Abbreviations: BSC: best supportive care; LCL: lower confidence level; UCL: upper confidence level; PSA: probabilistic sensitivity analysis; QALY: quality adjusted life year.

B2. ***Priority Question:*** *The hazard ratio (HR) applied to the parametric function to estimate overall survival after treatment with abiraterone is not based on the final results of the COU-AA-301 trial (as published by Fizazi et al. 2012). Instead, it is argued that the proportional hazard requirement was not met, and thus a time-dependent HR should be adopted (Appendix 14, page 243-244). The selected HR, increases to 1.39 at 25 months indicating a worse survival probability (probability per cycle) for abiraterone than for best supportive care. This HR is kept constant at 1.39 after 25 months.*

a. Please justify the choice of the HR; specifically, why was the HR presented on page 127 considered the best fit based on visual inspection, and why was the published (constant) HR of 0.74 not selected for the base-case analysis?

Survival curves for OS and PFS for enzalutamide and abiraterone were obtained by applying a hazard ratio (HR) to a reference survival curve (BSC). Where one HR is applied to the entire modelled period, the proportional hazards assumption must be made – that is, the treatment effect is proportional over time and the survival curves fitted to each treatment group have a similar shape.

Extensive testing for the validity of a proportional (constant) hazards assumption was performed. Given that original patient data for this trial were not available, data for the COU-AA-301 trial were digitized and the survival times were estimated using published methods (reference 115 of the MS[30]) as discussed in Section 7.3.1.1 on page 127. Three statistical tests and graphical inspection methods indicated that the proportional hazards assumption was not met. Moreover, authors in Fizazi et al[7] state that the assumption of a constant hazard was not met. Due to the violation of this assumption, the HR may not accurately reflect the treatment effect over time, especially beyond the observed time horizon, and it would be incorrect to assume a constant HR (published value 0.74). NICE DSU Technical Support Document 14 (reference 113 of the MS[25]) recommends the use of alternative methods. Different options were investigated to provide the best fit including different time-dependent formulations of the hazard ratio and piece-wise constant HR models. Both approaches resulted in good model fit; however, the piecewise model was not selected due to the arbitrary choice of the time intervals. Different time-dependent covariates were introduced in the model and were all statistically significant, confirming the dependence of the HR on time. The HR as a linear function of time provided a closer visual fit when compared to the KM curve for abiraterone, as shown in Figure 19 of the submission.

b. *Please justify the assumption to keep the HR at 1.39 after 25 months, and provide a sensitivity analysis which demonstrates the effect on the ICER of assuming instead that the HR is 1.0 (as there are no data after this time point in the paper published by Fizazi et al. 2012).*

As described in our response to B2a, the time-dependent HR as a linear function of time was chosen as a best fit for the observed data. This allows time-dependence for the HR and extrapolation beyond the study duration. As a conservative approach, the fitted model was not extrapolated beyond the study duration, instead we assumed a constant HR of 1.39, corresponding to value of the linear function at the time point of the last observation. 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. The results of assuming a constant HR of 1.0 after 25 months are presented in Table R8.

Table R8 Outcomes assuming a constant HR of 1.0 after 25 months

	Enzalutamide		Abiraterone		Incremental		
	Costs **(£)**	QALYs	Costs **(£)**	QALYs	Costs **(£)**	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,292
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,137
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,194
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,266
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,440
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,148
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,565

c. *Please provide the probabilistic outcomes (both mean outcomes as well as incremental outcomes) using all different HRs presented in Appendix 15; four piecewise HRs, three linear versus time HRs and the constant HR of 0.74 as reported by Fizazi et al. (2012).*

The results of the 8 scenarios requested by the ERG (four piecewise HRs, three linear versus time HRs and the constant HR of 0.74 as reported by Fizazi et al[7]) are provided in Appendix 1.

B3. ***Priority Question:*** *The utility values for on-treatment benefits for both enzalutamide ([redacted]) and abiraterone (0.04) were based on mapped FACT-P utilities.*

a. *Please provide a summary of the mean values, number of observations and dispersion (standard deviation) for the EQ-5D and FACT-P elements, stratified by being on-treatment, and by treatment group (for enzalutamide and best supportive care from the AFFIRM trial as well as for abiraterone and best supportive care from the COU-AA-301 trial).*

Descriptive statistics for the EQ-5D utility index (both collected as well as mapped values) and FACT-P total score and domains from the AFFIRM trial are presented in Table R9.

The manufacturer does not have the data from the COU-AA-301 trial. The on treatment benefit for abiraterone of 0.04 is the value reported in abiraterone CVZ submission (Reference 92 of the MS[31]).

