National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Enzalutamide for treating metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy [ID683]

You are asked to check the ERG report from Aberdeen Health Technology Assessment Group, University of York to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **24 April 2015** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Incorrect HR for IPCW OS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect HR and 95% CI. On page 2, the ERG report states: *When adjusting for treatment switching using the inverse probability of censoring weight (IPCW) method, the hazard ratio was [redacted] with 95% CI ([redacted]).*	Please, replace the sentence with the following one: *When adjusting for treatment switching using the inverse probability of censoring weight (IPCW) method, the hazard ratio was [redacted] with 95% CI ([redacted]).*	The HR and 95% CI reported by ERG correspond to the 16 September 2013 data cut-off, while the paragraph refers to the 30 June 2014 data cut-off.	The proposed amendment is accepted

Issue 2 Unclear sentence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 3, the following sentence is not sufficiently clear: *The COU-AA-302 trial compared abiraterone plus prednisone versus prednisone plus placebo and PREVAIL for enzalutamide.*	Please, replace the sentence with the following one: *The COU-AA-302 trial compared abiraterone plus prednisone versus prednisone plus placebo and PREVAIL enzalutamide* ***versus placebo***	The sentence would become clearer if the comparator in PREVAIL is added.	Not a factual error. The proposed revision is not accepted.

Issue 3 Data cut-off missing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 3, detail on which data-cut is used is missing:	Please, replace the sentence with the following one:	Given that several data cut-offs have been conducted for OS in COU-AA-302, it would be useful to	Not a factual error. The proposed revision is not accepted.

The OS in COU-AA-302 trial resulted in HR of 0.79, 95% CI (0.66, 0.95) in favour of abiraterone compared to placebo	***In the third interim analysis**, the OS in COU-AA-302 trial resulted in HR of 0.79, 95% CI (0.66, 0.95) in favour of abiraterone compared to placebo*	state which data cut-off the HR relates to, because this HR does not relate to the final analysis which provides a HR of 0.80 [0.69; 0.93] according to the presentation at ESMO and 0.81 [0.70; 0.93] in Ryan et al 2015	

Issue 4 Incorrect HR for time to initiation of cytotoxic therapy in COU-AA-302

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 3 there is a numerical error for the HR for time to chemotherapy initiation in COU-AA-302. *HR 0.62 95% CI (0.51, 0.72) for time to initiation of cytotoxic therapy*	Please update the HR value: *HR 0.61, 95% CI (0.51, 0.72) for time to initiation of cytotoxic therapy*	Incorrect value presented	The value is based on and matches the value presented by the company in Table B30 of the company submission. Therefore, the proposed revision is not accepted.

Issue 5 Inaccurate information regarding 2nd line treatments in PREVAIL

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
PREVAIL did not provide any recommendations regarding second or third line treatment. The treatment received after study drug discontinuation was decided	Please, replace the sentence with the following one: ***Given that many patients received a** 2nd line treatment that would not be usual practice in*	In PREVAIL, the choice of treatment upon study drug discontinuation was left to investigator discretion. The study protocol did not provide any recommendations regarding	The ERG believes the current text does not pose any problem in terms of appropriateness or transparency. The proposed

by the investigator. Thus the following sentence on page 5 is not strictly true: *PREVAIL permitting a number of 2nd line treatments that would not be usual practice in the UK the company adjusted the overall survival data using the IPCW method, though an alternative two stage method was also explored*	*the UK, the company adjusted the overall survival data using the IPCW method, though an alternative two stage method was also explored*	which second or third line treatment patients should receive. Thus, the sentence is not accurate.	revision is not accepted.

Issue 6 Incorrect net treatment benefit on EQ-5D for enzalutamide

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 6, the ERG report states: *The BSC arm was assumed to have the PREVAIL baseline quality of life of 0.844, while the net treatment effect of 0.021 was added to this for enzalutamide.*	Please replace the sentence by: *The BSC arm was assumed to have the PREVAIL baseline quality of life of 0.844, while the net treatment effect of **0.022** was added to this for enzalutamide.* The value for the net treatment effect is also incorrect on page 81 (mentioned twice) and in Table 65 (page 124). Please update the values stated on these pages.	The value for the net treatment benefit is incorrect.	The ERG accepts the proposed revision

Issue 7 Incorrect statement regarding different monitoring resource use

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 8 the ERG states that: *The rationale for the extent of the differences in routine monitoring resource use for the 1st line treatments does not appear to be presented.*	Please remove the sentence.	The rationale of the differences in monitoring resource use across first line treatments is clearly presented in the CS (page 191). Here it is stated that "The monitoring requirements and frequency was based on the post-chemotherapy enzalutamide STA (Table 61 in the manufacturer submission32), and modified based on the experience of UK clinical experts (Table B71)." The monitoring resource use in the model was based on the monitoring frequency stated in the post-chemo enzalutamide CS, the chemo-naïve and post-chemo abiraterone CS and the feedback received by 7 UK experts of which 6 were clinicians (reference number 9 in the CS). Furthermore, the rationale for the differences in monitoring between abiraterone and enzalutamide is stated as follows: "As enzalutamide does not require the additional monitoring required for	Not a factual error. No revision required. While the source of the differences in resource use being company derived expert opinion is stated and the differences in resource use are given, the rationale for the differences in resource use does not appear to have been presented.

		abiraterone[4]. The monitoring frequency was estimated at once every four weeks in the first three months, and once every 8 weeks thereafter." The frequency of scans for patients in first-line treatment is also stated in the CS; footnote to Table B71 "*According to clinical experts[9], 3 scans assumed during the course of treatment."	

