Single Technology Appraisal (STA)

Enzalutamide for the treatment of adult men with asymptomatic or mildly symptomatic metastatic hormone relapsed prostate cancer after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated

Section A: Clarification on effectiveness data

A1. PRIORITY Please clarify how the hazard ratios for overall survival (OS) presented in Table 32 (page 109) were calculated for 'IPCW ENZA vs ABI IA3' and 'IPCW ENZA vs ABI Final'.

The hazard ratios presented in Table B32 of the manufacturer submission have been obtained using a network meta-analysis based on a fixed effect model. We would like to clarify that the numbers in Table B32: IPCW ENZA OS vs ABI IA3: 0.79 [0.61, 1.03] and IPCW ENZA OS vs ABI FINAL: 0.78 [0.62, 0.99] are based on 16SEPT2013 data cut-off, rather than the 30 June cut-off. The correct results (based on the 30 June cut-off) are: IPCW ENZA OS vs ABI IA3: 0.82 [0.65, 1.05]; IPCW ENZA OS vs ABI Final: 0.81 [0.66, 1.01].

Details on methodology (including assessment of heterogeneity and inconsistency) and raw data used in the model are provided in Appendix K of reference 46 (FINAL Report_SR and NMA of Enzalutamide (Feb 2015) v4.0) which we re-submit herein. The results can be found in section K.3.3 (page 125) for the 'IPCW ENZA vs ABI IA3' analysis and in section K.3.4 (page 129) for the 'IPCW ENZA vs ABI Final' analysis.

A2. PRIORITY In Table B35 the relative risks (RR) presented do not appear to match the data. For example, for fatigue 310/871 in ENZA versus 218/844 in Placebo gives RR = 1.38 not the 0.57 presented. The percentage occurrence is higher for all adverse events (AEs) in the enzalutamide group than placebo, yet all the RRs are < 1 indicating less likely. Please check the calculations of RR and 95% CI and present the correct results.

We acknowledge that indeed, the RR presented in the MS were incorrect. Please find the correct values in the corrected Table B35 below. It should be noted that this table is not used for the economic model, and thus has no impact on cost-effectiveness.

	Overall incidence, n (%)		
AE	**ENZA (N=871)**	**PLA (N=844)**	**RR [95% CI]**
Fatigue	310 (35.59%)	218 (25.83%)	1.38 [1.19; 1.59]
Back pain	235 (26.98%)	187 (22.16%)	1.22 [1.03; 1.44]

	Overall incidence, n (%)		
AE	**ENZA (N=871)**	**PLA (N=844)**	**RR [95% CI]**
Constipation	193 (22.16%)	145 (17.18%)	1.29 [1.06; 1.57]
Arthralgia	177 (20.32%)	135 (16.00%)	1.27 [1.04; 1.56]
Decreased appetite	158 (18.14%)	136 (16.11%)	1.13 [0.91; 1.39]
Diarrhoea	142 (16.30%)	119 (14.10%)	1.16 [0.92; 1.45]
Hot flush	157 (18.03%)	65 (7.70%)	2.34 [1.78; 3.08]
Asthenia	113 (12.97%)	67 (7.94%)	1.63 [1.23; 2.18]
Weight decreased	100 (11.48%)	71 (8.41%)	1.36 [1.02; 1.82]
Oedema peripheral	92 (10.56%)	69 (8.18%)	1.29 [0.96; 1.74]
Hypertension	117 (13.43%)	35 (4.15%)	3.24 [2.25; 4.67]
Headache	91 (10.45%)	59 (6.99%)	1.49 [1.09; 2.05]
Fall	101 (11.60%)	45 (5.33%)	2.17 [1.55; 3.05]
Dizziness	76 (8.73%)	53 (6.28%)	1.39 [0.99; 1.95]
Haematuria	73 (8.38%)	49 (5.81%)	1.44 [1.02; 2.05]
Insomnia	70 (8.04%)	47 (5.57%)	1.44 [1.01; 2.06]
Nasopharyngitis	62 (7.59%)	42 (4.98%)	1.52 [1.04; 2.23]
Dysgeusia	66 (7.58%)	31 (3.67%)	2.06 [1.36; 3.13]
Upper respiratory tract infection	53 (6.08%)	30 (3.55%)	1.71 [1.11; 2.65]

A3. PRIORITY Please present additional post-hoc sub-group analyses as follows:

A. Split by steroid use at baseline for OS and for radiographic progression-free survival (rPFS) data from PREVAIL; that is, the equivalent data presented for the steroid use sub-group as for the sub-groups in figures B4 and B6 of the submission.