Table R9 Descriptive statistics for the EQ-5D and FACT-P by visit and treatment group

Parameter	Visit	ENZA			PLA		
		N	Mean	Std	N	Mean	Std
EQ-5D utility index (collected values)	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D utility index (mapped values)	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FACT-P total score	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physical Well Being Domain	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Visit	ENZA			PLA		
		N	Mean	Std	N	Mean	Std
	W85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social Well Being Domain	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Emotional Well Being Domain	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Functional Well Being Domain	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prostate Cancer Scale	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Visit	ENZA			PLA		
		N	Mean	Std	N	Mean	Std
	W61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	W97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b. *Please also provide the algorithm used to calculate the utility increments, and please describe how the utility increments were calculated based on the information provided in response to B3.*

To derive the treatment arm effect for patients in stable disease, the individual patient changes from baseline utility as implied by the FACT-P mapping function are calculated. A mixed model repeated measure model (MMRM) was then fitted controlling for baseline covariates. The model included the following covariates: treatment (enzalutamide or placebo), time (week 13, week 17, week 21, etc.), baseline utility and ECOG status (0-1 or 2), prior chemotherapy regimens (1 or ≥2), pain (<4 or ≥4, assessed from question #3 of the BPI), age (< 65 or ≥ 65) and fatigue (<7 or ≥7, assessed from question #3 of the BFI). The model assumed unstructured covariance among the within subject repeated measurements. The analysis was conducted using PROC MIXED in SAS. With the exception of baseline utility variable, all variables listed above were included in the CLASS statement of the procedure. The unique subject identifier was also included as a class variable. A REPEATED statement over the visits was included with the unique subject identifier as the SUBJECT variable in the REPEATED statement.

The adjusted mean change from baseline (LS mean) over 25 weeks of treatment for each arm was calculated using the LSMEANS statement (LS mean [redacted] (95% CI [redacted]; [redacted]], p=[redacted] for enzalutamide and [redacted] (95% CI [redacted]; [redacted]], p=[redacted] for placebo). The treatment benefit of [redacted] corresponds to the difference in the LS mean estimates for mean changes from baseline for enzalutamide versus placebo.

B4. ***Priority Question:*** *According to the NICE Methods Guide, probabilistic methods provide the best estimates of mean costs and outcomes in non-linear decision models. However, only the deterministic results are provided in the submission. Please provide the probabilistic outcomes (both mean outcomes as well as incremental outcomes) for all analyses presented in the results section (sections 7.7.1–7.7.9).*

The probabilistic results of the base case analysis are presented in the MS section 7.7.8. The probabilistic results of the scenarios presented in section 7.7.9 are provided in Appendix 2.

B5. *Utility loss associated with pain is included in the model by applying a utility decrement for the adverse events (AEs) and serious reportable events (SREs), and by using the 'on-treatment' utility gain, which introduces double counting (since utility*

benefits of enzalutamide and abiraterone were already included in the model). On page 189, it is stated that 'the model is relatively insensitive to the utility decrement for AEs and SREs' and thereby arguing that the 'double counting in utility values is not likely to have a big impact on the incremental cost effectiveness results'. However, the scenario analysis (section 7.7.69, table 88) were double counting was prevented (analysis 13) resulted in a higher ICER (£51,343 per QALY gained). Please provide detailed justification as to why the 'on-treatment benefit' for enzalutamide (expressed as a utility increment) was considered in addition to the disutility associated with AEs and SREs.

We explained in MS section 7.6.1, scenario 8 and 9, the following potential for double counting:

- Between AE disutility and on-treatment utility benefit
- Between SRE disutility and disutility for progression.

We acknowledge that the statement on page 189 of the MS was not clear in separating these two potential double counting effects. Patients can experience adverse events (AEs) only in the stable disease health state while they can experience skeletal related events (SREs) only in the progressed disease health state. Therefore utility decrements for the AEs are applied only in the stable disease while utility decrements for SREs are applied only in the progressed disease. Furthermore, the on-treatment utility gain was calculated using only those assessments prior to the documented disease progression, i.e. radiographic progression or SRE (page 147 of the MS) and applied only to in the stable disease. As a result, there is no double counting between the on-treatment utility gain and SREs.

As explained in the MS (page 147), there is significant evidence that enzalutamide is associated with improved quality of life (QoL) and that these QoL advantages could lead to a utility benefit over placebo. Therefore an "on-treatment" benefit for enzalutamide was considered in the model.

Recognising the potential of double counting by introducing disutilities associated with AEs, we have investigated its impact on the ICER and the results not taking into account any disutilities for AEs were presented in Table 88, analysis 8 (page 187). The ICER versus BSC in this analysis is £43,540 per QALY gained very similar to the base case results (£43,587 per QALY gained). 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.

