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Dear [redacted]

Re: Single Technology Appraisal – Abiraterone for the treatment of metastatic castration resistant prostate cancer following previous cytotoxic therapy

The Evidence Review Group Warwick Evidence and the technical team at NICE have now had an opportunity to take a look at the submission received on the 23 September, 2011 by Janssen. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **the end of Tuesday, 1st November 2011**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments, or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Matthew Dyer – Technical Lead (matthew.dyer@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell – Project Manager (jeremy.powell@nice.org.uk) in the first instance.

Yours sincerely

Dr Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1 **Priority Question. It is possible that abiraterone may be considered in the context of the supplementary advice for "end of life" treatments by the appraisal committee. To aid this process, should it arise, please provide evidence to demonstrate whether abiraterone meets all or some of these criteria.**

The case for abiraterone acetate to be considered by NICE under the Supplementary Advice on appraising EoL medicines is presented below:

1) The treatment is indicated for patients with a short life expectancy, normally less than 24 months

The prognosis of mCRPC patients is poor; the five-year survival rate for those with metastatic disease is significantly lower (31%) than compared to in patients with non-metastatic disease (almost 100%). The control arms of the COU-AA-301 and TROPIC studies indicate that after 1st line docetaxel treatment patients treated with prednisolone or mitoxantrone have a short, average life expectancy of approximately one year.

2) The treatment is licensed, or otherwise indicated, for small patient populations

Of the 4,400 mCRPC patients estimated to receive docetaxel in the UK, it is estimated that approximately 75% of these men would be eligible for treatment with abiraterone acetate (3,300 men). It is estimated that no more than 50% of these men would actually receive treatment with abiraterone acetate. These patient numbers are similar to patient numbers in other disease areas that have met NICE EoL criteria.

3) The treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment

Abiraterone acetate offers the mCRPC patient population a 4.6 month increase in median overall survival (OS) compared to prednisolone, representative of best supportive care (BSC). This result is aligned with the economic model which estimates that the expected mean OS for patients in England and Wales would be [redacted] years or [redacted] months.

To summarise, abiraterone acetate should be considered to meet end of life criteria as it extends life by over 4.5 months in this patient population, for whom there are no other NICE approved treatment options with evidence of improved survival. In the absence of abiraterone acetate, this patient population (estimated to be approximately 3000 patients), has a very short life expectancy of less than one year.

A2 **Priority request. Please provide a copy of the full trial report including the updated analysis for trial COU-AA-301. The full trial report has more detailed information than that contained in the submission.**

The CSR for the 'Primary' analysis and report for the 'Updated' analysis are attached. All data within these reports should be considered as AIC.

A3 **Priority request. About 90% of patients had bone metastases at entry (Table 25 page 85). Skeletal events may be more likely for patients with greater extent of bone disease. Was bone disease balanced between treatment arms? Please classify both arms according to the number of bone metastases, for example according to Soloway classification for bone scans: (0, <6, 6 to 20, Superscan).**

At study baseline, [redacted] of AAP and [redacted] of PP patients had evidence of bone metastasis. The clinical utility of the Soloway classification for the quantification of tumour burden in bone has not been validated or tested prospectively in randomised trials and as such was not collected prior to study entry. However, given the large sample size, it is likely that the tumour burden in bone was balanced as evidenced by the similar median baseline alkaline phosphatase, LDH and haemoglobin (see Table 12, p62 of the CSR).

A4 **Priority request. For purposes of defining the One Prior population a re-challenge with docetaxel was considered as part of the original regimen. Page 84 of the submission states "*due to the manner in which data was captured in the case report form, the exact proportion of men in COU-AA-301 who had docetaxel retreatment is not reported*". Please clarify if in the absence of *the exact* proportion it is possible to approximate the proportion from the available data?**

Firstly, we would like to clarify that we cannot accurately estimate the proportion of patients that were retreated with docetaxel as requested by the Evidence Review Group. It should be noted that data collection for this portion of the CRF was not monitored and as such physicians may have completed it inconsistently, specifically:

[redacted]

As described above there are clear challenges relating to accurately estimating the proportion of patients that had docetaxel retreatment. However, in response to the ERGs question, an algorithm was developed to approximately estimate the proportion of the 'One Prior Chemotherapy' group that may have had docetaxel retreatment. This algorithm is based on the start and end date of docetaxel treatment recorded in the CRF and the duration of time between multiple records for docetaxel under the assumptions that:

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Based on this analysis, Janssen estimates that a maximum of [redacted] of the 'One Prior Chemotherapy' group may have had docetaxel re-treatment.

A5 **Priority request. For the ITT and One Prior populations about 89% of patients were ECOG 0-1 and the rest were ECOG 2. Subgroup analysis for ITT population indicated lower survival benefit for ECOG 2 patients (Table 15 page 57 and Fig 8, submission page 56), however the numbers for ECOG 2 patients were low and the estimate associated with**

uncertainty. Nevertheless there is a possibility that there is a real difference and that ECOG 2 patients were under represented in the trial relative to a UK population that may be treated; please clarify if this could have inflated the survival benefit used in the economic analysis .

Firstly, we would like to refer the ERG to our response to question A14, where we provide the 'Updated' subgroup analyses. In the updated analyses, the apparent differential effect between ECOG groups is no longer apparent. There is however a difference in prognosis between these groups and this will of course impact the absolute benefit and cost-effectiveness. We address this further in our responses below.

NICE guidance restricts docetaxel use to those with a Karnofsky status greater than 60%, so the large proportion of eligible patients would be expected to be ECOG 0-1. Based on this, the ECOG status of patients in the COU-AA-301 study is likely to be reflective of the ECOG status of patients who will receive abiraterone acetate in the UK. In particular, the proportion of UK based patients within the COU-AA-301 study had an ECOG-2 rating and this was similar to that seen in the ITT population ([redacted] % vs 10% respectively), and in clinical practice it would not be expected that there would be a larger proportion of eligible ECOG 2 patients. Although initially, following the introduction of abiraterone acetate, there may be a higher proportion of ECOG 2 patients in the patient pool waiting to receive treatment, once abiraterone acetate becomes a treatment option for patients who have progressed during or after docetaxel treatment, the majority of patients going on to abiraterone acetate will have an ECOG status of 0-1, as per the COU-AA-301 study. For these reasons, patients with ECOG 2 status were not underrepresented in the COU-AA-301 and the survival benefit estimated in the model is likely to closely reflect the survival benefit that will be observed in the UK.

The ECOG was pre-specified as a stratification factor Table 15 and figure 8 (pages 57 & 56), suggest quite a large effect. Please clarify why ECOG status was not explored as a subgroup since it seems likely that the cost effectiveness estimates will differ quite markedly by baseline ECOG status?

To address this question we have explored the impact of ECOG status on the clinical and cost-effectiveness in more detail below. As stated above, a small proportion of patients eligible for abiraterone will have an ECOG status of 2. ECOG 0-1 patients will have greater absolute improvements in OS than the ECOG 2 patients for a given relative treatment benefit, and this could be expected to result in improved cost-effectiveness ratios. However, as [redacted]% of the 'One Prior Chemotherapy' subjects also had an ECOG 0-1 identical to the proportion of the ITT with ECOG 0-1 status. Unsurprisingly, the hazard ratio of [redacted] for the ECOG 0-1 subgroup is identical to the HR observed for the ITT population and the HR for the ECOG 2 subgroup is only fractionally higher ([redacted]), see Table 7 in question A7.

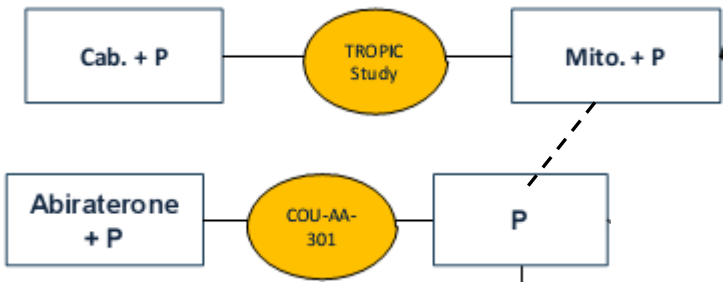
[redacted]

[redacted]

In summary, due to the similar HRs observed between the ECOG subgroups, coupled with the generally tolerable safety profile, it would not appear to be reasonable to exclude ECOG 2 patients from receiving abiraterone acetate, when the cost-effectiveness is similar and these patients have no other efficacious treatment options.

A6 **Priority request. Section 5.7.3 page 66 explains that there is no link between P (prednisone) and Mito + P in the network diagram (Fig 13) and that therefore an indirect comparison of clinical effectiveness cannot be justified. However, assumptions made in the economic model for the comparison of mitoxantrone with abiraterone are based on data from a trial of mitoxantrone used in first line therapy and used this trial to create the link for purposes of economic analysis.**

The link is provided by a trial (or trials) referenced as 45, 57, 58 in the submission text which recruit chemo-naive patients.



Please clarify if a hazard ratio derived from such an indirect comparison might offer a way of performing economic modelling of the comparison of abiraterone with mitoxantrone.

Overall survival

In the three studies mentioned above (Kantoff et al., (1999), Berry et al., (2002) and Tannock (1996)), mitoxantrone failed to demonstrate an OS benefit compared to corticosteroids, but did show evidence of a palliative benefit in patients with mCRPC in terms of delayed time to progression and time to treatment failure, pain control, and PSA response rate. The only study to report an HR was the Kantoff 1999 study, whereby no clinical OS benefit was observed, HR 1.0 (95% CI 0.8, 1.3). Furthermore, even if mitoxantrone had demonstrated a benefit in earlier lines of

treatment, extrapolating this to later lines is subject to great clinical as well as statistical uncertainty given the cumulative effects of prior chemotherapy in these patients.

Regarding this point, the recently published NICE DSU technical support document states "Synthesis of evidence from clinically heterogeneous populations, not only increases the risk of statistical heterogeneity and inconsistency, but often requires highly implausible assumptions, such as assuming that interventions are equally effective in a naïve population or in a population that has already failed on that intervention or has contra-indications to its use." (p10.) As mitoxantrone has failed to demonstrate an OS benefit over corticosteroids in these chemotherapy naive populations, then there is no reason to support the hypothesis that it would confer a survival advantage in a population who have failed a previous chemotherapy and are therefore more resistant to treatment and potentially at greater risk of cumulative chemotherapy side effects. This view is also supported by UK clinical opinion.

PFS

Regarding PFS, of the three studies mentioned above only Berry et al (2002) and Kantoff et al., (1999) reported PFS. Aside from the aforementioned issue of these studies being conducted in chemotherapy naive patients, these two studies also have differing definitions of PFS compared to the COU-AA-301 and TROPIC studies, which impacts the ability to perform a mixed treatment comparison on this outcome.