B. For rPFS please present this separately for the rPFS primary analysis from central review definition and for the rPFS definition used for the comparison with abiraterone.

As presented in Table B8 (page 56) in the manufacturer submission, only 4% of patients in the PREVAIL study received steroid more than 7 days at baseline, 35/872 (4.0%) in the enzalutamide arm and 36/845 (4.3%) in the placebo arm. Therefore the requested analyses on OS and rPFS from such a small subgroup will be at best volatile and uninformative.

A4. PRIORITY Please provide the corollary of table B18: Time to initiation of cytotoxic chemotherapy for the 30 June 2014 data cut which has not been presented. Similarly, please provide the corollary of cells B8:E25 of the *Second_line_treatment* worksheet of the electronic model for the 30 June 2014 data cut..

The June 30th data cut is a post-hoc analysis which was performed solely for the purpose of the economic model. Unfortunately the requested information on time to initiation of cytotoxic chemotherapy is not available for this data cut. However, the data is available for the June 1st 2014 cut (corresponding to the final OS data cut) and is presented in the table below.

Time to initiation of cytotoxic chemotherapy – 1st June cut-off date

	ENZA (N=872)	**PLA (N=845)**
Initiation of cytotoxic chemotherapy status		
Events [1]	[redacted]	[redacted]
Docetaxel first	[redacted]	[redacted]
Cabazitaxel first	[redacted]	[redacted]
Other chemo first	[redacted]	[redacted]
Censored [2]	[redacted]	[redacted]
Time to initiation of cytotoxic chemotherapy (months) [2][3]		
Censored	[redacted]	[redacted]
25th percentile	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75th percentile	[redacted]	[redacted]
P-value (unstratified) [4]	[redacted]	
Hazard ratio (95% CI)[4]	[redacted]	
Median follow-up time based on reverse Kaplan-Meier estimates (months)	[redacted]	[redacted]

[1] Based on the initiation of cytotoxic chemotherapy. When multiple cytotoxic chemotherapies were initiated, the first chemotherapy is used to determine the time to event. Patients who inititated multiple cytotoxic chemotherapies on the same day can be counted in more than one category.
[2] Patients who did not start cytotoxic chemotherapy at the time of analysis data cut-off are censored at date of last assessment indicating no evidence of cytotoxic chemotherapy usage.
[3] Based on Kaplan-Meier estimates.
[4] P-value is based on an unstratified log-rank test. Hazard ratio is based on a Cox regression model (with treatment as the only covariate) and is relative to placebo with <1 favoring enzalutamide..

In response to the request for the corollary of cells B8:E25 of the *Second_line_treatment* worksheet of the electronic model for the 30 June 2014 data cut, we assume that the review group is requesting the data corresponding to 16 September 2013 as cells B8:E25 refer to the 30

June 2014. The Table below provides the data for cells B8:E25 of the Second_line_treatment worksheet of the electronic model corresponding to the 16 September 2013 data cut-off.

First post-baseline antineoplastic treatment received in PREVAIL. September 2013 data cut-off. ITT population

Treatment	enzalutamide	BSC	Total
Total	872	845	1,717
No. of patients who discontinued and did not switch	375	603	978
switchers	129	180	309
No. of patients who discontinued	504	783	1,287
Docetaxel	228	401	629
Hormonal treatments	11	16	27
Lutamide	14	45	59
Enzalutamide	1	0	1
Abiraterone	61	90	151
Cabazitaxel	14	22	36
Provenge	10	9	19
Investigational	28	43	71
Other chemotherapy for prostate cancer cytotoxic	14	14	28
Other chemotherapy for prostate cancer non- cytotoxic	1	2	3
total n	382	642	1,024
total %	43.8%	76.0%	59.6%
% of taking any post-baseline treatment out of those who discontinued	75.8%	82.0%	79.6%

A5. PRIORITY It is unclear whether tables B59 and B60 relate to the interim data cut (16 September 2013) or the final data cut (30 June 2014). Please clarify this, and present the corollaries of tables B59 and B60 for the data cut which has not been presented, coupled with three estimates of treatment emergent periods these relate to.

Table B59 (page 155) in the manufacturer submission, relate to the interim data cut (16 September 2013).

The data for the 30JUNE2014 is presented in table below.