Issue 8 Typo

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 16, the "(" should be removed from the following sentence: *Both are currently under review by NICE,[15] (and hence unavailable, although abiraterone is available in England through the CDF.*	Please delete the "("; the sentence should read: *Both are currently under review by NICE,[15] and hence unavailable, although abiraterone is available in England through the CDF.*	Typo	This is a typo and not a factual error. The proposed revision is not accepted.

Issue 9 Incorrect reference

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 19, the reference to the following sentence should be the SPC *No special facilities are required for drug administration and product-specific monitoring (e.g. liver function tests or cardiovascular monitoring) is also not required. (Astellas Pharma, 2015)*	Please update the reference to the following sentence: *No special facilities are required for drug administration and product-specific monitoring (e.g. liver function tests or cardiovascular monitoring) is also not required. (**Enzalutamide SPC**)*	The stated information is already provided in the SPC therefore, the Xtandi SPC can be cited as the relevant reference.	Not a factual error. The proposed revision is not accepted.

Issue 10 Typo

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 26, the definition of the PREVAIL study in the following sentence is not accurate: *After reasonable exclusions, the company identified one, triple-blind phase III randomised controlled trial (RCT) of enzalutamide compared with placebo, the PREVAIL trial.*	Please replace the sentence with the following one: After reasonable exclusions, the company identified one, ***double***-blind phase III randomised controlled trial (RCT) of enzalutamide compared with placebo, the PREVAIL trial.	PREVAIL was a double- rather than a triple-blind RCT.	The ERG agree this is a typo but believe this does not pose any problem in terms of appropriateness or transparency. The proposed revision is not accepted.

Issue 11 Inaccurate p value for OS in PREVAIL

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 37, the p value should be <0.0001 rather than <0.001 in the following sentence: *Enzalutamide was found to significantly reduce the risk of mortality by 29.4% compared to placebo (unstratified HR = 0.706 with 95% CI (0.596 to 0.837), log-rank test p < 0.001).*	Please update the sentence with the following one: *Enzalutamide was found to significantly reduce the risk of mortality by 29.4% compared to placebo (unstratified HR = 0.706 with 95% CI (0.596 to 0.837), log-rank test p < **0.0001**).*	The p-value is inaccurate	The ERG p-value is technically still correct if not wholly specified, but the 95%CI represents the correct accuracy so not a factual error. The proposed revision is not accepted.

Issue 12 Incorrect median OS for placebo in PREVAIL

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 37, there is a numerical error in the median OS for placebo on the June 2014 data cut-off: *Median (95% confidence interval) overall survival was [redacted] for enzalutamide and [redacted] for placebo*	Please update the sentence with the correct HR value and adding the term "months": *Median (95% confidence interval) overall survival was [redacted] **months** for enzalutamide and [redacted] **months** for placebo*	Incorrect value presented. Median OS for placebo in the June 2014 data cut off is [redacted] months therefore, when rounding is applied it becomes [redacted] rather than [redacted].	It is the ERG's opinion the difference is minimal and does not affect transparency of results. The proposed revision is not accepted.

Issue 13 Inaccurate information regarding 2nd and 3rd line treatments in PREVAIL

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
PREVAIL protocol did not provide any recommendations regarding second or third line treatment. The treatment received after study drug discontinuation was decided by the investigator. Thus the following sentence on page 40 is not really true: *According to the trial protocol, this third line treatment should not be enzalutamide if they received it pre-docetaxel.*	Please remove the sentence.	The protocol does not forbid the use of enzalutamide post docetaxel if it has been used pre-chemo.	The ERG accepts this change.

Issue 14 Incorrect HR for unadjusted OS in PREVAIL

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect value in Table 8, on page 41 of the ERG report. The ERG report states the value [redacted] under the results for the unadjusted OS, 30 June 2014.	Please replace the value by: [redacted]	The lower end of the confidence interval is incorrect.	The ERG have used the same values given on page 94 of the company submission, therefore, the proposed revision is not accepted.

Issue 15 Lack of clarity regarding rPFS definitions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 43, the ERG states: *The company were unclear in their definitions of rPFS in relation to the differences between central review and investigator assessed*	The manufacturer would like the statement to be deleted	The manufacturer provided the definitions of central- and investigator-assessed rPFS in the response to the ERG clarification request. Assessment of PFS by a central radiologist as well as by the investigator is characteristic of oncology studies. Definition of rPFS was the same in both cases (centrally- and investigator-assessed). Irrespective of the central radiologist or the investigator assessing the rPFS this assessment was to be based on the RECIST 1.1 for soft tissue disease and the PCWG2 guidelines for bone disease. Accordingly, centrally-assessed and investigator-assessed rPFS at the May 2013 cut-off (central review: 0.186 [0.149, 0.231]; investigator: 0.219 [0.176, 0.273]; Table B16 in the CS) were comparable highlighting the fact that the same definition was used in both cases.	The ERG remain uncertain of the company definitions following clarification, therefore, the proposed revision is not accepted.