B6. The disutility for progressive disease was calculated as -0.085 based on Sandblom et al. (2004). Section 7.4.7 (page 152) states that: 'the utility decrement derived from the Sandblom study (-0.085) was considered the most appropriate value, as the collected time intervals (16-8 and 8-0 months before death) approximately match the time in stable and progressive disease for AFFIRM patients', which assumes that the decrease in utility from 16-8 months before death to 8-0 months before death represents the utility decrement for progression (page 154). However, these time intervals should match the time in stable and progressive disease states for patients in Sandblom et al. and not AFFIRM because in this calculation 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. Also, it is likely that some patients will still be progression free 8-0 months before death (for example, patients who die due to other causes than cancer) while others may have already progressed 16-8 months before death. Please provide a detailed justification as to why the disutility of -0.085 was taken from the Sandblom et al. study to estimate the utility for progressed patients, taking into account these comments.

HRQoL was only collected for patients on treatment in the AFFIRM study therefore it was not possible to calculate the disutility for progressive disease. We have investigated several methods to calculate this disutility (summarised below) and the results are presented in Table R10:

1. Derived from the AFFIRM study by estimating the impact of progression according to mPFS criteria (radiographic progression, first SRE or death) (page 147 of the MS):
    a. using the mapped values – decrement estimated as [redacted]
    b. using the collected EQ-5D values – decrement estimated as [redacted].
2. Using literature data (page 152 of the MS):
    a. derived from the Sullivan et al[32] (reference 133 in the MS) as described in the cabazitaxel NICE submission[33] (reference 134 in the MS) – decrement estimated as 0.070.
    b. derived from Sandblom et al[34] (Reference 122 in MS) as described in the cabazitaxel NICE submission[33] (Reference 134 in MS) – 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 as described in the abiraterone NICE submission[35] - post-progression utility value of 0.5 using the average from the utility 8-4 months and 4-0 months before death.

A literature value was preferred in the economic model because the analysis of the AFFIRM data only provides the utility decrement up to the start of progression, while it is likely that the utility further decreases over time in the months before death.

Sullivan et al[32] was an observational, multi-centre, multi-national cohort study (n=280) designed to explore HRQoL (EORTC QLQ-C30, FACT-P and EQ-5D) in a mCRPC population. The average age of subjects in the study was 72 and the population was 98% Caucasian. The average FACT-P prostate component score was 29.8 within the Sullivan et al cohort, while among UK patients it was 30.7. This compares to an average FACT-P prostate component score at baseline of [redacted] for enzalutamide patients and [redacted] for placebo patients (Table R9). The baseline EQ-5D for the total population was 0.635 and for the UK subset was higher at 0.715, although it is not clear how the EQ-5D utility was calculated. The study collected HRQoL at three further time-points (3, 6, and 9 months after baseline), however the study did not breakdown the analysis for those whose disease had progressed vs. those whose disease had not, therefore did not provide any additional data for the post-progression state.

Given that mCRPC patients are likely to spend their last 8 months of life in the progressed health state, Sandblom et al[34] provides the most appropriate data to be used in the model. Utility values from the Sandblom et al study (estimated from graph) ranged from 0.58 in patients with 8-12 months of remaining survival to 0.46 in those with less than 4 months remaining survival. Utility is relatively constant up till eight months before death, after which it

decreases. As criticised by the ERG in the abiraterone NICE submission (reference 135 in the MS) the derivation from Sandblom et al was considered inappropriate as it does not correct for the lower utility values observed in this study (approx 0.58 16-12 months before death) compared to the baseline utility in AFFIRM ([redacted], page 147 of the MS).

We acknowledge that there may be patients who may be progression free 8-0 months before death while others may have already progressed 16-8 months before death. Unfortunately the Sandblom et al paper does not provide information on the time in stable and progressive disease.

With the exception of 2.c above, the utility decrements identified all appear to be within the same range of utility values. Furthermore, as shown in Table R10 the model is not sensitive to disutility values for progressive disease. The probabilistic outcomes are presented in Appendix 3.

Table R10 Results of scenario analysis investigating different utility decrements for post-progression

	Analysis	ICER Enzalutamide vs. Abiraterone (£)	ICER Enzalutamide vs. BSC (£)
	Base Case	**14,795**	**43,587**
1	AFFIRM study using mapped values	**14,687**	**43,766**
	AFFIRM study using collected EQ-5D values	**14,809**	**43,564**
2	Literature data from Sullivan et al	**14,724**	**43,704**
	Literature data from Sandblom et al (absolute value)	**15,299**	**42,803**

B7. In table 59 (page 154) the reference for on-treatment benefit for abiraterone is given as 'Abiraterone CVZ submission (CFH rapport 12/01: abiraterone -Zytiga. Feb 2012)'. This report is not in English. Please provide the reference of the original source.

In agreement with NICE recommendations, none of the searches in the SLR were limited to any specific language.