Number and rates for SREs in PREVAIL (Stable Disease) – 30JUNE2014 data cut-off

	ENZA			PLA		
SREs	**n (events)**	**Pt years [1]**	**Rate**	**n (events)**	**Pt years [1]**	**Rate**
Spinal cord compression	44	[redacted]	[redacted]	22	[redacted]	[redacted]
Pathologic bone fractures	48	[redacted]	[redacted]	16	[redacted]	[redacted]
Radiation to bone	142	[redacted]	[redacted]	85	[redacted]	[redacted]
Surgery to bone	17	[redacted]	[redacted]	9	[redacted]	[redacted]
Total	251	[redacted]	[redacted]	132	[redacted]	[redacted]

[1] Patient-Years is calculated as the sum of each patient's length of on treatment period in days divided by 365.25.

It should be noted that Table B60 in the manufacturer submission does not present data from the PREVAIL study. The table presents the pooled SRE rates from AFFIRM and COU-AA-301 and thus does not refer to either of these data cuts. Pooled number of SREs and rates are presented in the Table. The treatment emergent period used for this analysis is 1,572.2 patient years, calculated as the sum of the patient years in AFFIRM (i.e., 768.8 patient years) and COU-AA-301 (i.e., 803.4).

A6. Please clarify whether patients in PREVAIL could remain on the study drug but also move onto, and concurrently receive, another anti-neoplastic drug (cytotoxic, hormonal and investigative treatments). If this was possible, for each arm of PREVAIL please present the number of patients this applied to for cytotoxic, hormonal and investigative treatments separately.

According to the protocol, patients were required to permanently discontinue treatment with study drug prior to the initiation of a cytotoxic chemotherapy or an investigational agent. The following were allowed during the treatment period after confirmed radiographic progression or skeletal-related event:

- Hormonal therapies including other antiandrogens and abiraterone acetate
- Biological antitumor treatments

In addition, hormonal treatment for treating complications of luteinizing hormone-releasing hormone treatment (eg, hot flashes) with medical monitor approval was allowed throughout the study.

The number of patients with concomitant hormonal, cytotoxic or investigational therapies are provided table below

Post-baseline concomitant antineoplastic therapy use

Concomitant therapy	Placebo (N=845)	Enzalutamide (N=872)
Abiraterone	5 (0.59%)	1 (0.11%)
Docetaxel	1 (0.12%)	0 (0.00%)
Hormonal treatments	5 (0.59%)	5 (0.57%)
Lutamide	13 (1.54%)	2 (0.23%)
Other chemo for prostate cancer non-cytotoxic	1 (0.12%)	0 (0.00%)
Provenge	5 (0.59%)	3 (0.34%)
Any concomitant therapy	27*	11

*It should be noted that three patients in the placebo arm used abiraterone and Provenge concomitantly prior to study drug discontinuation.

A7. Table B14 shows that 9 patients in the enzalutamide arm of the study received enzalutamide as a subsequent treatment. Please clarify if these patients had started first-line treatment with enzalutamide to which they were allocated.

The 9 patients taking enzalutamide as subsequent treatment had indeed been randomised to the enzalutamide arm. Seven of those 9 patients did first receive docetaxel-based chemotherapy upon discontinuation of enzalutamide, followed by re-treatment with enzalutamide upon discontinuation of docetaxel treatment. The other 2 patients did not have usage of chemotherapy documented but the re-treatment with enzalutamide did follow another therapy.

A8. Please clarify if the indirect comparison reported in Table B33 uses the standard Bucher method for adjustment and utilised data from Table B31.

The Bucher method was not used. Similar to the other reported outcomes, a network meta-analysis was performed, and the results in Table B33 correspond to a fixed effect model. Please note that section 6.7.5 only describes the methodology applied to survival outcomes (OS, rPFS, time to cytotoxic chemotherapy initiation and time to PSA progression). A different model was required for the binomial outcomes (best overall response: CR/PR and PD) and this is described in Appendix L (section 1 starting on page 146) of reference 46.

We confirm that the data used is the one presented in table B31 of the submission. The results of the network meta-analysis can be found in section L.4.3, in Table L.4.3 (page 152) for the “Complete and partial response” and in Table L.4.4 (page 154) for the “Progressive disease”.

A9. Please provide further details on the definitions of ‘investigator assessed rPFS’ and ‘independent central blinded review of rPFS’ in PREVAIL. Did each assessment use common protocols? If so, please provide details.

Radiographic disease progression comprised of 2 components: the soft tissue metastases (evaluated by CT or MRI scans) and the bone metastases (evaluated by radionuclide bone scans). The assessment schedule was at weeks 9, 17, 25, and then every 12 weeks thereafter.