		The manufacturer would also like to highlight that: - The central review was only conducted (as per protocol) for the first 410 events - The investigator assessed all progression events including the first 410.	

Issue 16 Ambiguous sentence regarding SREs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 44, the manufacturer would like the following sentence to be expanded to avoid misunderstanding: *The majority of SREs experienced were radiation to the bone (65.1% enzalutamide and 67.3% placebo).*	Please update the sentence with the following text: *The majority of SREs experienced were radiation to the bone (65.1% **of all SREs with** enzalutamide and 67.3% **of all SREs with** placebo).*	The sentence can be interpreted as >65% of patients in PREVAIL experiencing radiation to bone when in fact, this proportion was much lower ([redacted]% and [redacted]%, respectively [Table B17 in the CS]). The 65.1% and 67.3% values relate to the proportion of SREs that were radiation to bone (Table B17 in the CS).	The ERG believes this text does not pose any problem in terms of appropriateness or transparency. The proposed revision is not accepted.

Issue 17 Incorrect number of patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 44, there is a numerical error in table 10 for Time to initiation of cytotoxic chemotherapy for placebo. The number of placebo patients initiating cytotoxic chemotherapy (n=5151) is incorrect	Please correct the number; the right number of patients is ***515***	There is a numerical error. The "n" should be 515 rather than 5151.	The ERG accepts this change.

Issue 18 Redundant word

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 44, the term "was" is redundant and should be removed from the following sentence to improve clarity: The objective response rate was defined as proportion of patients with complete or partial response as best tumour response was statistically significantly higher with enzalutamide (58.8%) compared with placebo (5.0%), p <0.0001.	Please delete "was" so that the sentence reads as follows: *The objective response rate defined as proportion of patients with complete or partial response as best tumour response was statistically significantly higher with enzalutamide (58.8%) compared with placebo (5.0%), p <0.0001.*	The term "was" is redundant and it has a negative impact on the flow of the sentence.	This comment refers to a matter of English style and is not a factual error. The proposed revision is not accepted.

Issue 19 Typo

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 46 there is a typo in the following sentence: The BPI-SF was used to assess several pain-related outcomes. Pain progression was assessed using the worst pain (item number 3 of BPI), the pain severity composite score and the pain preference composite score.	Please update the sentence with the following one: *The BPI-SF was used to assess several pain-related outcomes. Pain progression was assessed using the worst pain (item number 3 of BPI), the pain severity composite score and the pain **interference** composite score.*	Typo.	The proposed revision is accepted

Issue 20 Incorrect caption in Table 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect heading in Table 12 on page 47. The ERG report states: *Adjusted LS mean (SE)*	Please replace the heading by: *Adjusted LS mean (**95% CI**)*	The values in the table seem to be 95% CI and not SE.	The proposed revision is accepted.

Issue 21 Numerical error in Table 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect values in Table 12 on page 47. The ERG report states the following values for the change in pain interference:	Please replace these values by: *Enzalutamide: 0.58 (0.3**7**, 0.**79**);* *Treatment difference: -0.41 (-0.6**2**, -0.**20**)*	The confidence interval values are incorrect.	The ERG's opinion is that these are rounding errors and differences are minimal. The proposed revision is not accepted.

Enzalutamide: 0.58 (0.36, 0.80); Treatment difference: -0.41 (-0.63, -0.19)			

Issue 22 Legend of Table 14 is incomplete

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Table 14 (page 50), part of the legend is missing	Please add the following to the legend: ***Events more common with enzalutamide vs placebo after adjusting for duration of treatment are shown in bold font.***	The new legend eases the understanding of the table.	This is not a factual error. The proposed revision is not accepted.

Issue 23 Legend of Table 15 is incomplete

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Table 15 (page 51), part of the legend is missing	Please add the following to the legend: ***Events with at least a 0.5% absolute increased incidence with enzalutamide vs placebo are shown in bold font.***	The new legend eases the understanding of the table.	This is not a factual error. The proposed revision is not accepted.

Issue 24 Missing significant AEs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 52, one of the AEs listed is not significantly different while one of the AEs which is significantly different is missing in the following sentence:	Please update the sentence with the following one: *There was a significantly higher incidence in the enzalutamide group compared to placebo*	One of the mentioned AEs (oedema peripheral) is not significantly more frequently reported with enzalutamide while one of the AEs (asthenia) which is more commonly	The ERG accepts this change.

There was a significantly higher incidence in the enzalutamide group compared to placebo for the following adverse events related to study medication: constipation, fatigue, oedema peripheral, pain in extremity, dysgeusia, headache, psychiatric disorders, dyspnoea, dry skin, hot flush, hypertension and flushing (Table B38, company submission).	*for the following adverse events related to study medication: constipation, fatigue,* ***asthenia****, pain in extremity, dysgeusia, headache, psychiatric disorders, dyspnoea, dry skin, hot flush, hypertension and flushing (Table B38, company submission).*	reported was missing.	