Study	PFS definition
COU-AA-301	Treatment discontinuation
TROPIC	Composite endpoint (defined as time between randomisation and the first date of progression as measured by PSA progression, tumour progression, pain progression, or death)
Berry 2002	Greater than 25% increase in sum of products of bi-dimensionally measurable masses, new soft tissue lesions or increasing bone lesions
Kantoff 1999:	Worsening performance status by ≥ 1, appearance of 2 or more new lesions on bone scan, or increase in PSA level ≥ 100% above pre-treatment baseline

Taking into account the rationale above, Janssen does not believe it is methodologically appropriate to conduct a mixed treatment comparison (MTC) on PFS, and the model base case reflects this. Sensitivity analysis has already been presented in our original submission that explored the impact of assigning a PFS benefit to mitoxantrone of 0.77, equivalent to the PFS benefit observed in the chemotherapy naïve patients in the Kantoff et al.,(1999) study.

A7 **Priority request. For the updated analysis please present the median overall survival in each arm separately by ECOG performance status at baseline:**

As requested, please find below the median OS for each arm of the COU-AA-301 study, split by ECOG performance status at baseline for the ITT and the 'One Prior Chemotherapy' populations.

Updated analysis Overall survival median months	AAP	PP	Net	HR	95% CI
ITT (n=1195)	15.8	11.2	4.6	0.74	0.638, 0.859
ECOG 0/1 (n= 1068)	17.0	12.2	4.8	0.74	0.63, 0.86
ECOG 2 (n=127)	7.3	7.0	0.3	0.77	0.50, 1.17
'One Prior Chemo' (n=832)	17.1	11.7	5.4	0.713	0.595,0. 855
ECOG 0/1 (n=739)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG 2 (n=93)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

However, interpretation of analysis for a subgroup of a subgroup becomes methodologically challenging due to small sample sizes.

A8 **Priority request. Of those discontinuing treatment, please clarify (1) what proportion met the pre-specified 3 criteria of the protocol outlined in section 6.3.1 (page 90); (2) what proportion met a subset of these; and (3) what proportion discontinued treatment for other reasons or reasons not noted.**

The three criteria for discontinuation in the COU-AA-301 study were PSA progression, radiographic progression or symptomatic progression (pain, skeletal related event (SRE), increased steroid, initiation of new anticancer therapy).

Janssen can clarify that [redacted] met all three criteria in the AAP arm and [redacted] in the PP arm. Unfortunately, due to the structure of the eCRF the progression criteria were only able to be selected if the 'met discontinuation criteria' button was checked in on the previous page of the eCRF. Therefore, for the vast majority of patients the progression criteria were not filled in as investigators selected another reason for discontinuation (dosing non-compliance, adverse event, initiation of new anticancer treatment, administration of prohibited medication and patient withdrawal of consent) .However, as noted in the original submission, several of these reasons, namely adverse events and initiation of a new anticancer treatment, are also linked to disease progression. Further evidence for this can be found in appendix 1, which lists the secondary reasons for patient discontinuation, many of which are linked to disease progression. Therefore, unfortunately Janssen is unable to provide the proportion for (2) and (3).

A9 **Priority request. Please present the parameter estimates for the curves fitted to overall survival for each arm, together with the relevant standard errors and AICs. Were BIC values collected? If so please also provide these in the table.**

As requested by the ERG, the table below presents the parameter estimates for the curves fitted to overall survival for each arm.

Updated analysis 1 prior chemo	Param 1 Intercept	s.e.	Param 2 Scale	s.e.	Param 3 Shape	s.e.	AIC	BIC
AAP								
Weibull	[redacted]							
Log-normal	[redacted]							
Log-logistic	[redacted]							
Exponential	[redacted]							
Gompertz	[redacted]							
Generalized gamma	[redacted]							
PP								
Weibull	[redacted]							
Log-normal	[redacted]							
Log-logistic	[redacted]							
Exponential	[redacted]							
Gompertz	[redacted]							
Generalized gamma	[redacted]							

A10 **Priority request. Please present the parameter estimates for the curves fitted to treatment discontinuation for each arm, together with the relevant standard errors and AICs. Were BIC values collected? If so please also provide these in the table.**

As requested by the ERG, the table below presents the parameter estimates for the curves fitted to treatment discontinuation for each arm.

Updated analysis 1 prior chemo	Param 1 Intercept	s.e.	Param 2 Scale	s.e.	Param 3 Shape	s.e.	AIC	BIC
AAP								
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP								
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A11 **Page 41 Section 5.3.3 Table 8 states that an exclusion criterion was: "*Surgery or local prostatic intervention within 30 days of the first dose".* Please clarify if this refers to first dose of abiraterone? Please indicate the numbers of patients in each arm that were excluded for this reason. Please explain the rationale for this criterion and how this might apply in clinical practice.**

Yes, Janssen can confirm that this is within 30 days of the first dose of study drug.

The rationale for this exclusion criterion is that this is a standard protocol exclusion criteria to ensure that a patient has recovered from the morbidities of a recent invasive surgical procedure. The number of patients excluded based solely on this criterion is likely to be very low since the more likely scenario would be for a patient to simply wait for 30 days from a surgical procedure before entering the study. This is no different to the requirement for patient to be ≥ 30 days after completion of chemotherapy or other systemic therapy for their cancer.

A12 **Please clarify what proportion of the ">1 prior" population had experienced re-challenge with the same first treatment.**

Using the same methodology as outlined in question A4, the estimated proportion of patients who may have had docetaxel rechallenge is estimated below.

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Based on these figures it is estimated that no more than [redacted] of patients within the '>1 Prior Chemotherapy 'group may have had docetaxel retreatment patients. Only [redacted] of patients in the study had received prior treatment with anthracyclines such as mitoxantrone, and no other prior chemotherapy agent was used by more than [redacted] of patients, therefore the proportion of patients likely to have experienced rechallenge with any chemotherapies other than docetaxel is likely to be very small.

A13 **Pg 120. Concomitant medication use. Please clarify why there is such a large difference in bisphosphonate use between progression free and progressed states; it does not seem reasonable for so many patients to start bisphosphonate only after they have progressed.**

In the COU-AA-301 trial, patients were permitted to continue on bisphosphonates if receiving the medication prior to Study day 1; addition of a bisphosphonate or change to the type of bisphosphonate was only allowed if a new SRE or bone progression event had occurred. Within this study, 36.67% of UK patients took bisphosphonates concurrently, however because bisphosphonate use after discontinuation was not captured, opinion was sought from a panel of oncologists and specialist nurses across England and Wales. This panel agreed that almost all mCRPC patients with symptomatic or progressive disease would receive bisphosphonates.

Please summarise the bisphosphonate percentages in each arm of the trial for the updated analysis for the ITT and the 1 prior chemotherapy populations. To the extent that it is available please also present the exposure to bisphosphonate use (mean doses) in each arm of the trial for the updated analysis for the ITT and the 1 prior chemotherapy populations.

The proportion of patients on bisphosphonates for the ITT and 'One Prior Chemotherapy' populations is presented in the table below.

Table 1. Percentage of patients on bisphosphonates for ITT and 1 prior chemotherapy populations.

	AAP	PP
ITT	[redacted]	[redacted]
One Prior Chemotherpapy	[redacted]	[redacted]

Six different bisphosphonates was concomitantly administered in the COU-AA-301 study, all were used in varying doses and formulations, and hence a combined mean dose of bisphosphonate cannot be calculated. The common bisphosphonate prescribed to patients in COU-AA-301 was IV zoledronic acid, see table below. Please note, the frequency of administration varied from patient to patient, however the most frequently recorded dose of i.v. zoledronic acid was [redacted] and this was consistent across the study arms and between the ITT and the 'One Prior Chemotherapy' population.

Table 2. Mean dose of bisphosphonates for ITT and 1 prior chemotherapy populations.

	ITT (n=1195)		One Prior Chemotherapy (n=832)	
	AAP (n= 797)	PP (n=398)	AAP (n= 557)	PP (n=275)
Bisphosphonate use recorded	[redacted]	[redacted]	[redacted]	[redacted]
IV Zoledronic acid prescribed	[redacted]	[redacted]	[redacted]	[redacted]

A14 **Page 56, Fig 8 provides subgroup analyses according to the primary analysis, however Page 55 of the submission states:**

[redacted] **Since the economic model is based on the One Prior population the consistency of OS within subgroups of this population is also of interest. Please clarify why this was not explored or supply the results of the analysis.**

The analysis conducted after 552 death events constituted the Primary analysis used in the regulatory submissions; analysis at the subsequent time point (the 'Updated' analysis) was only conducted for a selection of the primary analyses, and therefore the full set of subgroup analyses were not included in the full report on the 'Updated' analysis. Since then post-hoc analysis of all subgroups has been conducted on the 'Updated' data, which was recently presented at ESMO in September as an oral presentation, Fizazi, Scher, Molina et al., (2011), see figure below.

Variable	Subgroup	Median (months) AA	Placebo	HR	95% CI
All subjects	ALL	15.8	11.2	0.74	(0.64-0.86)
Baseline ECOG	**0-1**	**17**	**12.3**	**0.74**	**(0.63-0.86)**
	2	**7.3**	**7**	**0.77**	**(0.50-1.17)**
Baseline BPI	**< 4**	**18.4**	**13.9**	**0.69**	**(0.56-0.85)**
	≥ 4	**13.3**	**9.3**	**0.78**	**(0.63-0.96)**
No. prior chemo regimens	**1**	**17.1**	**11.7**	**0.71**	**(0.59-0.85)**
	2	**14.2**	**10.4**	**0.80**	**(0.61-1.03)**
Type of progression	**PSA only**	**18.3**	**13.6**	**0.63**	**(0.47-0.84)**
	Radiographic	**14.8**	**10.5**	**0.78**	**(0.65-0.93)**
Age, years	< 65	15	11.2	0.69	(0.53-0.91)
	≥ 65	16.2	11.1	0.76	(0.63-0.90)
	≥ 75	15.6	9.3	0.64	(0.48-0.85)
Visceral disease at entry	YES	12.9	8.3	0.79	(0.59-1.05)
	NO	17.1	12.3	0.69	(0.58-0.82)
Baseline PSA above median	YES	13.6	8.8	0.65	(0.53-0.79)
	NO	18.2	15.3	0.79	(0.63-0.99)
Baseline LDH above median	YES	10.4	8	0.77	(0.63-0.93)
	NO	20.8	18	0.75	(0.59-0.96)
Baseline ALK-P above median	YES	12.4	8.1	0.60	(0.50-0.74)
	NO	19.5	18	0.88	(0.69-1.12)
Region	N.A.	16.4	11.1	0.68	(0.56-0.83)
	Other	15.1	11.5	0.80	(0.64-1.00)

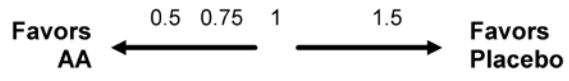


Figure 1. Overall survival benefit for subgroups in the 'Updated' analysis. LDH, lactate dehydrogenase; ALK-P, alkaline phosphatase.

The 'One Prior Chemotherapy' population is comprised of 70% of the ITT, and OS for the 'One Prior Chemotherapy' group split by ECOG status has already be presented in response to question A7. Exploring the impact of other subgroups within the 'One Prior Chemotherapy' population results in very small sample sizes, and therefore should be interpreted with caution.