Radiographic disease progression in bone (2 or more new lesions on radionuclide bone scan) observed at week 9 required 2 additional new lesions on a confirmatory scan at least 6 weeks later; radiographic disease progression in bone observed after week 9 required persistence of 2 new lesions on a confirmatory scan at least 6 weeks later. Radiographic disease progression in soft tissue did not require a confirmatory scan for purposes of analysis, although study sites were requested to obtain confirmatory soft tissue scans through week 13. Scheduled and confirmatory scans had a 1-week window for completion.

The definition of radiographic progression was clearly summarized in Table 1 in the synopsis and in Table 9.5.1.1.2-1 in the main body of all versions of the protocol, which were applicable to both the central review panel and the investigators.

The term "investigator assessed rPFS" refers to the radiographic Progression Free Survival based on the radiographic progression events as judged by the investigators.

The term "independent central blinded review of rPFS" refers to the radiographic progression free survival based on the radiographic progression events as judged by an independent group of reviewers. This group of independent reviewers consists of nuclear medicine physicians to assess the bone scans and radiologists to assess the CT/MRI scans. These reviewers had been appropriately trained to do the reading for the PREVAIL trial and followed a reading guideline as stated in the Independent Review Charter. No patient information nor treatment details were provided to these reviewers.

The outcomes of the reading from the investigators and the Independent central blinded review were highly consistent, as shown in Table 11-15 of the Clinical Study Report.

A10. In the network meta-analysis, investigator rPFS was used instead of the independent central blinded assessed rPFS. The only rationale for this seems to be: "Given that the analysis of the investigator assessed rPFS includes a higher number of events (N=889), this is the analysis used in the economic model." Please clarify the rationale for using investigator rPFS in the network meta-analysis and why a higher number of events made the outcome more useful for the economic analysis.

In PREVAIL centrally reviewed PFS was planned for the first 410 centrally reviewed events. The analysis for centrally reviewed PFS was performed at 06 May 2012, and included 439 events. Investigator assessed PFS on the other hand was evaluated for the entire duration of follow-up, and included 889 events at the data cut-off of 16 Sept 2013. As

investigator assessed PFS included 16 months more data, and as a result included more events, it was preferred for use in the network meta-analysis. It should be noted that for COU-AA-302 also the investigator assessed PFS was used, as this was the most mature PFS data available.

A11. The submission states that for TTD curves "*Proportionality of hazards, as assessed by loglog plots, was not met*". The data justifying this does not appear to have been presented. Please provide either the data summary underlying this assertion, or a more explicit reference to this within the references of the submission.

The validity of the proportionality of hazards assumption for TTD (for both data cut-off 16 September 2013 and 30 June 2014) is discussed in the extrapolation report (reference 81). Based on the results of the three statistical tests and visual examination of the log-cumulative hazard plots, the proportionality of hazards assumption does not hold for the TTD, irrespective of the data cut used. The log-cumulative hazard plots are provided below and in Appendix 1 of this reference, Figure A.1. 13 and Figure A.1. 15.

Figure A. 1 Log of negative log for TTD data-cutoff 16SEP2013 (ITT)