Issue 25 Missing data cut-off

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 52, given that the OS reported in the sentence is not the latest cut-off, the date of the cut-off should be mentioned. The related sentence is: *It has already been reported that enzalutamide was associated with a significant improvement in survival with a 29% decrease in the risk of death (HR = 0.706, 95% CI [0.596, 0.837]).*	Please update the sentence with the following one: *It has already been reported that enzalutamide was associated with a significant improvement in survival with a 29% decrease in the risk of death (HR = 0.706, 95% CI [0.596, 0.837])* ***in the September cut-off****.*	Given that the OS data differ across data cut-offs, it will clarity if the date of the cut-off is mentioned.	The ERG believe this text does not pose any problem in terms of appropriateness or transparency. The proposed revision is not accepted.

Issue 26 Incorrect rates for patients dying due to disease progression

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 52, the rates in the following sentence are incorrect: *A lower proportion of patients died due to disease progression in the enzalutamide arm (27.6) than the placebo arm (35.4) with RR (95% CI) = 0.78 (0.66, 0.93).*	Please update the sentence with the following one: *A lower proportion of patients died due to disease progression in the enzalutamide arm (**21.0**%) than the placebo arm (**26.9**%) with RR (95% CI) = 0.78 (0.66, 0.93).*	The rates mentioned in the sentence correspond to those for all deaths rather than the percentage of patients dying due to disease progression. These values were also incorrect in the initial CS but were corrected in the revised CS.	The proposed revision is accepted.

Issue 27 Typo

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 53, there is a typo in the term "*cauda equine syndrome*"	Please update the term with the following one: *"cauda equin**a** syndrome"*	Typo	The ERG believes this text does not pose any problem in terms of appropriateness or transparency. The proposed revision is not accepted.

Issue 28 Unclear sentence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 53, in the following sentence it should be clarified that the percentages provided for	Please update the sentence with the following one:	The sentence is inaccurate because the stated percentages relate only to the control arm.	The proposed revision is accepted.

PREVAIL relate only to the control arm: *The two trials were similar in terms of the patient population except all patients in COU-AA-302 were on a corticosteroid (100% in COU-AA-302, 30.2% in PREVAIL (but only 4% at baseline)).*	*The two trials were similar in terms of the patient population except* ***for the proportion of*** *patients on a corticosteroid* ***in the control arm*** *(100% in COU-AA-302, 30.2% in PREVAIL (but only 4% at baseline)).*		

Issue 29 Incorrect proportion of patients with ECOG 1 in COU-AA-302

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 54, there is an error in the following sentence: *Both studies recruit patients of ECOG = 0 or ECOG = 1 only, but PREVAIL had a higher proportion with ECOG = 1 (31.9% versus 24.5% in COU-AA-302). The baseline characteristics of men in both trials are presented in Table 16.*	Please update the % of patients with ECOG 1 in COU-AA-302 with the following: Both studies recruit patients of ECOG = 0 or ECOG = 1 only, *but PREVAIL had a higher proportion with ECOG = 1 (31.9% versus 24.**4**% in COU-AA-302). The baseline characteristics of men in both trials are presented in Table 16.*	The proportion of patients with ECOG 1 in COU-AA-302 is 24.4% rather than 24.5%.	The ERG believes this difference is minimal, therefore the proposed revision is not accepted.

Issue 30 Misleading sentence regarding rPFS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 54, the following sentence should modified as the	Please update the sentence with the following one:	The provided information is misleading as it suggests that only	This is not a factual error. The proposed revision is not

rPFS included in the ITC was investigator-assessed in both, PREVAIL and COU-AA-302 studies: *Data for PREVAIL for rPFS was investigator assessed rather than central review.*	*Data for PREVAIL **and COU-AA-302** for rPFS was investigator assessed rather than central review.*	the PREVAIL PFS included in the ITC was investigator-assessed. The value for COU-AA-302 PFS in the ITC also relates to investigator-assessed rPFS.	accepted.

Issue 31 Lack of consistency in the number of decimals

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 54, the OR and the lower 95% CI limit for best overall response (complete or partial response) are provided with two decimals whereas the highest limit has only one decimal. The sentence is: *Odds of best overall response (complete or partial) was higher for enzalutamide than abiraterone (OR = [redacted]).*	Please add the second decimal: *Odds of best overall response (complete or partial) was higher for enzalutamide than abiraterone (OR = [redacted]).*	Given that the other values are given as two decimals, the second decimal for the upper bound of the 95% CI should be added as well for consistency.	The ERG believes this difference is minimal, therefore, the proposed revision is not accepted.

Issue 32 Typo

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 57, there is typo in the	Please correct the typo with:	Typo.	The ERG believes this text does

table cell: "Time to OSA progression"	*Time to **PSA** progression*		not pose any problem in terms of appropriateness or transparency. The proposed revision is not accepted.