A15 **Page 57 of the submission states:**

The decision problem specifies that three specific subgroups should be explored in this submission:

- ***baseline ECOG status***
- ***extent of prior taxane exposure (reflected in the analysis as number of prior chemotherapy treatments)***
- ***time since taxane treatment.***

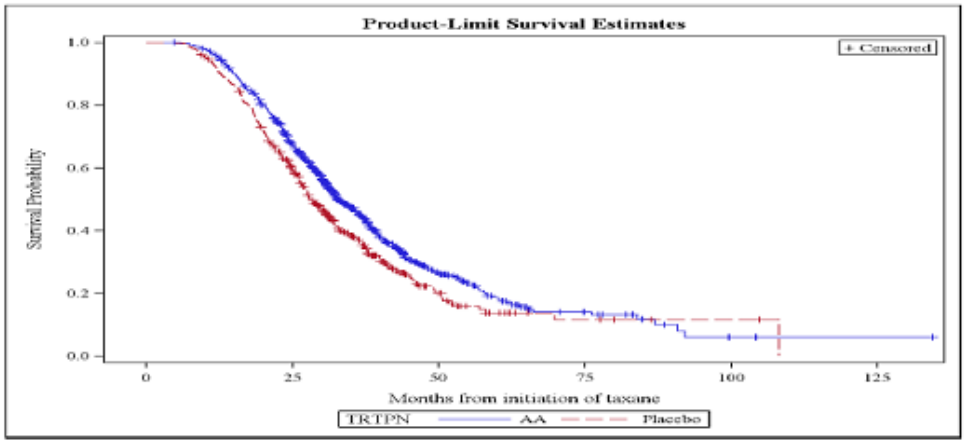
The ERG were unable to find information in the submission about possible influence of taxane experience on survival other than the statement (page 57):

[redacted]

The graphs below are taken from the FDA medical report for abiraterone.

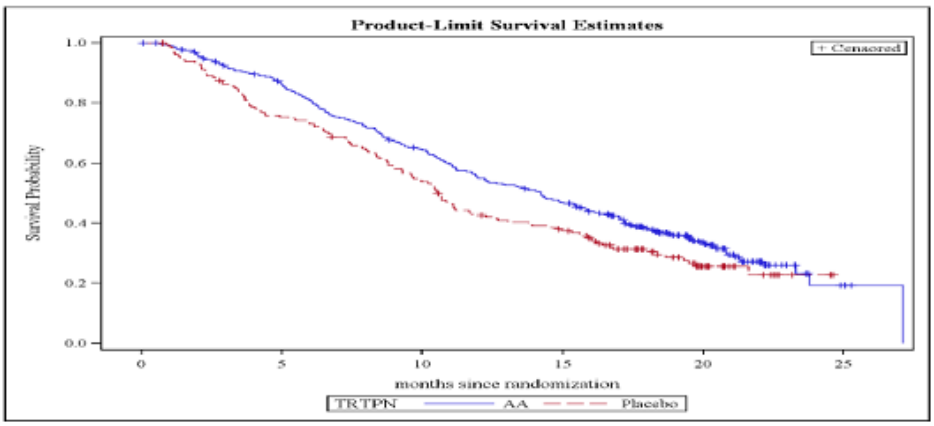
Please confirm if the depicted results are based on primary analysis or updated analysis, and comment on their applicability for the One Prior population modelled in the submission.

Figure 6: Sensitivity Survival Analysis from the Initiation of Prior Docetaxel Treatment



	Median mos (95% CI)	Nominal P-value
AA	32.7 (31.2, 35.9)	0.0017
Placebo	28.1 (26.5, 30.7)	

Figure 7: Survival Analysis from the Discontinuation of Prior Docetaxel Treatment



	Median mos (95% CI)	Nominal P-value
AA	23.9 (22.7, 25.4)	0.0004
Placebo	20.2 (18.6, 21.4)	

The figures above were an exploratory sensitivity analysis was conducted by the FDA on the 'Primary' data set [redacted]xResults from these analyses demonstrate that the OS benefit of AAP is maintained when calculated from either the first or last dose of docetaxel. [redacted] Following the pattern observed for OS, between the ITT and one prior chemotherapy population, the one prior chemotherapy population should be expected to have longer survival from the point of discontinuation of prior docetaxel treatment than observed in the figure above. [redacted]

A16 **The table below shows the median survival for the control group in the AA-301 study. Also shown are results presented by Armstrong et al (Clinical Cancer Research16 (1) 203-211) describing post progression survival after failure of Docetaxel with mCRPC patients.**

Group and analysis	Median overall survival (months)
AA-301 control arm ITT primary analysis	10.9
AA-301 control arm ITT updated analysis	11.2
AA-301 control arm 1 Prior Population updated analysis	11.7
Post Docetaxel (all)	14.5
Post Docetaxel (completed 10 cycles treatment)	20.8
Post Docetaxel (did not complete 10 cycles treatment)	11.4

Please clarify if you consider the AA-301 population to be similar to The Armstrong population that failed to complete 10 cycles.

In the Armstrong study (further analysis from Tannock 2004), subjects at enrolment were chemotherapy naive, whereas in the COU-AA-301 study all subjects had experienced at least one prior chemotherapy regimen. Although some of the baseline characteristics appear similar between the two studies with respect to age, race, % bone metastases, and evidence of progression at entry, the underlying disease appears more severe at baseline in the COU-AA-301 study, as would be expected in a population that had been exposed to prior chemotherapy compared to a chemotherapy naive population. Specifically, the COU-AA-301 population had far higher mean baseline PSA (439ng/ml vs ~115ng/ml) and had a higher proportion of patients with a Gleeson score 8 or above (52% vs 30%). Janssen also estimate that approximately [redacted]% of patients within the 'One Prior Chemotherapy' population may have been re-challenged with docetaxel, whereas patients in the Armstrong study only received one line of docetaxel chemotherapy during the study. The COU-AA-301 study also included patients who had stopped treatment with docetaxel due to toxicity however these patients were excluded from the Armstrong study. Furthermore, these two studies should not be directly compared, due to differences in progression definition used in the two analyses. The Armstrong study reports OS from the point of first progression event (pain, tumour or PSA) whilst the large proportion (70%) of subjects in the COU-AA-301 study at baseline had evidence of progression as assessed by radiographic progression +/- PSA progression.

To make an accurate comparison of the two study populations would require the patient characteristics for the Armstrong study at the point of progression or the characteristics of subjects in the COU-AA-301 study at the point of the first dose of chemotherapy, neither of which are available.

A17 **Skeletal related events: (Please also refer back to the "baseline balance" [A3] clarification question. Section 5.9.2 page 74 the submission states:**

[redacted]

However the FDA Medical Review for abiraterone states as follows:

The use of bisphosphonates, once standard care for patients with mCRPC, was remarkably different between the pre-study and on-study periods and the percentages of concomitant bisphosphonate use during study was considerably higher than those of disease progression documented in both arms, making it difficult to evaluate any effect of abiraterone acetate on the incidence of skeletal-related event or time to first skeletal-related event in the trial.

Please clarify the discrepancy (see also question A8).

According to the protocol, an addition of a bisphosphonate or change to the type of bisphosphonate was only allowed if a new SRE or bone progression was documented. The pre-study use of bisphosphonates was reported in 29 (4%) patients assigned to the abiraterone acetate arm and in 16 (4%) patients assigned to the placebo arm. The on-study use of bisphosphonates did increase to [redacted]% patients receiving abiraterone acetate [redacted]% patients receiving placebo. The FDA review states that this is a discrepancy, as these on-study bisphosphonate use rates are much higher than the discontinuation rate of 28% for disease progression in the two arms at the 'Primary' time point and approximately [redacted] in the 'Updated' time point. However, patients also discontinued treatment in COU-AA-301 to start a new anticancer treatment, due to investigator decision and due to death, all of which are also linked to disease progression; in the AAP arm this equates to an additional [redacted] of subjects. In addition, although the reason for discontinuation may have been classed as an adverse event or other reason, many of these events can also be linked to disease progression, Appendix 1. In summary, the reasons the majority of subjects discontinued treatment was likely linked to disease progression and not only for 28% of patients as reported in the FDA review.

With regards to whether the use of bisphosphonates may have confounded the incidence of SREs or time to first SRE, any use of bisphosphonates in the study would have actually been biased against AAP. Firstly, there was a lower use of bisphosphonates in the AAP arm (approximately 6% lower) compared to placebo. Secondly, bisphosphonates could only be started following an SRE or bone progression and the occurrence of these events in AAP subjects occurred later as evidenced by the delay in time to first SRE and the longer time to radiographic progression for the AAP subjects. Hence, PP subjects were more likely to start bisphosphonates earlier than AAP subjects and were also more likely to require bisphosphonate initiation. Therefore, the reduced number of SREs and the delay in SREs observed in the AAP arm compared to PP, is more likely to have been attenuated by the increased use, and earlier use, of bisphosphonates in the PP arm.

A18 **Section 5.9.2 page 69 of the submission states:**

"AEs were also standardised for the duration of treatment exposure in the analysis. Three AEs were identified that may occur more frequently in the AAP group:

[redacted]

According to the FDA Medical review "*this approach has never been used in oncology drug or biologic review to determine adverse reactions"*. And *In general, this methodology attenuated the differences between the treatment arms.* Please clarify the discrepancy.

Although the standardisation of AEs for duration of treatment exposure has not been reported for other oncology drugs, this approach is more relevant for an oral, 'treat to progression' drug such as abiraterone acetate, as patients had a longer time on treatment in the AAP arm compared to the PP arm in the COU-AA-301 study. It is a common, standard approach across other disease areas. In addition, many AEs are related to disease progression so it is important to adjust these for treatment exposure. Although this approach may appear to attenuate the differences between the two treatment arms, it is important to consider the impact of length of exposure on the occurrence of these AEs.

A19 **Please provide an interpretation on the higher rate of vascular disorders for abiraterone than in placebo group shown in table 22 on page 73 of the submission**.

A higher rate of Grade 3/4 vascular disorders occurred in the AAP arm compared to the PP arm, ([redacted] respectively in the 'Updated' analysis), due to increased incidence of hypertension, deep vein thrombosis and hypotension.

The discussion on clinical safety in the EPAR stated (p67):

"The most common adverse drug reactions observed in the overall abiraterone acetate group (n=1,070) were peripheral oedema, hypokalemia, urinary tract infection, and hypertension. Consistent with the pharmacologic mechanism of action of abiraterone, mineralocorticoid-related toxicities (based on the SMQ grouping), such as fluid retention/edema (31% versus 22%), hypokalemia (17% versus 8%), and hypertension (10% versus 8%) were observed more frequently for patients treated with abiraterone acetate and prednisone compared with those treated with placebo and prednisone, respectively, in Study COU-AA-301. However, when standardized for longer exposure time, only hypokalemia (47 events/100 P-Y versus 29 events/100 P-Y, respectively) and fluid retention/edema (71 events/100 P-Y versus 65 events/100 P-Y, respectively) were found to occur more frequently in the abiraterone group than in the placebo group (not hypertension). "

The SPC states that as abiraterone acetate "may cause hypertension, hypokalaemia and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition"..." Blood pressure, serum potassium and fluid retention should be monitored before treatment and at least monthly thereafter."