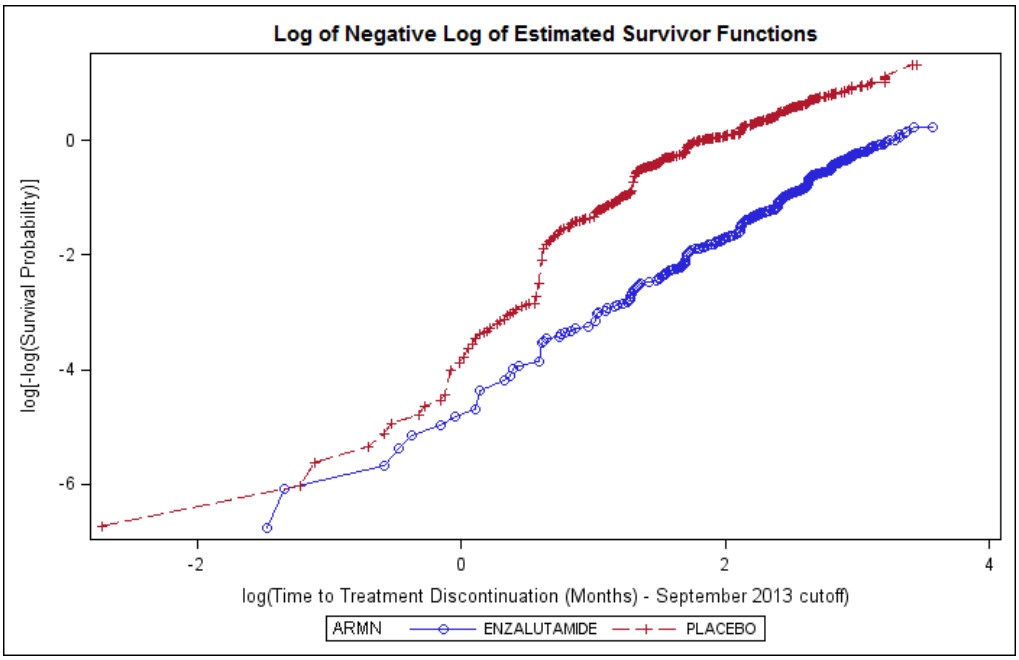
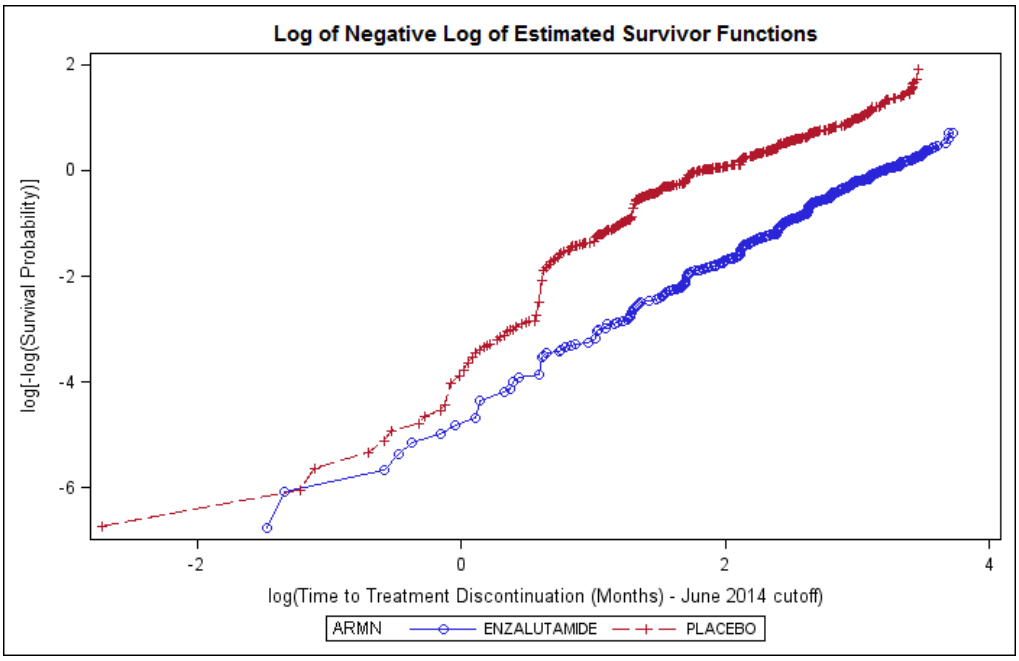


Figure A. 2 Log of negative log for TTD data- cutoff 30Jun2014 (ITT)



A12. A. Please present the patient distribution in terms of patient numbers by week, split by arm for the data underlying the 43.9 day estimate of the mean time to initiation of cytotoxic chemotherapy after study drug treatment discontinuation.

B. Please confirm which data cut was used to calculate the 43.9 day estimate and present the corollary of this data for the data cut which has not been presented.