Issue 33 Cut-off for TTD

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 114 the ERG describes its preference for the September 2013 data cut-off due to this being before unblinding. As a result of this the ERG preferred scenario uses September 2013 TTD curves. The ERG also includes a scenario using September 2013 for OS. The ERG however does not mention that the cut-off for abiraterone (IA3) is also post-unblinding.	The manufacturer would like the ERG to add the following caveat to all the scenarios using the September 2013 cut-off: "It should be noted that this scenario should be interpreted with caution as it compares pre-unblinding (enzalutamide, BSC) data with post-unblinding data (abiraterone)."	Although the manufacturer prefers the most mature data, the ERG has a preference for pre-unblinding data. When pre-unblinding data is used in the analysis consistency is preferred between treatment arms.	Not a factual error.

Issue 34 Inaccurate statements regarding the use of the indirect vs a naïve comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 58 the ERG states: *"The ERG accepts that the treatment in the control groups are different, but it is by no means clear that completely*	The manufacturer requests for these statements to be removed.	In the original submission Astellas presented a scenario (scenario 6) using an adjusted indirect comparison for Abiraterone OS. It is thus an incorrect statement to	Not a factual error. No revision required.

ignoring the indirect results in favour of a naïve single group comparison of the active treatment arms of the two trials will give more accurate results." On page 8 the ERG states: "*It is not clear that the naïve indirect comparison with abiraterone would provide a sound base for the cost effectiveness estimates."* On page 142 a similar statement is made: "*The naïve comparison with abiraterone also increases the uncertainty around the cost effectiveness estimates for this comparison."*		mention that the results were "completely ignored". The adjusted indirect comparison showed enzalutamide being dominant over Abiraterone. Combining the results from the two alternative options (base case and the adjusted indirect comparison) provides confidence in the range of possible cost effectiveness estimates. The uncertainty mentioned by the ERG is thus not justified.	

Issue 35 Incomplete information regarding rPFS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 59, in the following sentence the manufacturer would like to highlight that investigator-assessed rather than the centrally-assessed rPFS was also used in the chemo-naïve abiraterone submission to NICE.	The manufacturer would like the following to be added: *However the ERG are not clear why central review was not used for all events, and what impact that may have had on the numbers defined as progressed/not progressed.* ***To note,***	As stated in Ryan et al 2014, the initial 378 progression events in COU-AA-302 were assessed by a central radiologist. From thereafter, events were assessed exclusively by the investigator	This is not a factual error. The ERG remains confused as to why the central review was not used for all events. The proposed revision is not accepted.

However the ERG are not clear why central review was not used for all events, and what impact that may have had on the numbers defined as progressed/not progressed.	***rPFS in COU-AA-302 was also centrally assessed for the first 378 events while any events taking place thereafter were assessed exclusively by the investigator.***		

Issue 36 Data should be AIC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 60, data in Table 19 should be AIC.	Please highlight and underline all data in Table 19 as they are AIC.	The data are AIC and should be marked as such.	The proposed revision is correct and is accepted for this issue

Issue 37 Legend missing from Table 20

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
For the indirect treatment comparisons presented in Table 20 (page 60), more comparable rPFS cut-offs should be used for enzalutamide and abiraterone to reduce the methodological differences which can bias the results. In addition, a legend should be added explaining what assumptions have been taken for	The comparative central review PFS should be recalculated with the correct values for COU-AA-302. Centrally-assessed rPFS is provided in Ryan et al 2014	Assessment of rPFS was comparable between PREVAIL and COU-AA-302. In both cases, rPFS was assessed by a central radiologic review up to the first interim analysis and by the investigator throughout the study. In the case of PREVAIL, the protocol stated that "radiographic disease progression was evaluated by independent central radiology	The ERG believes this text represents the data as presented in the company submission and does not pose any problem in terms of appropriateness or transparency. The proposed revision is not accepted.

abiraterone.		review until at least the first 410 rPFS events were confirmed centrally by independent review". In the case of COU-AA-302 the independent radiology review was applied to the first 378 events. Although for abiraterone, only the results of third interim analysis for rPFS are provided in the CS (Table B30), three rPFS cut-offs have been published for COU-AA-302. The manufacturer believes that at least for central reviewed rPFS, the ITC should be conducted using the central-reviewed rPFS for enzalutamide and abiraterone. This would reduce the methodological differences associated with using different assessor (central vs investigator) and number of events (439 in PREVAIL vs 644 in the COU-AA-302 IA3) for the comparison. In addition a legend explaining the limitations of the ITC presented in Table 20 should be provided as the abiraterone rPFS currently used for	

		all ITCs is that of IA3 (investigator-assessed PFS after 644 events). This definition is only comparable to that for sensitivity analysis number 6 in the table.	

Issue 38 Typo and inaccurate wording

Description of problem	Description of proposed amendment	Justification for amendment	ERG respose
On page 61, there is a typo in first bullet point: • *significantly longer overall survival despite a higher proportion of placebo patients being able to switch to other therapies will survival benefit*	Please update the first bullet point with the following: • *significantly longer overall survival despite a higher proportion of placebo patients* ***switching*** *to other therapies* ***with*** *survival benefit*	There was a typo in the sentence. In addition, given that the next-line of treatment was not specified in PREVAIL, placebo and enzalutamide patients were equally "able" to switch to treatments with a survival benefit, depending on the investigators discretion. Thus, the sentence should be modified.	The ERG believes this text does not pose any problem in terms of appropriateness or transparency. The proposed revision is not accepted.