A20 **Fig 10 (page 59) shows time to treatment discontinuation as a proxy for time to progression. Various time to progression estimates (e.g. treatment cessation, radiological progression etc) are mentioned in the submission. Please supply a single graph for the one prior population (abiraterone arm) showing all of the various estimates so as to allow easy comparison; similarly for the placebo arm.**

The figures showing all estimates of progression are provided in the figures below for both the AAP and PP arms.

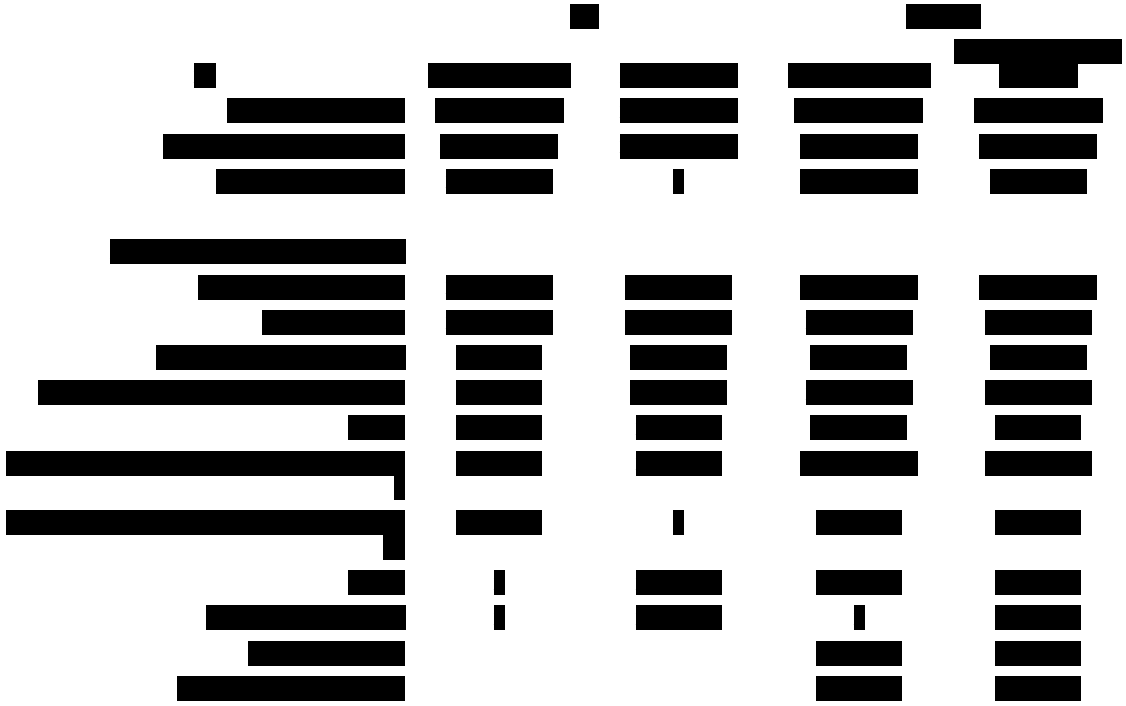
Figure 2.

Figure 3.

A21 **Please clarify if discontinuations (numbers and / or reasons) differed between study centres or geographical areas? (e.g. Between UK centres and rest; between USA and non-USA).**

Reasons for treatment discontinuation for UK and Non-UK subjects and is reported in the table below.

Table 3. Reasons for treatment discontinuations per sponsor review for UK vs non UK subjects



A22 **In the time to progression KM plots (Figs 10, 11, 12; pages 59 to 60)) for the placebo arm there is a very marked decline in the curve at about 3 to 4 cycles (e.g. arrow on Fig 12 below). This implies that somewhere between 50 and hundred patients are withdrawing from treatment over a short period of 3 weeks at about 60 days after start of treatment. This could be due to a failure of blinding at some sites and patient / physician decision to stop treatment and transfer to an alternative care. Please list reasons for treatment cessation over this period, comment and / or suggest alternative explanations.**

All study personnel and investigators were blinded to patient treatment assignment. The marked decline in patients withdrawing from treatment in the placebo arm is likely due to clinician decision to withdraw the patient due to unequivocal clinical progression. These patients have such a short life expectancy that that in many cases clinicians would not keep the patients on a drug that was not showing evidence of halting disease progression. Referring to the figures provided in our response to question A20, it is clear that indeed the curves for time to PSA and radiographic progression exhibit the identical pattern.

A23 **We found fig 16 in submission page 92 interesting but could not find a textual reference to the figure either in section 6.3.1 *Progression free survival* or section 6.3.7. Please clarify /explain figure more fully. Please interpret the departure from an exponential decline that occurs for the lowest line at about 0.5 years.**

This figure is referring to the PFS curves used in the economic model, the previous two paragraphs (although not cross-referenced in the text) relate to Figure 16. The steep drop off observed for the orange line is the average treatment duration assumed for the mitoxantrone arm which is dependent on the maximum number of cycles patients receive. The PFS curves for mitoxantrone and prednisolone are identical in the model base case.

A24 **Figures 21 and 22 (pages 100 and 101) do not show a parametric fit to TTP for the placebo arm. Please clarify if a parametric fit for this data was used in any sensitivity analysis, and if so what was the fit (see also tables below)?**

A parametric fit was not used in the base case nor in sensitivity analysis for the PP arm, as it was determined that the KM data was the most appropriate to use in the model as all progression events were captured in the PP arm, and therefore there was no need to extrapolate the data.

A25 **Please tabulate from which cycle of the model the 10% rule (5% for discontinuations) and move from KM curve to parametric curve applies for each of the curves fitted:**

As requested by the ERG, below is a table of the model cycle number that the parametric curve was fitted for each arm for OS and treatment discontinuation.

	Model cycle from baseline
OS curve AAP	cycle 32
OS curve PP	cycle 30
Treatment discontinuation AAP	cycle 33
Treatment discontinuation PP	No extrapolation

A26 **For the updated analysis please present the data elements of 5.5.3.2 (page 58 onward, Progression free survival) separately for the ITT and for the 4 patient groups of the stratification factors: 1 prior chemo, 1+ prior chemo, ECOG0/1 and ECOG2**

Updated analysis rPFS median months	AAP	PP	Net	HR (if available)	P value (If available)
ITT					
ECOG 0/1	[redacted]	[redacted]	[redacted]	[redacted]	
ECOG 2	[redacted]	[redacted]	[redacted]	[redacted]	
'One Prior Chemotherapy'					
ECOG 0/1	[redacted]	[redacted]	[redacted]	[redacted]	
ECOG 2	[redacted]	[redacted]	[redacted]	[redacted]	

Updated analysis mPFS median months	AAP	PP	Net	HR (if available)	P value (If available)
ITT					
ECOG 0/1	[redacted]	[redacted]	[redacted]	[redacted]	
ECOG 2	[redacted]	[redacted]	[redacted]	[redacted]	
'One Prior Chemotherapy'					
ECOG 0/1	[redacted]	[redacted]	[redacted]	[redacted]	
ECOG 2	[redacted]	[redacted]	[redacted]	[redacted]	

If available please present a similar analysis for the median time to (mPFS or rPFS)

The mPFS definition includes radiological progression therefore analysis of time to mPFS or rPFS cannot be conducted.

A27 **For the updated analysis please present the median times to discontinuation in each arm separately by ECOG performance status at baseline:**

Updated analysis Treatment discontinuation median months	AAP	PP	Net	HR (if available)	P value (If available)
ITT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG 0/1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
'One Prior Chemotherapy'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG 0/1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A28 **For the updated analysis please append to Table 22 pages 72 to 74, the number of patients discontinuing due to SAE differentiated by arm, including the subheadings e.g. psychiatric disorders, to the extent that this was recorded within the trial.**

The table below summarises the incidence of treatment emergent adverse events leading to discontinuation of study medication in the 'Primary' and 'Updated' analysis.

	'Primary'		'Updated'	
	AAP (n=791)	PP (n=394)	AAP (n=791)	PP (n=394)
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified	[redacted]	[redacted]	[redacted]	[redacted]
Injury poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Renal and Urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]

A29 **It is not altogether clear what data was used to generate the parametric fits for OS (and times to progression that are shown in Figs 17 to 20 etc pages 98 to 101). For example, was all the data in the K-M plots as shown in figs 7 and 9 etc used (but excluding when less than 10% left at risk for OS and 5% for progression)? Or was the fit made to the 21 day cycle points as depicted in K-M sheets within the economic model (using cycles 0 to 36)? If the latter why not use all the K-M data, and how were the 21 day data points obtained? Please clarify.**

Janssen acknowledges that this should have been made clearer in the original submission. Parametric model fitting in all cases were based on all data points observed in the patient level COU-AA-301 trial data as shown in figures 9 and 12 of the submission.

A30 **If within figure 17 (page 98) the data for the AA observed applies the 10% cut-off please re-present this figure including these data points. Please present a similar analysis for figure 18 (page 99).**

For parametric model fitting in all cases were based on all data points, days to event, in the patient level COU-AA-301 trial data, amended figures are provided in the answer to A34 below.

A31 **Within the modelling for AAP using the exponential distribution for extrapolation, please clarify what proportion of the overall undiscounted survival is estimated using the KM curve and what proportion is estimated through extrapolation? Similarly, what are the proportions for PP.**

The extrapolation of overall survival started based on the cut off of 10% patients at risk. For the AAP arm, overall survival was estimated based on KM curve until the survival rate was less than 35.78% in the trial. 66.7% of overall undiscounted life years were estimated using the KM curve, and 33.3% of the overall undiscounted life year was estimated through extrapolation.

For the PP arm, overall survival was estimated based on the KM curve until the survival rate is less than 30.21% in the trial. 72.2% of the overall undiscounted life year was estimated using the KM curve, and 27.8% of overall undiscounted life years were estimated through extrapolation.

A32 **Within the modelling for AAP using the Weibull distribution for extrapolation, please clarify what proportion of the overall undiscounted survival is estimated using the KM curve and what proportion is estimated through extrapolation? Similarly, what are the proportions for PP.**

The extrapolation of overall survival started based on the cut off of 10% patients at risk. For the AAP arm, overall survival was estimated based on the KM curve until survival rate was less than 35.78% in the trial. 79.8% of the overall undiscounted life years were estimated using the KM curve, and 20.2% of the overall undiscounted life years were estimated through extrapolation.

For the PP arm, overall survival was estimated based on KM curve until survival rate is less than 30.21% in the trial. 78.6% of the overall undiscounted life year were estimated using the KM curve, and 21.4% of the overall undiscounted life year were estimated through extrapolation.

A33 **In describing the handling of overall survival Section 6.3.7 on page 97 states:**

"As events were not observed for all patients in COU-AA-301, curves were extrapolated with reference to the rate of progression up till that point, in the base case the extrapolation assumed a constant hazard rate (exponential curve), as has been previously advocated".

In this context please clarify the meaning of *"with reference to the rate of progression up till that point".*

Janssen acknowledges that this should have been clarified in the original submission. The difference in survival proportions observed between the first and last data points of the KM curves (until 10% at risk) was converted to a constant and rate applied for the extrapolation period. Please find further details in Section 6.3.7 of the original submission.