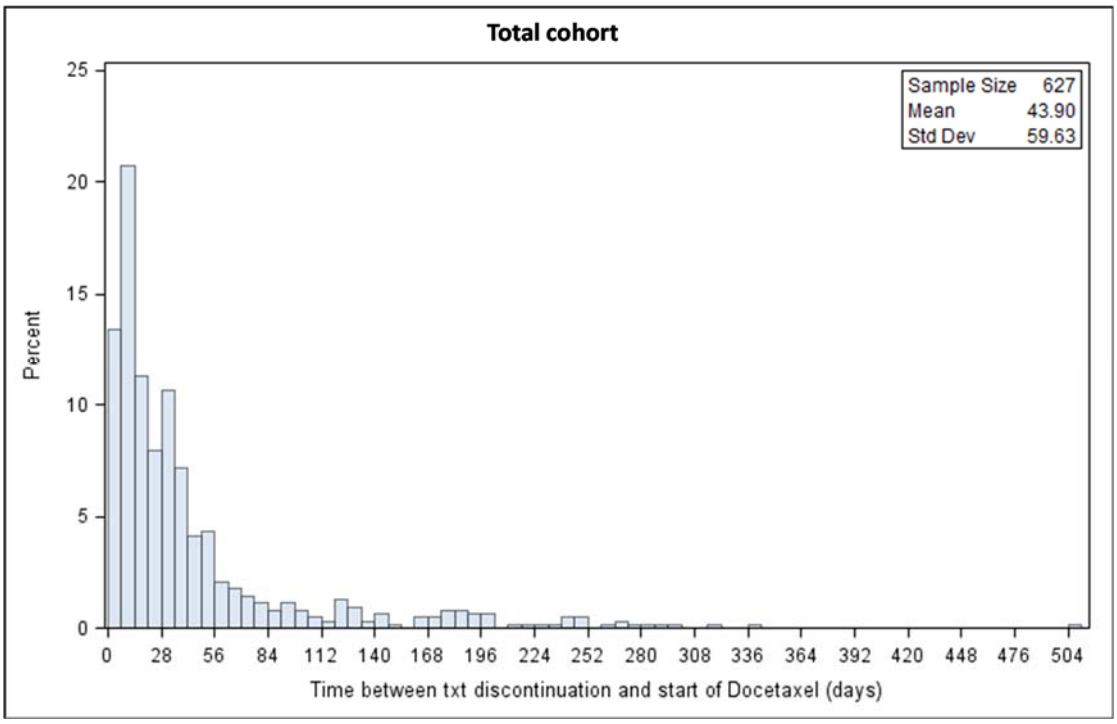
C. Please also present the corollary of this data for initiation of antineoplastic therapy.

To be concise, weeks after treatment discontinuation have been requested, but if the corollary of days after treatment discontinuation is simpler to present within an excel spreadsheet this is equally acceptable.

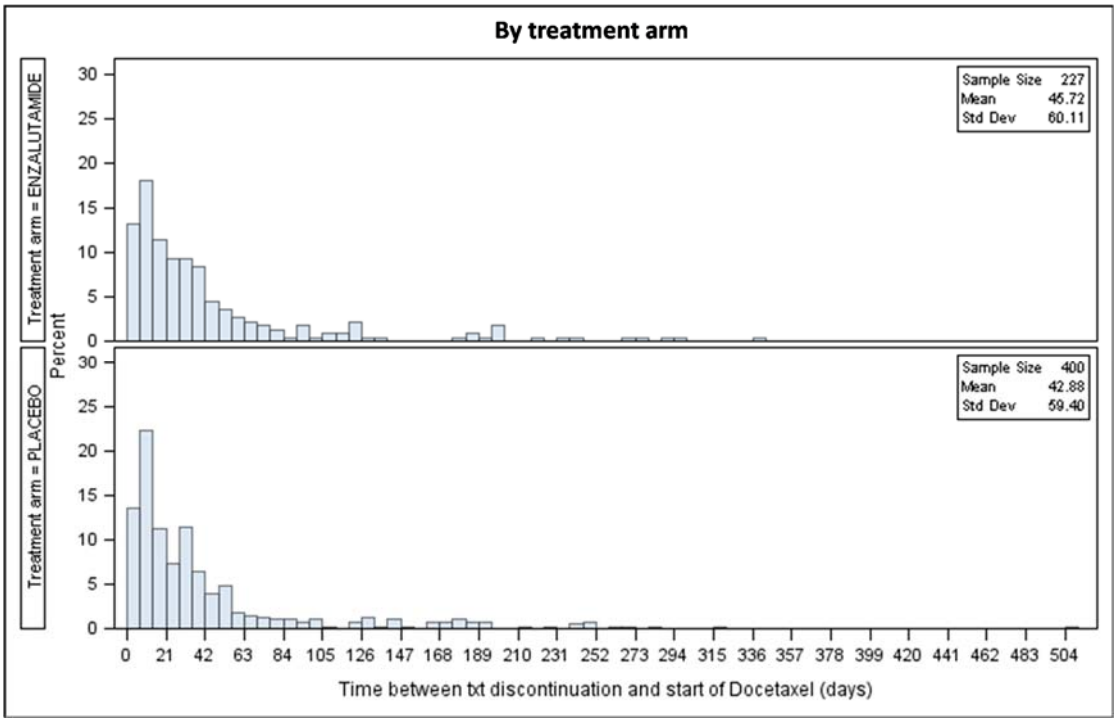
The 43.9 day estimate presented in the model (cell E40 in the *Second_line_treatment* worksheet of the electronic model) corresponds to the 16 September 2013 data-cut off. We would like to rectify that this value represents the mean time to initiation of docetaxel chemotherapy after study drug treatment discontinuation (overall cohort), and not the mean time to initiation of cytotoxic chemotherapy after study drug treatment discontinuation. The patient distribution underlying the 43.9 day estimate is presented in figure 1 below, for the overall cohort (A) and by treatment arm (B).