The three references cited in the abiraterone CVZ submission are:

- de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. May 26 2011;364(21):1995-2005
- Wu EQ, Mulani P, Farrell MH, Sleep D. Mapping FACT-P and EORTC QLQ-C30 to patient health status measured by EQ-5D in metastatic hormone-refractory prostate cancer patients. Value Health. Sep-Oct 2007;10(5):408-414.
- Anderson P, Benford M, et al. Real-world physician and patient behaviour across countries: Disease-specific programmes – a means to understand. Current medical research and opinion. Vol. 24, no 11. 2008, 3063-3072.

These three references are submitted as pdf files. However, they only support the method. 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.

Section C: Clarification on Search Methods

C1. Please clarify which database hosts were used for all searches, e.g. Embase (OvidSP).

The database used for each of the searches was:

- PubMed.gov for PubMed
- Wiley Online Library for Cochrane
- ProQuest (Dialog DataStar) for EMBASE and EconLit.

C2. Please provide strategies and host for the Medline In-Process searches.

A search in Medline In-Process was not conducted as we believe Pubmed already includes all Medline In-Process citations.

C3. Please explain why you searched PubMed and Medline.

To identify relevant studies published in those journals that are included in PubMed and Medline but not in EconLit or EMBASE.

C4. Please clarify whether a published/verified study design filter was used in the searches in tables 94, 95 and 96 in section 10.2.4. If a validated study design filter was used, please provide a full reference to the filter.

A study design filter was not included.

C5. Please give the exact date span for the databases used in all searches, e.g. Medline (OvidSP): 1946-2013/07/09

All searches covered the period between January 01, 1993 and January 02, 2013.

C6. Some of the line combinations in table 97 in section 10.2.4 are incorrect. The search strategy consists of 23 lines; however, in line 20 #42, #43, #44 and #45 have been combined. Please provide a strategy with correct combinations.

Indeed, line 20 as well as lines 22 and 23 (all in red) were incorrect. Table below replaces Table 97 from the MS.

Table 97: Search terms and search strings for quality of life in PubMed/Medline

Search	Search string	Hits
	Part I: Prostate Cancer	
1	"Prostatic Neoplasms"[Mesh Terms]	66,314
2	prostat*[Title/Abstract]	107,191
3	CANCER[Title/Abstract] OR CARCINOMA*[Title/Abstract] OR MALIGNANT*[Title/Abstract] OR TUMOR[Title/Abstract] OR TUMORAL[Title/Abstract] OR TUMOUR[Title/Abstract] OR INTRAEPITHELIAL*[Title/Abstract] OR ADENOCARCIN*[Title/Abstract]	1,347,667
4	#2 AND #3	79,681
5	#1 OR #4	89,380
	Part II: Castration resistant	
6	HORMONE-REFRACTORY	2,422
7	HORMONE-RESISTANT	476
8	HORMONE-INDEPENDENT	890
9	ANDROGEN-INDEPENDENT	2,755
10	ANDROGEN-RESISTANT	100
11	CASTRATION-RESISTANT	1,208
12	(PROSTATE[Title/Abstract] OR PROSTATI*[Title/Abstract] OR PROSTATA*[Title/Abstract] OR HORMONE*[Title/Abstract] OR CASTRAT*[Title/Abstract] OR ANDROGEN[Title/Abstract]) AND (REFRACT* OR RESIST*[Title/Abstract] OR INDEPENDENT[Title/Abstract] OR ESCAPE*[Title/Abstract])	41,325
13	HRPC OR AIPC OR CRPC	1,410
14	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	41,484
15	#5 AND #14	13,819
	Quality of life	
16	quality of life[MeSH Terms]	95,343
17	health status[MeSH Terms]	83,782
18	patient satisfaction[MeSH Terms]	53,703
19	("quality of life"[Title/Abstract] OR "quality-of-life"[Title/Abstract] OR QoL[Title/Abstract] OR "patient reported outcome"[Title/Abstract] OR "patient-reported outcome"[Title/Abstract] OR (patient report*[Title/Abstract]) OR satisfaction[Title/Abstract] OR "EQ-5d"[Title/Abstract] OR EQ5d[Title/Abstract] OR Euroqol[Title/Abstract] OR "FACT-P"[Title/Abstract] OR "FACT P"[Title/Abstract] OR "FACT-G"[Title/Abstract] OR "FACT G"[Title/Abstract] OR "visual analogue scale"[Title/Abstract] OR "VAS"[Title/Abstract] OR "Brief Fatigue Index"[Title/Abstract] OR BFI[Title/Abstract] OR "QLQ C30"[Title/Abstract] OR QLQ-C30[Title/Abstract])	202,141
20	#16 OR #17 OR #18 OR #19	329,923
	Part IV: Humans only	
21	("animals"[MeSH Terms]) NOT humans[MeSH Terms]	1,958,989
22	#15 NOT #21	2,895
	Total	
23	#20 AND #22	280

C7. The line numbering and some of the line combinations in table 103 are incorrect. The line numbering starts after the search term 'Prostatic Neoplasms'[MeSH Terms]' resulting in line combinations like '14: #5 AND #14'. Please provide a strategy with correct line numbering and combinations.