Issue 39 Incorrect 5-year survival rate

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect value. On page 73, the ERG report states: *Firstly, the placebo and*	Please replace the sentence by: *Firstly, the placebo and enzalutamide gamma OS curves cross before the year 5 point, with 5*	The value [redacted]% is incorrect. The correct value was provided in the erratum and in the updated submission dated 10MAR2015.	The ERG accepts the proposed revision.

enzalutamide gamma OS curves cross before the year 5 point, with 5 year survival rates of [redacted]% in the placebo arm and [redacted]% in the enzalutamide arm.	*year survival rates of [redacted]% in the placebo arm and [redacted]% in the enzalutamide arm.*		

Issue 40 Inaccuracy regarding 2nd and 3rd line treatments recommendations in PREVAIL

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
PREVAIL protocol did not provide any recommendations regarding second or third line treatment. The treatment received after study drug discontinuation was decided by the investigator. Thus the following sentence on page 77 is not entirely correct: *This is based upon PREVAIL data from the BSC arm: of the 844 who ceased 1st line therapy or switched to enzalutamide, 713 went on to receive a 2nd line antineoplastic therapy though among these due to trial design only 410 received docetaxel.*	Please remove the wording "due to trial design" and replace the sentence by: *This is based upon PREVAIL data from the BSC arm: of the 844 who ceased 1st line therapy or switched to enzalutamide, 713 went on to receive a 2nd line antineoplastic therapy though among these only 410 received docetaxel.*	The trial design have not imposed any restrictions on the 2nd line treatment patients were offered. This was the decision of the investigators of the trial.	The ERG believes this text does not pose any problem in terms of appropriateness or transparency. The proposed revision is not accepted.

Issue 41 Typo

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Typo in the following sentence on page 77: *But within the BSC arm those, 80.9% of those ceasing treatment for reasons other than death move on to receive 3rd line enzalutamide.*	Please remove the word "those" and replace the sentence by: *But within the BSC arm, 80.9% of those ceasing treatment for reasons other than death move on to receive 3rd line enzalutamide.*	To improve clarity	This is not a factual error. The proposed revision is not accepted.

Issue 42 Inaccurate information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states on page 77: "*For 3rd line enzalutamide and abiraterone the median number of administrations of 8.3 and 7.4, as reported in Scher et al and Fizazi et al respectively, coupled with these being monthly or 4.3 weeks apart suggests median treatment durations of 36.0 weeks and 32.1 weeks.* " This is incorrect	Please replace the sentence with the following one: "*For 3rd line enzalutamide and abiraterone the median treatment duration of 8.3 and 7.4 months, as reported in Scher et al. and Fizazi et al. respectively suggests median treatment durations of 36.0 weeks and 32.1 weeks.*"	The stated numbers (8.3 or 7.4) are the median treatment duration in months, not the median number of administrations. Enzalutamide and abiraterone are administered daily.	The ERG accepts the proposed revision.

Issue 43 Potential use of utilities from Wolff and Diels in the stable disease state

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG argues on page 65 that Wolff et al and Diels et al might provide quality of life estimates for the stable disease health state. However, the estimates from these studies may not be representative as they included much broader population than PREVAIL.	The manufacturer suggests to add a note on page 65 explaining that: *"The Wolff and Diels papers did not exclude patients with symptomatic disease, whereas this was an exclusion criterion from PREVAIL. As symptomatic disease decreases quality of life, the estimates from these studies may not be suitable for the stable disease health state."*	PREVAIL only included patients with asymptomatic or mildly symptomatic disease (i.e., < 4 on BPI question 3), and this restriction is also present in the label indication. This restriction was not applied in the Wolff or Diels study. As symptomatic disease (i.e. pain) will have a big impact on quality of life, the estimates from these studies may not be appropriate for the stable disease health state of the model.	Not a factual error. The ERG mainly argues that the Diels et al and Wolff et al references provide information that may help assess the changes in utility associated with progressing through the disease from a single source, rather than picking values for the different health states from a range of disparate sources.

Issue 44 Incorrect net treatment benefit on EQ-5D for enzalutamide

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect value. On page 81, the ERG report states: *This resulted in a treatment effect estimate of a gain of 0.021 from enzalutamide over placebo.*	Please replace the sentence by: *This resulted in a treatment effect estimate of a gain of 0.022 from enzalutamide over placebo.*	Incorrect value	The ERG accepts the proposed revision.

Issue 45 Unclear sentence and incorrect value

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Wording is confusing and one value incorrect. On page 81, the ERG report states: *Patients in the enzalutamide arm who had not discontinued and progressed to 2nd line had the mean baseline quality of life of 0.844 plus the treatment effect of 0.021, resulting in a quality of life of 0.866.*	Please replace the sentence by: *Patients in the enzalutamide arm who had not discontinued and* ***had not*** *progressed to 2nd line had the mean baseline quality of life of 0.844 plus the treatment effect of 0.02**2**, resulting in a quality of life of 0.866.*	To improve clarity and correct the treatment effect value.	The ERG accepts the proposed revision to the treatment effect of 0.21 to 0.22 but rejects the other proposed changes.