Figure 1 Distribution of time between study drug treatment discontinuation and start of docetaxel – 16Sept2013 cut-off

A



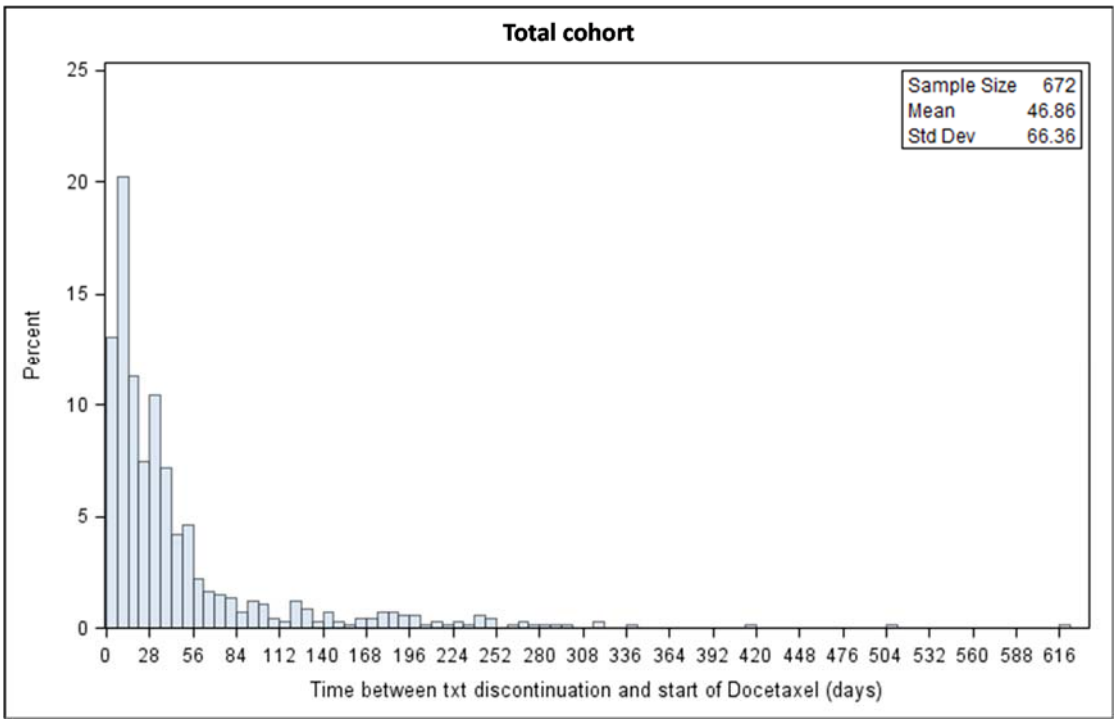
B



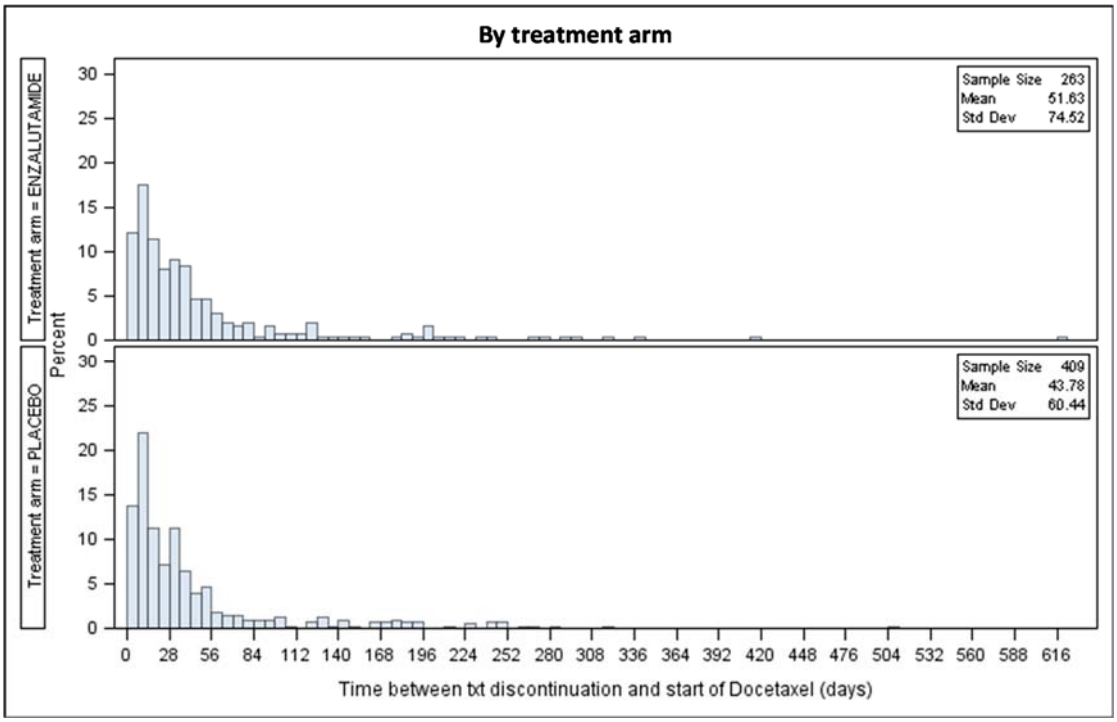
The patient distribution of time between study drug treatment discontinuation and start of docetaxel for the 30JUNE2014 data cut-off is presented in figure 2 below, for the overall cohort (A) and by treatment arm (B).

Figure 2 Distribution of time between study drug treatment discontinuation and start of docetaxel – 30JUNE2014 cut-off

A



B



For clarity, we also provide in the excel spreadsheet attached the number of patients by week, split by arm, for the following:

- Time between study treatment discontinuation and start of Docetaxel chemotherapy – 16 September 2013 cut-off
- Time between study treatment discontinuation and start of cytotoxic chemotherapy – 16 September 2013 cut-off
- Time between study treatment discontinuation and start of antineoplastic – 16 September 2013 cut-off
- Time between study treatment discontinuation and start of Docetaxel chemotherapy – 30 June 2014 cut-off
- Time between study treatment discontinuation and start of cytotoxic chemotherapy – 30 June 2014 cut-off
- Time between study treatment discontinuation and start of antineoplastic – 30 June 2014 cut-off

The number of patients on top of each treatment arm column represent the number of patients who discontinued study treatment. For all the analyses presented in the excel spreadsheet, the first antineoplastic treatment is considered (i.e. the second line treatment).

A13. Please clarify:

A. What events were treated as events and what were treated as censoring events within the Kaplan Meier curves that underlie the rPFS curves of the electronic model.

As a reminder, we would like to clarify that the rPFS curves used in the economic model correspond to the rPFS based on investigator assessment using the interim OS data cut-off date, i.e. 16 September 2013, and these curves have been used in scenario 7 only. The model base case uses the TTD curves, discussed in A13B.