The numbering in the first column was incorrect. Search #1 corresponded to "Prostatic Neoplasms"[Mesh Terms] and not to prostat*[Title/Abstract] as indicated in Table 103 in the MS.

Table 103: Search terms and search strings for the economic review in Cochrane Library

Search	Search string	Hits
1	“Prostatic Neoplasms”[Mesh Terms]	2,825
2	prostat*[Title/Abstract]	5,924
3	CANCER[Title/Abstract] OR CARCINOMA*[Title/Abstract] OR MALIGNANT*[Title/Abstract] OR TUMOR[Title/Abstract] OR TUMORAL[Title/Abstract] OR TUMOUR[Title/Abstract] OR INTRAEPITHELIAL*[Title/Abstract] OR ADENOCARCIN*[Title/Abstract]	55,917
4	#2 AND #3	3,438
5	#1 OR #4	4,008
	Castration Resistant	
6	HORMONE-REFRACTORY	261
7	HORMONE-RESISTANT	56
8	HORMONE-INDEPENDENT	10
9	ANDROGEN-INDEPENDENT	83
10	ANDROGEN-RESISTANT	2
11	CASTRATION-RESISTANT	55
12	(PROSTATE[Title/Abstract] OR PROSTATI*[Title/Abstract] OR PROSTATA*[Title/Abstract] OR HORMONE*[Title/Abstract] OR CASTRAT*[Title/Abstract] OR ANDROGEN[Title/Abstract]) AND (REFRACT* OR RESIST*[Title/Abstract] OR INDEPENDENT[Title/Abstract] OR ESCAPE*[Title/Abstract])	2,549
13	HRPC OR AIPC OR CRPC	155
14	#7 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	2,584
15	#5 AND #14	594
	Economic studies and resource utilisation	
16	(economic* or pharmacoeconomic* or "economic evaluation" or cost or costs or budget or expenditure or "hospital finance" or “resource utilization” or “resource utilisation” or “resource use” or productivity or absenteeism or hospitalisation or hospitalization or ICU or "intensive care" or practiti* or GPs or "last year of life" or LYOL or "life’s end" or "end of life" or "palliative care" or "terminal care" or "terminally ill" or palliat* or absenteeism):ti,ab,kw or work and loss:ti,ab,kw or terminal* and (care or caring or ill or illn*):ti,ab,kw	54,812
17	"economics"[MeSH Terms]	19,979
18	("costs and cost analysis"[MeSH Terms])	18,514
19	"health status"[MeSH]	4,568
20	productivity[MeSH Terms]	244
21	hospitalization[MeSH Terms]	10,365
22	budget[MeSH Terms]	45
23	expenditure[MeSH Terms]	225
24	EQ-5d" or EQ5d or Euroqol or "time trade off" or TTO or HUI or QLQ-C30 or "QLQ C30" or Q-TWiST or "Q TWiST" or utility or utilities or disutility or disutilities:ti,ab,kw	4,530
25	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	62,821
26	#15 AND #25	96

C8. Please provide more detail about the information gained through ‘Google and other search engines’, such as the names of the other search engines and search terms used to retrieve results.

Only Google was used to conduct further searches. These were limited to identify relevant data from the websites listed in the reply to question C11. In addition, Google was used to search the CEA Registry available at https://research.tufts-nemc.org/cear4/SearchingtheCEARegistry/SearchtheCEARegistry.aspx.

The search terms used for the different searches using Google were:

- Prostate cancer for the CEA Registry
- Prostate cancer as part of the abstract body for all the conferences websites.

C9. Please clarify whether published quality of life filters were used in tables 97, 98 and 99 in section 10.2.4. If a validated study design filter was used, please provide a full reference to the filter.

No quality of life filters were included.

C10. Please clarify whether published economic filters were used in tables 102, 103 and 104 in section 10.10.4. If a validated study design filter was used, please provide a full reference to the filter.

No economic filters were included.

C11. Please provide the search strategies and web addresses for all conference searches undertaken.

The conferences searched were:

- ASCO and ASCO-GU: http://meetinglibrary.asco.org/abstracts
- ESMO: http://www.esmo.org/Science-Education/Abstracts-Meeting-Reports
- AUA: http://www.aua2013.org/abstracts/index2.cfm
- EUA: http://www.uroweb.org/events/abstracts-online/
- ECCO: https://www.ecco-ibd.eu/publications/congress-abstract-s.html
- ISPOR: http://www.ispor.org/research_study_digest/research_index.asp

These websites were hand-searched using hormone refractory or hormone independent or androgen independent or androgen resistant or castration-resistant prostate cancer as keywords.