Issue 46 Inaccurate sentence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 94 the ERG states on the scenario using the PPRS percentage: "*Note that this scenario analysis also applies this discount to the cost of abiraterone, though not to the costs of any other drugs within the modelling.*" This is not fully correct	The manufacturer proposes to remove the note	The discount was applied to the cost of enzalutamide, abiraterone, as well as all other drug costs (i.e. docetaxel and concomitant medication).	The ERG accepts the proposed revision.

Issue 47 Incorrect statement on 5-year survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 100, the ERG report states: *For the percentage modelled as surviving at 5 years in the BSC arm the company and ERG modelling suggests [redacted]%, while the extrapolation report suggests [redacted]%. The reason for this discrepancy is unclear, and there is no means of further examining the values given in the extrapolation report.*	Please remove the sentence.	This statement is incorrect. Erratum 4 explains that the percentages of patients alive at 5 and 10 years corresponding to the 30JUN2014 data cut-off using the IPCW analysis from the extrapolation report (Table 19 Estimated percentages of patients alive at 5 and 10 years – IPCW analysis) were incorrect for the placebo arm. The correct values are provided in the erratum and the percentages of patients alive at 5 years corresponding to the 30JUN2014 data cut-off is [redacted]%.	The ERG accepts that a revision is required. The following sentence should be appended to the sentence on page 100 of the ERG report. A company erratum revised the [redacted] value to [redacted]%

Issue 48 Incorrect statement regarding clinical effectiveness inputs in the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 101 the ERG argues that the values of Table B37 of the clinical effectiveness do not cross check with the values of Table B62 of the economics and the electronic model. The ERG provides "arthralgia or fatigue" as	The manufacturer proposes to remove the section and to specify that the rates do cross-check.	As described in 7.3.1.6, the model incorporated the most commonly occurring AEs with a severity ≥ grade 3 and an incidence ≥2%. As arthralgia and fatigue both have an incidence <2% they were not included as per the methodology.	Not a factual error. No revision required

examples. However, the ERGs statement is incorrect.			

Issue 49 Statement on cost-effectiveness to be removed

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 105, the ERG states that "The implied cost effectiveness of 3rd line treatment relative to palliative care is £210k per QALY in the BSC arm and £214k per QALY in the enzalutamide arm". This assessment of "cost-effectiveness" is based on comparison of the annual costs and annual QALYs accrued in the subsequent, rather than parallel health states of 3rd-line treatment and palliative care. As this analysis does not represent the cost-effectiveness of 3rd-line treatment **versus** palliative care, it is factually inaccurate to ascribe the title of "implied cost-effectiveness to this analysis. Analysis of this type is repeated several times in this section.	The manufacturer proposes that all references to the implied cost-effectiveness of enzalutamide post-chemo are removed.	As the analysis described by the ERG is a comparison of costs and QALYs in subsequent health states, all reference to "cost-effectiveness" should be removed and the analysis more accurately described as assessing the impact on costs and QALYs of changes in the patient flow through the model.	Not a factual error. No revision required

Issue 50 Statement to be removed

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 119, the ERG states the following: "*If the current company model had been consistent with that which it supplied for TA316, the cost effectiveness estimate for enzalutamide compared to BSC of the current submission would be worse*". No evidence of inconsistency between the current model and the post-chemo model have been presented to justify this statement.	Remove statement	The ERG has correctly ascertained that changes in the flow of patients in the model does not impact overall survival. Furthermore, the ERG has assessed the impact of changes in the patient flow through the model on costs and QALYs. However, these assessments do not provide evidence of inconsistency between the current model and the post-chemo model. Furthermore, the life years gained for patients in the Enzalutamide arm of the post-chemo model ([redacted] [discounted], [redacted] [undiscounted], provided in the manufacturer's response to clarification questions) are remarkably consistent with the life years gained across the 3rd-line treatment and palliative care health states of the BSC arm of the current model ([redacted] [discounted], [redacted] [undiscounted], calculated in the 'Calculations WW' sheet of the model as SUMPRODUCT(H10:H555,$AF$10:$AF$555,$AE$10:$AE$555)*cycle_length + SUMPRODUCT(I10:I555,$AF$10:$AF$555,$AE$10:$AE$555)*cycle_length and SUMPRODUCT(H10:H555,$AF$10:$AF$555)*cycle_length + SUMPRODUCT(I10:I555,$AF$10:$AF$555)*cycle_length, respectively. Some discrepancy is to be expected, as these are not entirely comparable patient populations and the data from PREVAIL includes patients receiving treatments other than enzalutamide.	Not a factual error. No revision required. In the opinion of the ERG the statements are correct, based upon the information supplied within the ERG report that the company objects to under issue 49.

Issue 51 Incorrect QoL value

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect value. On page 125, the ERG report states: *The quality of life for those in the enzalutamide arm who remain on 1st line treatment is assumed to be 0.022 better than that of those remaining on 1st line treatment in the BSC arm, resulting in a quality of life value of 0.864.*	Please replace the sentence by: *The quality of life for those in the enzalutamide arm who remain on 1st line treatment is assumed to be 0.022 better than that of those remaining on 1st line treatment in the BSC arm, resulting in a quality of life value of 0.866.*	Incorrect value	The ERG accepts the proposed revision.