A34 **With reference to Fig 17 – 20 (pages 99 to 101): visual inspection indicates that the Weibull parametric fits for OS especially (also for treatment discontinuation in figs 21, 22) provide good fits (and look superior to the exponential). For ease of comparison please provide a Figure for the Weibull fit to the whole of the K-M data set (as fig 9) for OS, separately for abiraterone and placebo; and similarly for time to treatment cessation (K-M data set as Fig 12) [updated analyses and one prior population]). Indicate where the 10% and 5% at risk occurs or please specify the times at which these occur.**

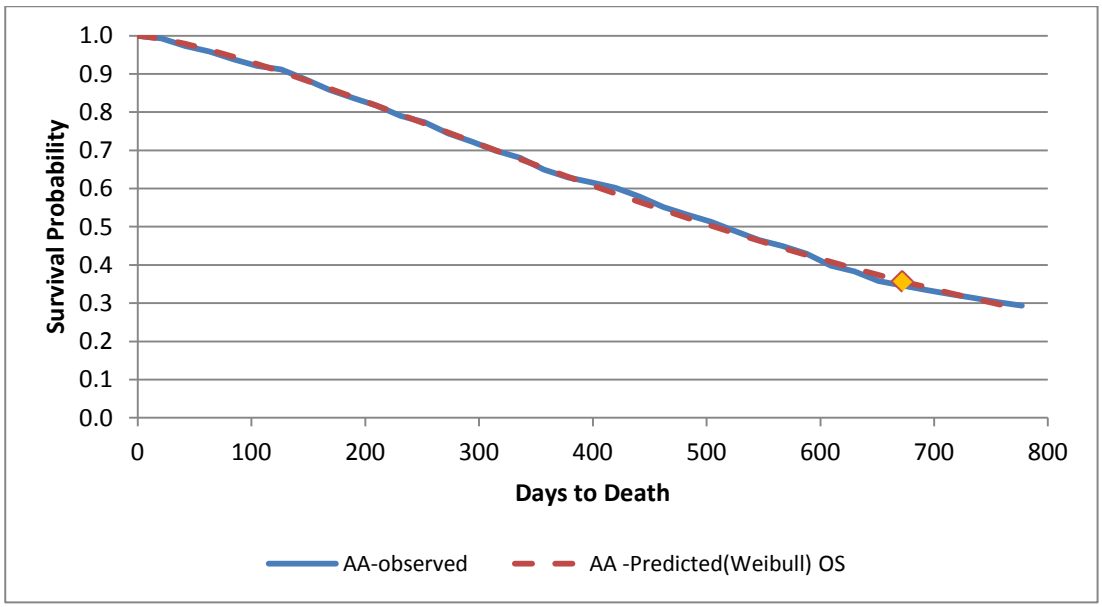


Figure 4. Parametric Curve Fits - Overall Survival – 'One Prior Chemotherapy' - AAP: 0-800 Days. Yellow diamond indicates the point of day 672 when 10% at risk occurs. 5% at risk occurs at day 714.

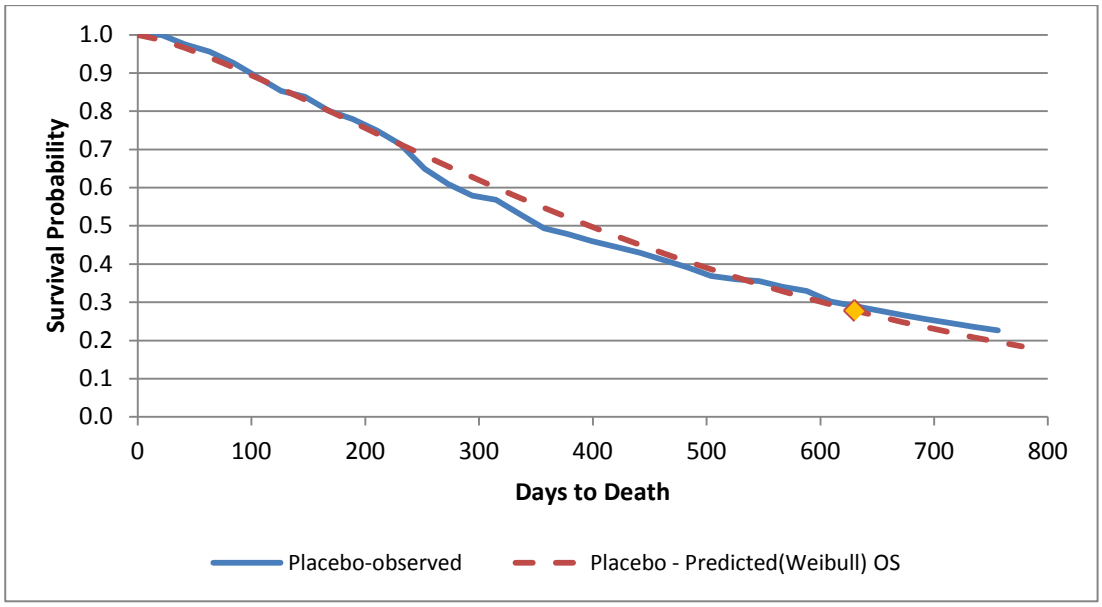


Figure 5. Parametric Curve Fits - Overall Survival – 'One Prior Chemotherapy' - PP: 0-800 Days. Yellow diamond indicates the point of day 630 when 10% at risk occurs. 5% at risk occurs at day 693.

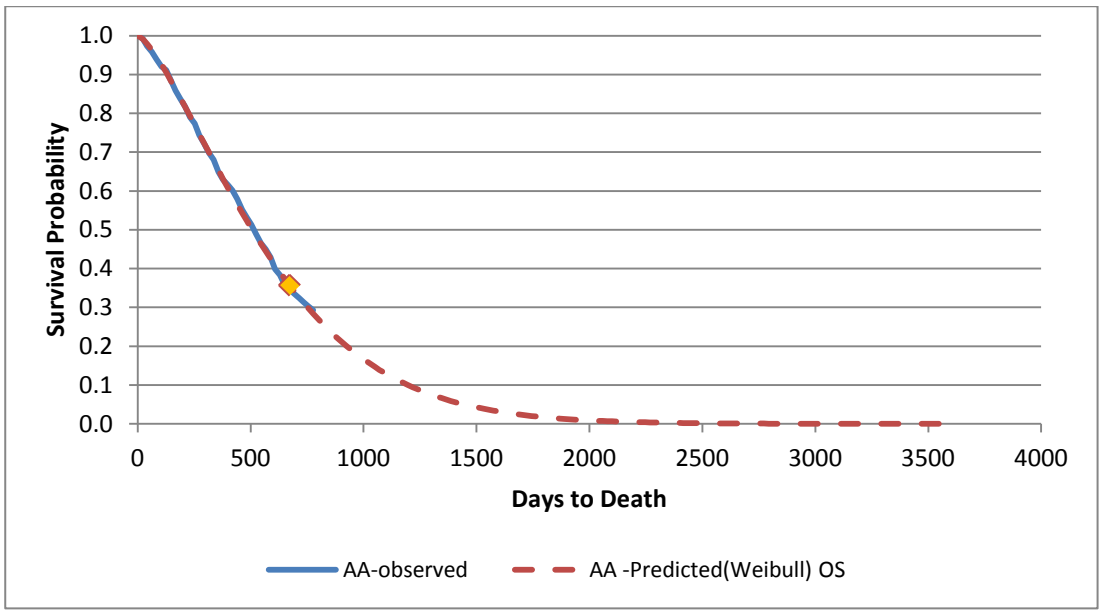


Figure 6. Parametric Curve Fits - Overall Survival – 'One Prior Chemotherapy' - AAP: 0-4,000 Days. Yellow diamond indicates the point of day 672 when 10% at risk occurs. 5% at risk occurs at day 714.

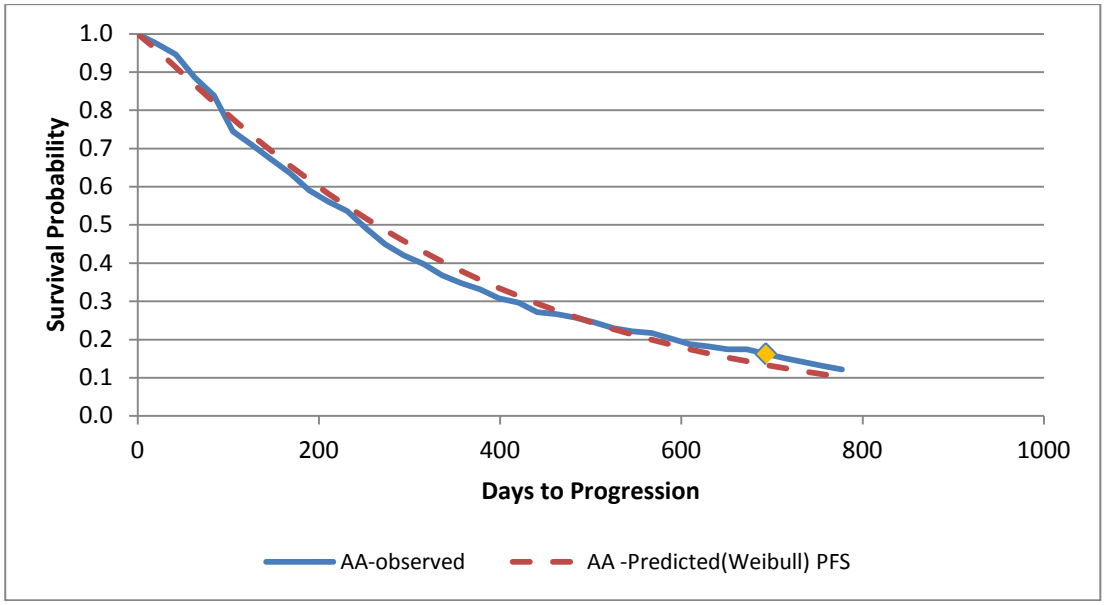


Figure 7. Parametric Curve Fits - PFS - 'One Prior Chemotherapy': AAP 0-4,000 Days. Yellow diamond indicates the point of day 609 when 5% at risk occurs. 10% at risk occurs at day 525.

Parametric functions were not fitted to the PFS curves on the PP arm as all patients in the PP arm had progressed at the time that the 'Updated' analysis was conducted.

Section B: Clarification on cost-effectiveness data

B1 **Priority request. Please clarify how progression is defined within the data underlying the Adelphi utility mapping exercise [AIC elements of appendix 15 page 196 to 200]?**

The COU-AA-301 clinical trial data were used to generate the utility values for the pre-progression state only, therefore only the data from the 'on treatment' period was included in the analysis. Data captured from the time of progression was not included in the analysis.

B2 **Priority request.**

a) What proportion of observations within the trial based utility data set had the time dependent indicator of progression set to 0?

Disease progression was assumed to reflect treatment discontinuation. Per the protocol, FACT-P scores were collected only while patients were on treatment and data from the discontinuation visit (point of progression) was not included in the utility analysis. The table below supporting question c, provides the summary information for patients prior to treatment discontinuation.