C12. Please clarify which host you used for the Cochrane searches. It does not look like the search syntax by Wiley (Cochrane Library) which is usually used.

The host used was Wiley Online Library.

C13. Please clarify if Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR) were included in the Cochrane database searches.

Yes, CENTRAL and CDSR were included in the searches.

Appendix 1.

Priority question B2C. Probabilistic outcomes using all different HR functions for abiraterone overall survival (OS)

Table A1. 1: PSA results enzalutamide vs. abiraterone – abiraterone HR as a linear function of time (Base case) 27

Table A1. 2: PSA results enzalutamide vs. abiraterone – abiraterone constant HR of 0.74 as reported by Fizazi et al. (2012) 27

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Table A1. 7: PSA results enzalutamide vs. abiraterone – abiraterone HR as a piecewise model, cut off: 21 months 29

Table A1. 8: PSA results enzalutamide vs. abiraterone – abiraterone HR as a piecewise model, cut offs: 6, 18 months 29

Table A1. 1: PSA results enzalutamide vs. abiraterone – abiraterone HR as a linear function of time (base case)

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,795
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,576
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,762
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,690
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,004
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	40,908
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,921

Table A1. 2: PSA results enzalutamide vs. abiraterone – abiraterone constant HR of 0.74 as reported by Fizazi et al. (2012)

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,972
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,481
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,010
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	41,612
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,600
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5,752
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,307

Table A1. 3: PSA results enzalutamide vs. abiraterone – abiraterone HR as a linear function of ln(time) (up to month 25 then kept constant)

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,085
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,865
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,701
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,009
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,681
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,035
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,022

Table A1. 4: PSA results enzalutamide vs. abiraterone – abiraterone HR as a linear function of SQRT time (up to month 25 then kept constant)

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,343
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,183
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,551
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,130
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,460
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4,883
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,255

Table A1. 5: PSA results enzalutamide vs. abiraterone – abiraterone HR as a piecewise model, cut off: 20 months

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,476
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,406
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,747
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,547
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,355
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3,150
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,982

Table A1. 6: PSA results enzalutamide vs. abiraterone – abiraterone HR as a Piecewise model, cut off: 19 months

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,388
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,335
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,037
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,348
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,184
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9,818
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,623

Table A1. 7: PSA results enzalutamide vs. abiraterone – abiraterone HR as a piecewise model, cut off: 21 months

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,326
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,446
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,776
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,671
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,772
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3,625
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,859

Table A1. 8: PSA results enzalutamide vs. abiraterone – abiraterone HR as a piecewise model, cut offs: 6, 18 months

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,842
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,707
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,426
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,980
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,877
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,349
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,030

Appendix 2

Priority question B4, probabilistic results for all scenarios presented in section 7.7.9 of the MS.

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Table A2. 4: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 1b - Time Horizon 6 years ... 34
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Table A2. 1: PSA results enzalutamide vs. BSC - table 88 MS, analysis 1a - Time Horizon 4 years

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44,469
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44,395
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,805
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	53,897
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	38,683
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	71,794
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	35,028

Table A2. 2: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 1a - Time Horizon 4 years

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,828
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,711
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,706
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,084
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,353
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11,369
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,194

Table A2. 3: PSA results enzalutamide vs. BSC - table 88 MS, analysis 1b - Time Horizon 6 years

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,611
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,464
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,133
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	54,075
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,643
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	67,383
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,583

Table A2. 4: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 1b - Time Horizon 6 years

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,793
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,666
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,742
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,213
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,003
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-45,938
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,584

Table A2. 5: PSA results enzalutamide vs. BSC - table 88 MS, analysis 1c - Time Horizon 8 years

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,587
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,300
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,229
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	53,887
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,863
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	73,409
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	33,868

Table A2. 6: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 1c - Time Horizon 8 years

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,795
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,597
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,698
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,113
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,911
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	93,497
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,882

Table A2. 7: PSA results enzalutamide vs. BSC - table 88 MS, analysis 2a - Discount rate costs and effects – 0%

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	42,343
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	42,043
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,313
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	52,922
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	35,473
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	58,869
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30,920

Table A2. 8: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 2a - Discount rate costs and effects – 0%

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,718
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,476
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,144
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,770
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,352
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-50,388
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,719

Table A2. 9: PSA results enzalutamide vs. BSC - table 88 MS, analysis 2b - Discount rate costs and effects – 1.5%

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	42,879
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	42,608
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,391
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	53,007
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	35,781
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	64,945
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30,574