Issue 52 Incorrect QoL value

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect value. On page 125, the ERG report states: *This suggests that the quality of life losses relative to baseline should be applied to the mean baseline quality of life value of 0.864 for those who remain on 1st line treatment, resulting in quality of life values of 0.780 in the BSC arm and 0.802 in the enzalutamide arm.*	Please replace the sentence by: *This suggests that the quality of life losses relative to baseline should be applied to the mean baseline quality of life value of 0.844 for those who remain on 1st line treatment, resulting in quality of life values of 0.780 in the BSC arm and 0.802 in the enzalutamide arm.*	Baseline value is incorrect.	The ERG accepts the proposed revision.

Issue 53 Incorrect ERG implementation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG implemented the costs for LHRH analogues within the Input_Parameters worksheet by adding £16 to cells F49:F58 (ERG Report page 131-132). This modification refers to the wrong cells and results in incorrect model results.	No change should be made to F54:58 in the model as the value for these cells is retrieved from F49:F53. This leads to double counting of the £16. The description of the scenario should be updated on page 131 and page 132, and all scenarios making use of this calculation need to be rerun.	Incorrect modification by the ERG. The additional £16 is added twice for 2nd and 3rd line treatments. As a result of this, all scenarios including the modification are incorrect.	The ERG accepts that the ERG implementation is incorrect. This has minimal impact upon results, revising the ex PAS ICERs from £113,047 per QALY to £112,878 per QALY for the comparison with BSC and £40,776 per QALY to £40,842 per QALY for the comparison with abiraterone

Issue 54 Statement on Gamma OS curves to be removed

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 120 and page 132 the ERG states that the Gamma OS curves used incorrect referencing. This is based on the ERG using a previous version of the model, and not taking the erratum into account.	The manufacturer proposes to leave out these comments.	The updated model, as well as an updated submission and an erratum have been provided to the ERG.	The ERG accepts that a revision is required to highlight that it is the originally submitted model that the ERG has revised and that the company subsequently revised this during the course of the assessment. Footnote dd should be revised to read Implemented within the Overall_survival worksheet by revising the referencing to cell

			BX96 within columns CD, CI, CN, CS and CX to refer to cells CC96, CH96, CM96, CR96 and CW96 respectively. Note that during the assessment the company also submitted a revised model that incorporated these changes.

Issue 55 Statement on 3rd line treatment to be removed

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 141 the ERG states: *"Whether those in the enzalutamide arm and the abiraterone arm would receive a 3rd line treatment after 2nd line docetaxel or would proceed straight to palliative care. The company assumes not, while the ERG assumes that all the treatment arms and not just the BSC arm would receive a 3rd line treatment after 2nd line docetaxel."*	The manufacturer would like the ERG to reconsider the statement.	There is uncertainty as to whether oncologists and physicians will administer post-chemo enzalutamide or abiraterone to patients who had received any of these two agents in the chemo-naïve setting. The manufacturer is of the opinion that treating doctors will be reluctant to use any of these two drugs if any of them have been given in the chemo-naïve setting because of potential cross-resistance. This has been confirmed by the experts consulted. Additionally a Specialised Services	Not a factual error. No revision required.

		Circular sent by NHS England to Area Teams in August 2014 stated that enzalutamide and abiraterone should not be routinely commissioned for sequential use.	

Issue 56 Statement on QoL to be modified

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 141 the ERG states: *What quality of life values should be applied. The company adds the net treatment effect to the PREVAIL baseline value, while the ERG subtracts the changes from baseline for each arm from the PREVAIL baseline value. The company also draws a variety of values from disparate sources, the company literature review of which is in the opinion of the ERG incomplete. The ERG applies values that suggest a smaller difference in quality of life between 1st line and 3rd line, drawing supporting evidence for this from the company PREVAIL and AFFIRM baseline EQ-5D values and from the Diels et al paper.*	The manufacturer would like the ERG to refine the statement as the literature values used by the ERG can be argued to be inappropriate as well	As already mentioned, some of the utility values suggested by the ERG would not be applicable to the model population. For baseline values, PREVAIL is the most appropriate source of quality of life. PREVAIL is the largest study conducted to date in asymptomatic or mildly symptomatic disease (i.e., < 4 on BPI question 3).	Not a factual error. No revision required.

Issue 57 Statement on differences in resource use to be removed

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 142 the ERG states: *Whether the resource use for 1st line treatments should be differentiated by arm to the extent suggested by the company. This has a particularly marked effect upon the comparison with abiraterone where routine monitoring visits are assumed to be twice as frequent as for enzalutamide.*	The manufacturer would like to ask this sentence to be removed.	The frequency of monitoring visits for abiraterone are based on the required monitoring schedule stated in the abiraterone SPC. The differences in the resource use across first line treatments are based on feedback received from 6 UK clinicians from different clinical practices. As already highlighted, patients on BSC (and thus not on treatments with the capacity to delay disease progression) will undergo frequent CT scans to detect early progression that would lead to initiation of chemotherapy (docetaxel).	Not a factual error. No revision required.