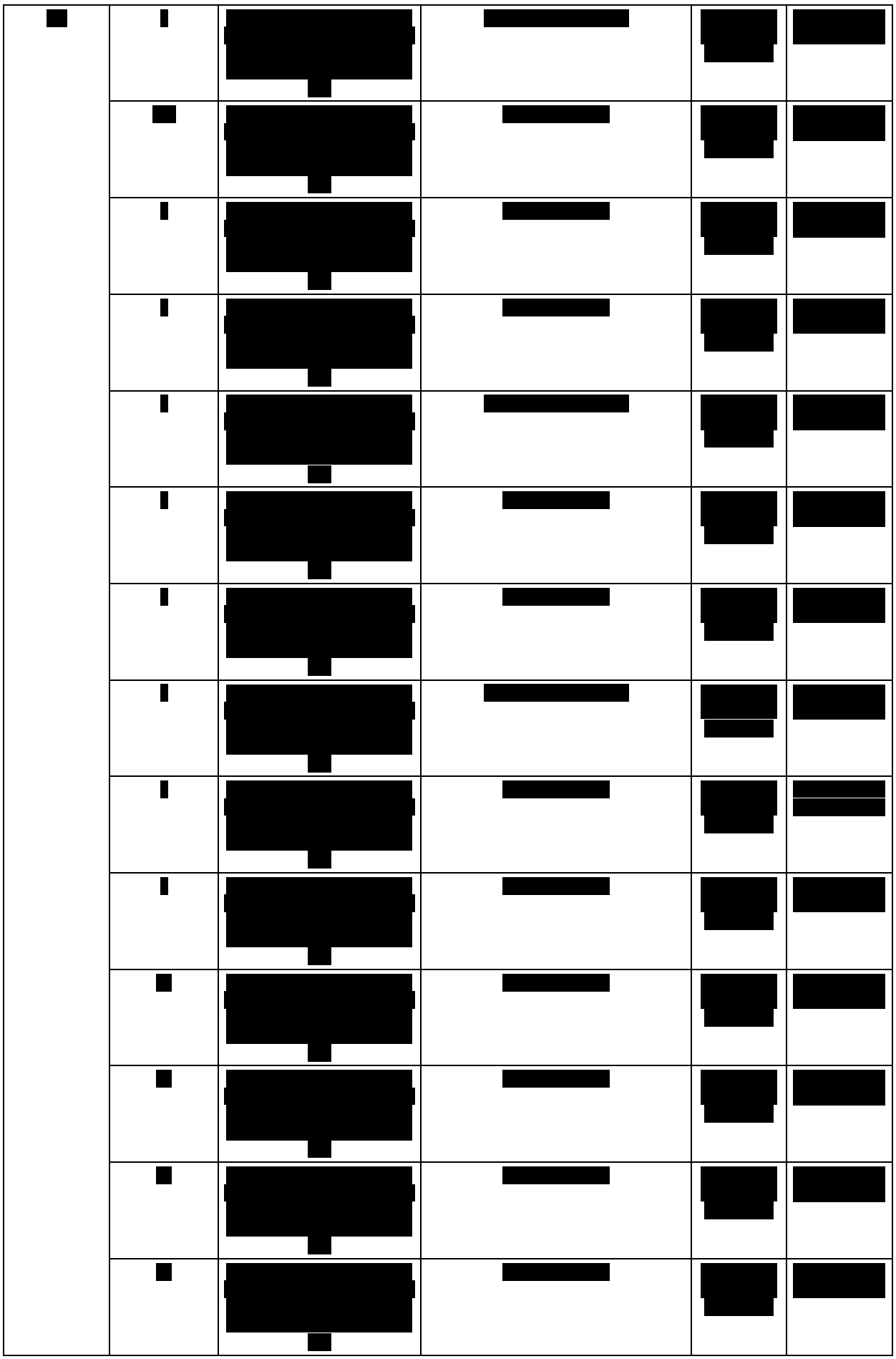
b) What proportion of SAEs within the trial based utility data set had the time dependent indicator of progression set to 0?

As above, all the utility analyses were conducted on data collected while patients are still on treatment, data from the discontinuation visit was not included in this analysis.

c) Please provide a summary of the mean values, number of observations and dispersion (s.d.) for the FACT-P elements for the trial based utility data with the time dependent indicator of progression set to 0, separately for the AAP arm and the PP arm.

Summary tables of this information is provided below.

Group	CYCLE NUM	Variable	N	Mean	Std Dev
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

d) Please provide a summary of the mean values, number of observations and dispersion (s.d.) for the FACT-P elements for the trial based utility data from the EoT observations.

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B3 **Priority request. Pg 104 section 6.4.3 (also refer to C5 above)**

AA-301 FACT-P results encompass adverse events and are used to estimate utility (in progression-free state for AA and Placebo). Important adverse events altering QOL are SREs. Protocol violations resulted in greater use of bisphosphonates than planned, and this use will reduce SRE events. According to the submission (page 74):

[redacted] **However, because of bisphosphonate use and perhaps because of lack of comparability between groups (see question E) the extent to which this may be attributed to abiraterone is doubtful (see comment of FDA quoted above). Therefore, please clarify if the utility benefit given to abiraterone versus placebo in the modelled progression-free state can actually be attributed to abiraterone.**

As discussed in the response to question A17, the reduced number of SREs and the delay in SREs observed in the AAP arm compared to PP, is more likely to have been attenuated by the increased use, and earlier use, of bisphosphonates in the PP arm.

With respect to the utility benefit seen on treatment with AAP, the majority of patients were not experiencing an SRE whilst on treatment and the difference between the two treatment arms was small, but significant ([redacted]% of the AAP arm and [redacted]% of the PP arm at 18 months), it is likely that the majority of the utility benefit experienced by patients is more likely due to the quality of life benefits (pain and fatigue) that were observed in these patients. These pain and fatigue benefits are further supported by the benefits observed for patients with respect to functioning as assessed with the FACT-P tool. Furthermore, [redacted], meaning that the impact of these SREs on QoL would not have been captured in the on treatment QoL assessments.

B4 **Priority request. Please provide a copy of the on-line survey among oncologists (6.3.5, page 94-95), together with the individual respondent results in electronic format, if possible in excel format; e.g. one expert response per worksheet.**

The results from the quantitative online survey were used as a basis for discussion during the consensus meeting with UK oncologists and nurses. There was variation in the output of the quantitative survey and therefore the consensus meeting was used to agree estimates that could then be used in the modelling. The output from the consensus meeting (and a follow-up discussion via webex) is therefore more appropriate to consider as the output from this was used to derive the assumptions used in the model on treatment pathways, resource use associated with treatments and resource use associated with adverse events. The report from the consensus meeting and follow-up webex are attached.

B5 **Priority request. Please provide the disaggregate spreadsheet costing that underlies tables 41, 42, (page 123 to 124) 81 and 82 (page 207); i.e. resource use in natural units, unit costs applied, sources of unit costs.**

Disaggregated spreadsheet costing underlying Tables 41 and 42 are provided in the accompanying Microsoft Excel file entitled "B5 NICE Response UK Abiraterone Adverse Event Cost Calculation.xls". Disaggregated costing underlying Tables 81 and 82 are as follows and further detail can be found in Appendix 2 of this document.

Resource	Unit Cost	Code (Description)	Source
GP Visit	£53.00	10.8b (Per clinic consultation lasting 17.2 minutes.)	Unit costs of Health and Social Care. PSSRU 2010
Nurse (RN) Visit	£12.00	10.6 (Per Consultation in GP Practice.)	Unit costs of Health and Social Care. PSSRU 2010
Oncologist Visit	£196.00	370 (Medical Oncologist - Consultant First Attendance Non-Admitted Face to Face.)	National Schedule of Reference Costs Year 2009-10 - NHS Trusts and PCTs combined file.
Hospitalisation	Numerous hospitalisations were included in the trial-based MRU analysis. A summary of hospitalisations, including unit costs, codes and descriptions, is included in the accompanying .rtf file entitled "NICE Response_Hospitalisations and Other Costs_MRU Analysis Tables 81 and 82.rtf" For hospitalisations involving an ICU admission, £710 was added to cost of admission (Code XC07Z – Adult Critical Care – 0 Organs Supported; Source: National Schedule of Reference Costs Year 2009-10 - NHS Trusts and PCTs combined file. Critical Care Services - Adult: Critical Care Unit.)		National Schedule of Reference Costs Year 2009-10 - NHS Trusts and PCTs combined file. Non-Elective Inpatient HRG Data.
Other	Numerous "other" procedures were included in the trial-based MRU analysis. A summary of hospitalisations, including unit costs, codes and descriptions, is included in the accompanying .rtf file entitled "NICE Response_Hospitalisations and Other Costs_MRU Analysis Tables 81 and 82.rtf"		Listed in file.

B6 **Priority request. Sections 6.7.2 & 6.7.3 (page 129) REQUESTS *Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.* AND *Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.* The submission states *Not applicable***

However, within the model sheets the model is called a MARKOV MODEL.

Although the model may not strictly be a Markov model it is possible to provide the graphs requested i.e. proportion of each cohort in each state (pre-progression, post-progression and dead) versus time. In fact this is more or less what is depicted in the diagrammatic representation of the model structure (Fig 15). Please provide such graphs, preferably without discounting.

The figures requested are presented below and capture the proportion of patients in each health state over time in both the AAP and the PP arm.