Table A2. 10: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 2b - Discount rate costs and effects – 1.5%

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,752
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,566
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,102
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,343
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,676
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44,539
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,366

Table A2. 11: PSA results enzalutamide vs. BSC - table 88 MS, analysis 2c - Discount rate costs and effects – 5%

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44,113
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,817
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,034
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	54,455
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,881
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	63,954
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,686

Table A2. 12: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 2c - Discount rate costs and effects – 5%

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,827
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,641
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,897
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,824
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,106
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	33,211
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,225

Table A2. 13: PSA results enzalutamide vs. BSC - table 88 MS, analysis 3 - Use a fixed HR for abiraterone OS

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,587
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,337
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,061
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	54,081
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,521
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	69,455
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	33,091

Table A2. 14: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 3 - Use a fixed HR for abiraterone OS

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,972
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,481
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,010
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	41,612
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,600
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5,752
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,307

Table A2. 15: PSA results enzalutamide vs. BSC - table 88 MS, analysis 4 - Apply on ITC on mean OS to the abiraterone arm

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,587
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,255
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,875
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	53,718
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,428
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	61,092
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,831

Table A2. 16: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 4 - Apply on ITC on mean OS to the abiraterone arm

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,034
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,532
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,570
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,261
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,959
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	34,681
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,788

Table A2. 17: PSA results enzalutamide vs. BSC - table 88 MS, analysis 5 - Use Log Logistic model for OS reference curve (AFFIRM placebo)

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,623
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,525
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9,547
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	34,173
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,014
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,476
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,813

Table A2. 18: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 5 - Use Log Logistic model for OS reference curve (AFFIRM placebo)

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8,899
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8,881
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8,594
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9,392
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8,781
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4,482
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8,869

Table A2. 19: PSA results enzalutamide vs. BSC - table 88 MS, analysis 6 - Use mPFS instead of TTD for PFS

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,396
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,186
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10,819
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	56,344
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	34,371
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	76,525
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,348

Table A2. 20: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 6 - Use mPFS instead of TTD for PFS

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,476
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,234
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,421
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10,392
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,282
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30,393
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,371

Table A2. 21: PSA results enzalutamide vs. BSC - table 88 MS, analysis 7 - Use Log Logistic model for PFS reference curve (AFFIRM placebo)

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47,807
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47,571
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,199
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	58,724
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	40,458
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	72,895
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,763

Table A2. 22: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 7 - Use Log Logistic model for PFS reference curve (AFFIRM placebo)

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,215
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,932
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,797
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,807
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,014
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-13,362
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,306

Table A2. 23: PSA results enzalutamide vs. BSC - table 88 MS, analysis 8 - No disutility for AEs

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,540
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,231
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,905
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	54,044
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,552
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	68,969
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,491

Table A2. 24: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 8 - No disutility for AEs

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,783
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,531
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,628
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,830
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,722
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	98,999
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,380

Table A2. 25: PSA results enzalutamide vs. BSC - table 88 MS, analysis 9 - No disutility for SREs

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,802
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,435
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,864
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	54,159
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,713
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	72,377
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30,611

Table A2. 26: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 9 - No disutility for SREs

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,801
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,592
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,460
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,619
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,835
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	91,815
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,898

Table A2. 27: PSA results enzalutamide vs. BSC - table 88 MS, analysis 10 - No disutility for AEs or SREs

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,754
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,462
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,150
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	53,429
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,694
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	67,119
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,355

Table A2. 28: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 10 - No disutility for AEs or SREs

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,789
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,625
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,631
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,483
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,732
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11,556
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,575

Table A2. 29: PSA results enzalutamide vs. BSC - table 88 MS, analysis 11a - Utility values for health states used in abiraterone CVZ submission

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	38,399
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	38,224
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,088
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,257
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,788
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	60,361
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,413

Table A2. 30: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 11a - Utility values for health states used in abiraterone CVZ submission

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,882
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,728
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,229
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11,611
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,761
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	186,153
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,830

Table A2. 31: PSA results enzalutamide vs. BSC - table 88 MS, analysis 11b - Pre-progression value of 0.80 post-progression of 0.50

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	37,147
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	37,000
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,534
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	42,478
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	33,097
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	52,953
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,807

Table A2. 32: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 11b - Pre-progression value of 0.80 post-progression of 0.50

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,702
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,555
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,404
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9,785
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,619
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	153,818
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,765

Table A2. 33: PSA results enzalutamide vs. BSC - table 88 MS, analysis 12 - Use mapped utility values for baseline ([redacted]) and progressed disease (decrement of [redacted]) utility

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,036
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	42,628
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,825
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	53,817
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	35,618
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	61,648
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,245

Table A2. 34: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 12 - Use mapped utility values for baseline ([redacted]) and progressed disease (decrement of [redacted]) utility

