17/10/11

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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.

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.

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).

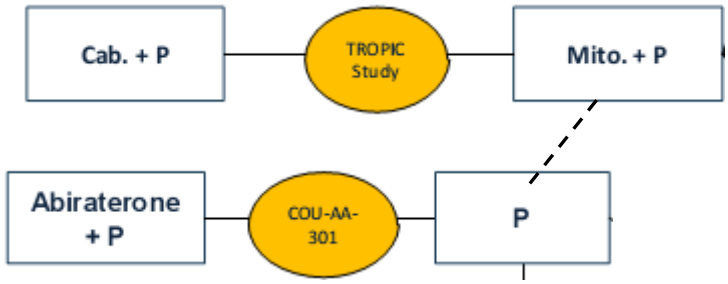
A4 **Priority request.** For purposes of defining the One Prior population a re-challenge with docetaxel was considered as part of the original regimen. Page 84 of the submission states "*due to the manner in which data was captured in the case report form, the exact proportion of men in COU-AA-301 who 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?

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 .

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?

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.

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

Updated analysis Overall survival median months	AAP	PP	Net	HR (if available)	P value (If available)
ITT					
- ECOG 0/1					
- ECOG 2					
1 prior chemo					
- ECOG 0/1					
- ECOG 2					

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.

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.

Updated analysis 1 prior chemo	Param 1	s.e.	Param 2	s.e.	Param 3	s.e.	AIC
AAP							
Weibull							
Log-normal							
Log-logistic							
Exponential							

Gompertz							
Generalized gamma							
PP							
Weibull							
Log-normal							
Log-logistic							
Exponential							
Gompertz							
Generalized gamma							

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.

Updated analysis 1 prior chemo	Param 1	s.e.	Param 2	s.e.	Param 3	s.e.	AIC
AAP							
Weibull							
Log-normal							
Log-logistic							
Exponential							
Gompertz							
Generalized gamma							
PP							
Weibull							
Log-normal							
Log-logistic							
Exponential							
Gompertz							
Generalized gamma							

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.

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

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. 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.

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.

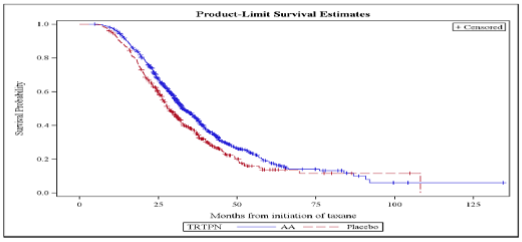
A15 Page 57 of the submission states:

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.*

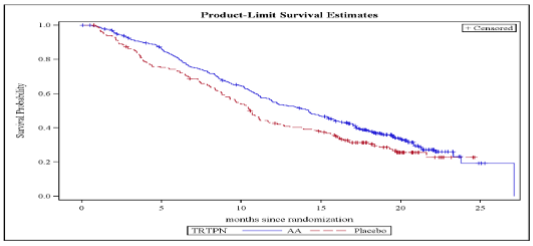
The ERG were unable to find information in the submission about possible influence of taxane experience on survival other than the statement (page 57): "[redacted]

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 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.

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.

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, one 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).

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.

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.

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.

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).

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. 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.

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.

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)?

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:

	Model cycle, or weeks from baseline
OS curve AAP	
OS curve PP	
Treatment discontinuation AAP	
Treatment discontinuation PP	

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 mPFS median months	AAP	PP	Net	HR (if available)	P value (If available)
ITT					
- ECOG 0/1					
- ECOG 2					
1 prior chemo					
- ECOG 0/1					

- ECOG 2					

Updated analysis rPFS median months	AAP	PP	Net	HR (if available)	P value (If available)
ITT					
- ECOG 0/1					
- ECOG 2					
1 prior chemo					
- ECOG 0/1					
- ECOG 2					

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

Updated analysis mPFS or rPFS median months	AAP	PP	Net	HR (if available)	P value (If available)
ITT					
- ECOG 0/1					
- ECOG 2					
1 prior chemo					
- ECOG 0/1					
- ECOG 2					

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					
- ECOG 0/1					
- ECOG 2					
1 prior chemo					
- ECOG 0/1					
- ECOG 2					

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.

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.

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).

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.

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.

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".*

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.

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]?

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?

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

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.

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.

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.

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.

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.

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.

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

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?

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

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.

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?

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.

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

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

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.

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?

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

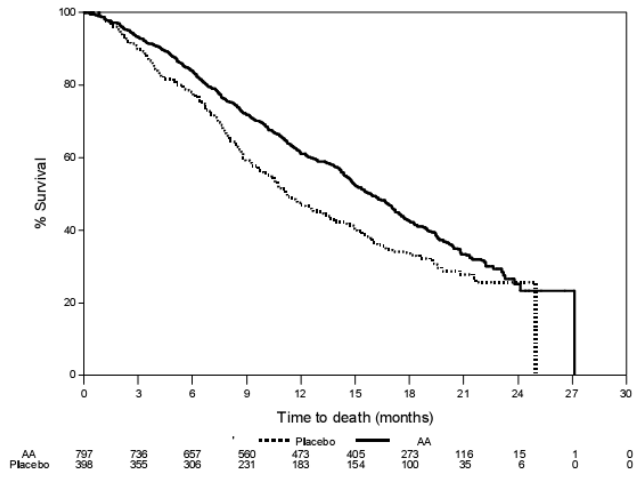
B18 Pg 198 (Predictors tested). Please clarify why SREs are not included?

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?

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?

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



AA=abiraterone acetate

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

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

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