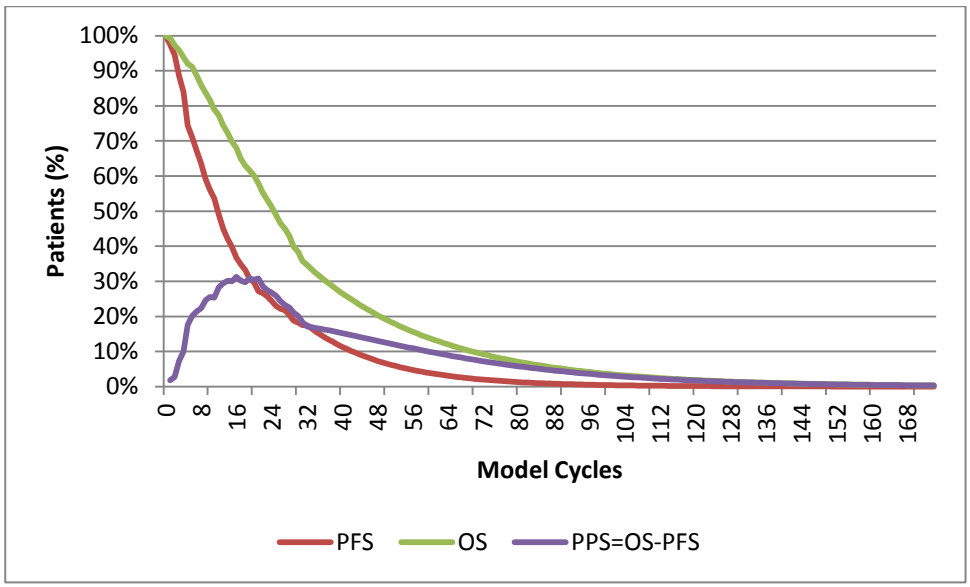


Figure 8. Proportion of the cohort in each health state over time – AAP arm

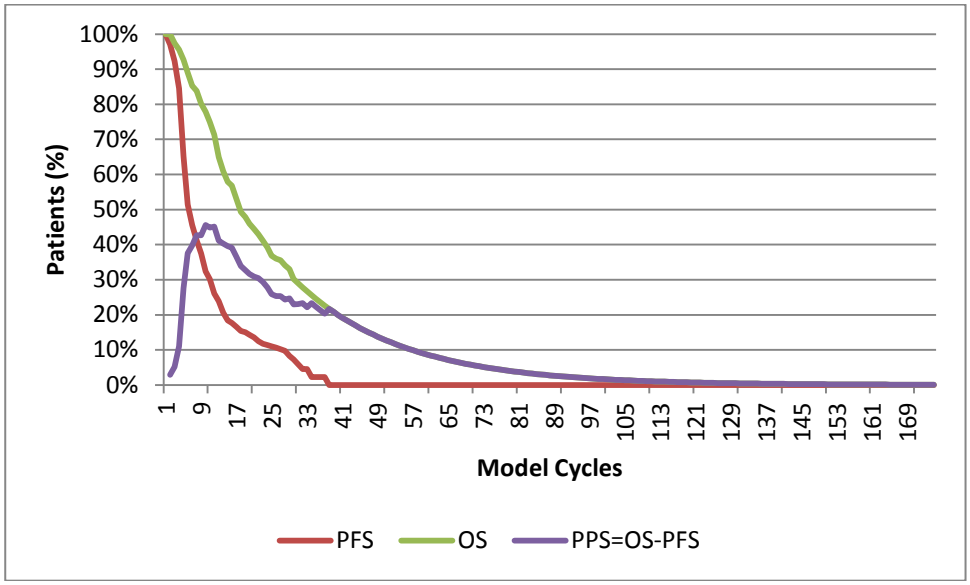


Figure 9. Proportion of the cohort in each health state over time – PP arm

Table 4. QALY accrual over time.

	AAP		PP	
Model Cycle	Progression Free QALY	Progressive Disease QALY	Progression Free QALY	Progressive Disease QALY
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]
29	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]
31	[redacted]	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]	[redacted]
34	[redacted]	[redacted]	[redacted]	[redacted]
35	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]
37	[redacted]	[redacted]	[redacted]	[redacted]
38	[redacted]	[redacted]	[redacted]	[redacted]
39	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]
41	[redacted]	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]	[redacted]
43	[redacted]	[redacted]	[redacted]	[redacted]

44	[redacted]	[redacted]	[redacted]	[redacted]
45	[redacted]	[redacted]	[redacted]	[redacted]
46	[redacted]	[redacted]	[redacted]	[redacted]
47	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]
49	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]
51	[redacted]	[redacted]	[redacted]	[redacted]
52	[redacted]	[redacted]	[redacted]	[redacted]
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54	[redacted]	[redacted]	[redacted]	[redacted]
55	[redacted]	[redacted]	[redacted]	[redacted]
56	[redacted]	[redacted]	[redacted]	[redacted]
57	[redacted]	[redacted]	[redacted]	[redacted]
58	[redacted]	[redacted]	[redacted]	[redacted]
59	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]
61	[redacted]	[redacted]	[redacted]	[redacted]
62	[redacted]	[redacted]	[redacted]	[redacted]
63	[redacted]	[redacted]	[redacted]	[redacted]
64	[redacted]	[redacted]	[redacted]	[redacted]
65	[redacted]	[redacted]	[redacted]	[redacted]
66	[redacted]	[redacted]	[redacted]	[redacted]
67	[redacted]	[redacted]	[redacted]	[redacted]
68	[redacted]	[redacted]	[redacted]	[redacted]
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70	[redacted]	[redacted]	[redacted]	[redacted]
71	[redacted]	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]	[redacted]
73	[redacted]	[redacted]	[redacted]	[redacted]
74	[redacted]	[redacted]	[redacted]	[redacted]
75	[redacted]	[redacted]	[redacted]	[redacted]
76	[redacted]	[redacted]	[redacted]	[redacted]
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83	[redacted]	[redacted]	[redacted]	[redacted]
84	[redacted]	[redacted]	[redacted]	[redacted]
85	[redacted]	[redacted]	[redacted]	[redacted]
86	[redacted]	[redacted]	[redacted]	[redacted]
87	[redacted]	[redacted]	[redacted]	[redacted]
88	[redacted]	[redacted]	[redacted]	[redacted]
89	[redacted]	[redacted]	[redacted]	[redacted]
90	[redacted]	[redacted]	[redacted]	[redacted]

91	[redacted]	[redacted]	[redacted]	[redacted]
92	[redacted]	[redacted]	[redacted]	[redacted]
93	[redacted]	[redacted]	[redacted]	[redacted]
94	[redacted]	[redacted]	[redacted]	[redacted]
95	[redacted]	[redacted]	[redacted]	[redacted]
96	[redacted]	[redacted]	[redacted]	[redacted]
97	[redacted]	[redacted]	[redacted]	[redacted]
98	[redacted]	[redacted]	[redacted]	[redacted]
99	[redacted]	[redacted]	[redacted]	[redacted]
100	[redacted]	[redacted]	[redacted]	[redacted]
101	[redacted]	[redacted]		
102	[redacted]	[redacted]		
103	[redacted]	[redacted]		
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105	[redacted]	[redacted]		
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108	[redacted]	[redacted]		
109	[redacted]	[redacted]		
110	[redacted]	[redacted]		
111	[redacted]	[redacted]		
112	[redacted]	[redacted]		
113	[redacted]	[redacted]		
114	[redacted]	[redacted]		
115	[redacted]	[redacted]		
116	[redacted]	[redacted]		
117	[redacted]	[redacted]		
118	[redacted]	[redacted]		
119	[redacted]	[redacted]		
120	[redacted]	[redacted]		
121	[redacted]	[redacted]		
122+	[redacted]	[redacted]		

B7 **Please provide a copy of the ISPOR poster presentation for the Adelphi utility exercise.**

The podium presentation for the Adelphi utility exercise is due to be delivered at ISPOR at the 14th Annual European conference on the 5th Nov 2011 and is attached.

B8 **The mapping function derived from the Adelphi data set in table 75 of appendix 15 (page 197) provides a linear model of the EQ-5D score on the FACT-P dimensions. The economic reviver is not familiar with the cited reference: Szende,A., Oppe,M., & Devlin,N. *EQ-5D value sets: inventory, Comparative Review and User Guide*. Please clarify what the EQ-5D score has been mapped onto: is this an EQ-5D utility derived from the UK social tariff? How similar are the ADELPHI patients (submission Appendix 15 pages 196-200) and the AA-301 patients?**

The EQ-5D utility is derived from the UK social tariff (EQ-5D Value Sets: Inventory, Comparative Review and User Guide Edited by Agota Szende, Mark Oppe and Nancy Devlin on behalf of the EuroQol Groups Task Force on Value Sets (2007)). The table on page 69 of this reference is used to translate EQ-5D values into utilities (reference attached). This is the standard UK value set originally developed by Dolan et al (Med Care 1997; 35(11):1095-1108).

The mean age, BMI, performance status, of these Adelphi and AA-301 subjects are very similar, see table below.

	Adelphi (n=291)	COU-AA-301 (n=1195)
Mean age	[redacted]	69.2
Mean BMI	[redacted]	27.5
Ethnicity	[redacted]	
White		93%
Black		4%
Hispanic/Spanish		
Other		3%
Performance status	[redacted]	90% were ECOG 0-1
Chemotherapy status	[redacted]	
No chemotherapy		0%
Current chemotherapy		0%
Prior Chemotherapy		100%
Distant metastasis	[redacted]	
Node		44%
Bone		90%
Other		Can't determine
Mean FACT-P	[redacted]	106.3

The mean FACT-P scores were higher (better HRQL) in the COU-AA-301 patients than the Adelphi data set (106.3 vs [redacted]), however this is to be expected as the COU-AA-301 subjects were all post-chemotherapy patients, whereas the Adelphi sample included a range of patients from chemotherapy naive patients to those who had several lines of chemotherapy and a large proportion ([redacted]) of patients who were currently receiving chemotherapy.

B9 **Please clarify if within the Adelphi utility mapping exercise the entire EU Adelphi data set is used or only UK patient data?**

The Adelphi dataset included 291 patients from several EU countries with CRPC, the UK subset was too small to conduct any analysis in. The utilities calculated using this algorithm were based on a UK-specific EQ-5D value set.

B10 **Please outline why a unified model of AEs, pain progression, PSA response and AAP arm on/off or PP arm on/off treatment was not developed, but rather the two separate models.**

The goal of the utility analysis was to create an equation that could be used to compare AAP with PP and other chemotherapy comparators not in the COU-AA-301 trial. The disease progression/response endpoints collected for the chemotherapy comparator, e.g. mitoxantrone, were very limited and reported differently in the TROPIC* study than in the COU-AA-301 trial. The

definition of Grade 3 and 4 events were similar across trials, although reporting of these across trials differed.

Two separate regression models were considered in our analysis. A regression model that included starting baseline utility and treatment was able to capture the direct and full utility impact of AAP versus PP while patients were on treatment, the time during which FACT-P scores were collected. Conservatively, the treatment effect seen with AAP was applied to the mitoxantrone arm of the model. However, given that chemotherapies such as mitoxantrone generally have more adverse events than AAP or PP, it was important to apply a disutility for this while on treatment. To estimate an unbiased effect of AE on utility, the model that considered all mediating variables such as pain progression, and PSA response was fitted(for more detailed explanation please see appendix 15 "Identifying Predictors that Impact EQ5D Utility Score") .

*In the reporting of the TROPIC grade 3/4 AEs with a frequency lower than 5% in both arms (mitoxantrone + prednisone or cabazitaxel + prednisone) were not reported.

B11 **Please clarify if for the Impact of Treatment model, the data set is restricted to all FACT-P data points collected with the time dependent indicator of progression set to 0?**

Yes, the treatment effect is only during the on treatment period. Any additional impact on HRQoL through progression is captured by transition to the post-progression state in the model.

B12 **Please clarify section 5.5.3.6 page 62 of the submission by defining "palliation/improvement" and "progression" and "progression/degradation". Please supply copies of the relevant inventories.**

Definition of palliation/improvement and the definition of Progression/degradation: Each of the three outcomes measures was analysed to determine the proportion of subjects experiencing progression/degradation and palliation/improvement on each PRO measure. The change thresholds were required to be maintained for two consecutive follow-up visits for the BPI-SF and BFI measures; however, since the FACT-P was not measured at every cycle/visit, the change thresholds were only required to be met at one follow-up visit.

Definition of time to PRO Progression/Degradation and time to PRO Palliation/Improvement: The difference between treatment groups in median time to progression/degradation and palliation/improvement on each PRO measure was determined.

Please note that within Table 17 of the submission the text in the table "PRP improvement" should read "PRO deterioration".