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,421
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,251
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,566
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,324
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,281
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2,139,749
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,602

Table A2. 35: PSA results enzalutamide vs. BSC - table 88 MS, analysis 13 - Exclude on treatment utility gain

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51,343
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51,075
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,303
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	68,535
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	41,453
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	94,677
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	33,587

Table A2. 36: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 13 - Exclude on treatment utility gain

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,720
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,577
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,841
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,019
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,083
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9,068
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,613

Table A2. 37: PSA results enzalutamide vs. BSC - table 88 MS, analysis 14 - Same on treatment utility gain for enzalutamide and abiraterone

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,587
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,380
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,008
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	54,298
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,450
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	67,304
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,044

Table A2. 38: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 14 - Same on treatment utility gain for enzalutamide and abiraterone

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,652
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,513
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,597
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,824
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,284
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7,690
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,997

Table A2. 39: PSA results enzalutamide vs. BSC - table 88 MS, analysis 15 - Assume routine visits are alternated between nurse and consultant

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,026
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	42,780
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,669
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	53,441
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,029
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	57,539
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,139

Table A2. 40: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 15 - Assume routine visits are alternated between nurse and consultant

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,494
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,319
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,276
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,702
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,156
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6,631
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,302

Table A2. 41: PSA results enzalutamide vs. BSC - table 88 MS, analysis 16 - Include active treatment costs post-progression

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,987
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,715
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,360
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	42,134
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,264
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44,373
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,019

Table A2. 42: PSA results enzalutamide vs. abiraterone - table 88 MS, analysis 16 - Include active treatment costs post-progression

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,920
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,704
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,335
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7,871
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,832
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-170,518
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,929

Table A2. 43: PSA results enzalutamide vs. abiraterone – cost minimisation scenario, as presented in table 89 MS

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Enzalutamide is less costly and as effective
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Appendix 3

Priority question B6, impact of different utility decrements for progression.

Table A3. 1: PSA results enzalutamide vs. BSC - utility decrements for post-progression from AFFIRM study using mapped values 49
Table A3. 2: PSA results enzalutamide vs. abiraterone - utility decrements for post-progression from AFFIRM study using mapped values 49
Table A3. 3: PSA results enzalutamide vs. BSC - utility decrements for post-progression from AFFIRM study using collected EQ-5D values 49
Table A3. 4: PSA results enzalutamide vs. abiraterone - utility decrements for post-progression from AFFIRM study using collected EQ-5D values 50
Table A3. 5: PSA results enzalutamide vs. BSC - utility decrements for post-progression from literature data from Sullivan et al 50
Table A3. 6: PSA results enzalutamide vs. abiraterone - utility decrements for post-progression from literature data from Sullivan et al 50
Table A3. 7: PSA results enzalutamide vs. BSC - utility decrements for post-progression from literature data from Sandblom et al (absolute value) 51
Table A3. 8: PSA results enzalutamide vs. abiraterone - utility decrements for post-progression from literature data from Sandblom et al (absolute value) 51

Table A3. 1: PSA results enzalutamide vs. BSC - utility decrements for post-progression from AFFIRM study using mapped values

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,766
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,527
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,312
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	55,406
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,247
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	84,133
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30,595

Table A3. 2: PSA results enzalutamide vs. abiraterone - utility decrements for post-progression from AFFIRM study using mapped values

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,687
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,530
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,890
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,299
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,641
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,076
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,461

Table A3. 3: PSA results enzalutamide vs. BSC - utility decrements for post-progression from AFFIRM study using collected EQ-5D values

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,564
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,224
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,845
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	53,967
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,611
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	65,192
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,538

Table A3. 4: PSA results enzalutamide vs. abiraterone - utility decrements for post-progression from AFFIRM study using collected EQ-5D values

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,809
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,596
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,687
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,997
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,804
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-135,453
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,487

Table A3. 5: PSA results enzalutamide vs. BSC - utility decrements for post-progression from literature data from Sullivan et al

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,704
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,434
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,639
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	54,097
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,344
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	68,332
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	33,605

Table A3. 6: PSA results enzalutamide vs. abiraterone - utility decrements for post-progression from literature data from Sullivan et al

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,724
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,531
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,141
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,134
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,641
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,282
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,298

Table A3. 7: PSA results enzalutamide vs. BSC - utility decrements for post-progression from literature data from Sandblom et al (absolute value)

	Enzalutamide		BSC		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	42,803
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	42,558
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,646
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,718
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	37,507
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	70,391
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	34,564

Table A3. 8: PSA results enzalutamide vs. abiraterone - utility decrements for post-progression from literature data from Sandblom et al (absolute value)

	Enzalutamide		Abiraterone		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,299
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,020
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,832
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,001
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,717
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,371
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,354

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