The data presented on our submission was generated on the 'Updated' dataset and the final full report for all these PRO analyses is not yet available.

B13 **Table 29 (pages 95 to 97 of submission) lists a disutility for grade 3/4 Adverse Events while on treatment Mitoxantrone 0.023. Please explain how this does not represent "double counting" of disutilities already listed in the table.**

The disutility due to Grade 3/4 AEs whilst on mitoxantrone of 0.023 calculated in the model is the mean disutility applied to each patient whilst on mitoxantrone; this is calculated from the disutility and the rate of associated individual AEs for patients on mitoxantrone. The individual AEs are not directly used in the model but are used to calculate the mean 0.023 disutility used in the model.

The mean 0.023 disutility of mitoxantrone was calculated as the weighted average using data from the second column and the fifth column in the table below. 0.023 = sumproduct(Mean Disutility, Incremental AE rates of mitoxantrone vs. abiraterone).

	Mean Disutility	AE rates for abiraterone acetate	AE rates for mitoxantrone	Incremental AE rates for mitoxantrone vs. abiraterone acetaet = AE rates for mitoxantrone – AE rates for abiraterone acetate
Neuropathy	[redacted]	[redacted]	0.8%	**0.5%**
Neutropaenia	[redacted]	[redacted]	58.0%	**57.9%**
Febrile Neutropaenia	[redacted]	[redacted]	1.0%	**0.6%**
Thrombocytopenia	[redacted]	[redacted]	2.0%	**0.6%**
Anaemia	[redacted]	[redacted]	5.0%	**-2.8%**
Oedema	[redacted]	[redacted]	0.0%	**-1.8%**
Hypokalaemia	[redacted]	[redacted]	0.0%	**-4.4%**
Hypertension	[redacted]	[redacted]	0.0%	**-1.3%**
Arthralgia	[redacted]	[redacted]	1.0%	**-4.1%**
Asthenia	[redacted]	[redacted]	2.0%	**-1.3%**
Diarrhea	[redacted]	[redacted]	0.3%	**-0.8%**
Dyspnea	[redacted]	[redacted]	1.0%	**-0.8%**
Fatigue	[redacted]	[redacted]	3.0%	**-6.1%**
Nausea	[redacted]	[redacted]	0.3%	**-1.8%**
Vomiting	[redacted]	[redacted]	0.0%	**-2.7%**

B14 **Section 6.4.4 (page 105 & Appendix 15 (page 196-200).**

The submission states that an error was identified in Wu's algorithm such that nonsensical results were generated (utility > 1), and that an independent algorithm was constructed employing Wu's methodology. Please provide example(s) in which nonsensical results are generated from Wu but sensible results from the new algorithm. Also clarify all the acronyms in table 75 and also the acronym OLS

We attempted to reproduce the average utility value in the Wu et al. publication by inserting the identical input data that Wu et al. used (mean FACT-P variables; baseline patient characteristics) into the mapping equation presented. In doing this, we found a second discrepancy in the Wu et al. publication. The Wu et al. publication cites the mean BMI at 72.4. It is clear that this is a typographical error (the mean age value is mistakenly used for mean BMI as well). To confirm this, we consulted the source publication for the input data that Wu et al. used, a summary of mCRPC observational study quality of life findings by Sullivan et al.[1] In the Sullivan article, we found that the mean BMI was 27, and confirmed the mean age to be 72.4. When applying input data from Figure 1 and using average characteristics of the study population published by Wu et al. (including the corrected value for BMI) to the mapping algorithm, we arrived at an average mapped utility of 1.11, compared to the value of 0.62 reported by Wu et al. Furthermore, when the unadjusted Wu algorithm was applied to the COU-AA-301 data the mean utility was 1.0655 which is nonsensical, in contrast when the algorithm derived from the Adelphi study produced a mean utility of [redacted] within the same dataset.

The abbreviations in Table 75 of the submission refer to Physical Well Being (PWB), Social Well Being (SWB), Emotional Well Being (EWB), Functional Well Being (FWB), FACT-P Subscale (PCS) and Body Mass Index (BMI). OLS is ordinary least squares.

[1] Sullivan PW, Mulani PM, Fishman M, Sleep D. Quality of life findings from a multicenter, multinational, observational study of patients with metastatic hormone-refractory prostate cancer. Qual Life Res. 2007;16:571-575.

B15 **Pg 105 section 6.4.4 the submission states: "*The 10-fold cross validation R results for all four models were evaluated".* Please clarify what 4 models are referred to.**

We can clarify that we are referring to the following models: OLS, Gamma, Median, and Tobit models. See ISPOR presentation attached by Spencer and Diels (2011).

B16 **The source of the 2% cost saving in unplanned MRU costs for AAP versus PP in table 55 (page 132) is not immediately obvious. Please clarify if this is solely due to discounting and differential timings, or are there other reasons?**

The difference between the unplanned MRU costs for AAP and for PP was mainly due to the difference in progression free survival. Cohort in PP arm spends longer in the progression disease health state. And consequently consumes more progressed unplanned MRU. Cost discounting also affect the difference, but the impact is minimal. Eliminating cost discounting will decrease the increment from 2.4% to 2.1%.

B17 **Pg119. Please clarify why Un-scheduled MRU in the post-progression state is not modelled?**

The unscheduled, event driven MRU data from the trial was only collected during the time on treatment and does not include resource use in the post-progression period. These costs seemed mainly driven by disease progression (hence a one-off unscheduled MRU cost in progression free state). The assumption made in the model is that the unscheduled resource use during the post progression period would be similar to that near the progression event. A monthly unscheduled MRU cost is assigned to the post progression period to account for differential survival between treatments.

B18 **Pg 198 (Predictors tested). Please clarify why SREs are not included?**

SRE was tested but the effect was not statistically significant.

B19 **For the one prior population please clarify what was the number of hospitalisations observed in each arm and what were the reasons for the hospitalisations?**

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
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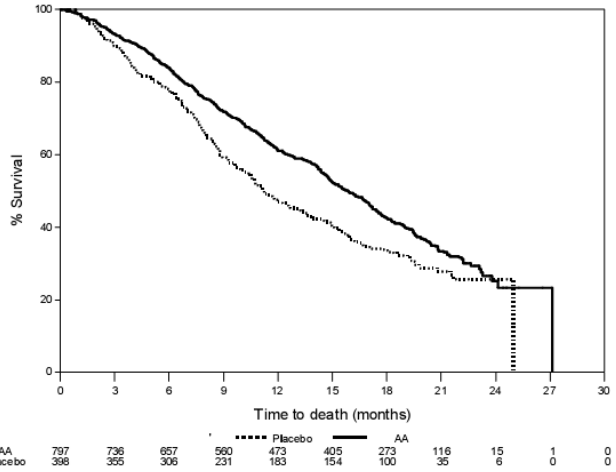
Section C: Textual clarifications and additional points

C1 **A large amount of information in the submission is highlighted in yellow. Why is much of this material highlighted when the information is already in the public domain (e.g. figure 7 ITT overall survival and the figure 2 from the FDA statistical report document on abraterone; see below)? Please amend your confidentiality marking in line with what is already in the public domain?**

[redacted]

Figure 2 Updated Kaplan-Meier Overall Survival Curves, ITT Population



AA=abiraterone acetate

[Adapted from Study Report COU-AA-301-OS-update Figure 1]

The FDA reviews have been reviewed to identify any data that may have been inappropriately marked as 'in confidence'. The figure referred to above has been marked as AIC, as although a similar figure has been presented in the FDA statistical review, the figure in the FDA statistical review did not contain the points of censoring. Janssen acknowledges that there is a large amount of information marked as 'in confidence' in the submission, due to the presentation of data used in the clinical and economic sections being from the 'Updated' time point and for the 'One Prior Chemotherapy' population. Janssen is happy to discuss the unmarking of any other data that the ERG believes to be in the public domain.

C2 **Pg 94, Section 6.3.5 : "Clinical experts". Please clarify if all the experts that were canvassed were based in the UK?**

All clinicians consulted in the online survey and subsequent consensus meeting were clinicians practicing in the UK.

C3 **Table 34, (page 113). Please correct the utility for ITT post progression; and confirm that the small differences between ITT and one prior population utilities shown in the table are correct.**

These differences between the ITT and one prior chemotherapy populations are correct.

Thank you for pointing out the error in this table. ITT utility post-progression should be 0.50 not 0.05

C4 **Some references in the bibliography appear to be incomplete e.g. 50, 51, 52, 59, 60. Please correct the references accordingly.**

Janssen acknowledges the volumes and page numbers on the following references were omitted from these references in the bibliography. Please find the corrections below.

50. Ou,Y. *et al.* Randomized, placebo-controlled, phase III trials of sunitinib in combination with prednisone (SU+P) versus prednisone (P) alone in men with progression metastatic castration-resistant prostate cancer (mCRPC). *Journal of Clinical Oncology* **29 no 15 suppl.**, (2011). 2011 ASCO Annual Meeting. Abstract number 4515.

51. Salimichokami,M., Aminian,S., Ayati,M., & Sanadi-Zadeh,M. Evaluation of efficacy and safety of a metronomic/anti-angiogenic regimen of low-dose oral cyclphosphamide, thalidomide, and dexamethsone in pts with chemotherapy-resistant, castration-refractory prostate cancer in Iran. *Journal of Clinical Oncology* **28 no 15 suppl.**, (2010). 2010 ASCO Annual Meeting. Abstract number e15091.

52. Saad,F. *et al.* Phase II randomized study of custirsen (OGX-011) combination therapy in patients with poor-risk hormone refractory prostate cancer (HRPC) who relapsed on or within six months of 1st-line docetaxel therapy. *Journal of Clinical Oncology* **26 no 15 suppl.**, (2008). 2008 ASCO Annual Meeting. Abstract number 5002.

59. Ismail,J.R., Bystricky,B., Moylan,E., & Reilly,S. Mitoxantrone-based treatment in taxane-refractory advanced hormone refractory prostate cancer. *Journal of Clinical Oncology* **28 no 15 suppl.**, (2010). 2010 ASCO Annual Meeting. Abstract number e15137.

60. Morales et al. Mitoxantrone as second-line chemotherapy in patients with castrate-resistant prostate cancer. *Annals of Oncology* **21 (Suppl. 8),** (2010). 35th ESMO Congress. Abstract number 962.

Appendix 1.

[redacted]	[redacted]	[redacted]
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Updated Data: AA Treatment discontinuation due to AE

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Updated Data: AA Treatment discontinuation due to AE

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Updated Data: AA Treatment discontinuation due to AE

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Updated Data: AA Treatment discontinuation due to AE

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Updated Data: AA Treatment discontinuation due to AE

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Updated Data: Placebo Treatment discontinuation due to AE

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Updated Data: Placebo Treatment discontinuation due to AE

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Updated Data: Placebo Treatment discontinuation due to AE

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Updated Data: Placebo Treatment discontinuation due to AE

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Updated Data: AAP Treatment discontinuation for Other Reason

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Unit Cost Applied for Other Resources in UK

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Unit Cost Applied for Other Resources in UK

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Unit Cost Applied for Other Resources in UK

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Unit Cost Applied for Other Resources in UK

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