rPFS survival was the time from randomisation to the first objective evidence of radiographic disease progression assessed by the investigator or death due to any cause within 168 days after treatment discontinuation, whichever was first. Radiographic disease progression included soft tissue disease progression and confirmed bone disease progression.

The censoring rules for the rPFS based on investigator assessment are the same as the primary analysis and are presented in the following table. If a patient met the criteria for more than one censoring rule, the patient was censored with the earliest censoring date.

Censoring rule	Date of censoring
Patients who have no baseline or no post-baseline assessments	Date of randomisation
Patients who have not progressed or died	Date of the last radiographic assessment showing no evidence of disease progression prior to the data cut-off date
Patients who have not progressed but died after 168 days following treatment discontinuation	Date of the last radiographic assessment prior to or on 168 days after treatment discontinuation
Patients whose tumour assessment scan modality changes temporarily or permanently prior to objective evidence of disease progression	Date of the last radiographic assessment showing no evidence of disease progression prior to temporary or permanent change of tumour assessment modality
Patients with bone PD events required to confirm per protocol, but not confirmed or with no documented confirmation scans for any reason	Date of last radiographic assessment without evidence of bone disease progression
Patients who have SREs prior to confirmatory scan for bone disease progression	Date of last bone radiographic assessment without evidence of bone disease progression prior to SRE
Patients who have radiation therapy prior to objective evidence of disease progression or prior to confirmatory scan for bone disease progression	Date of last soft tissue or bone radiographic assessment without evidence of soft tissue or bone disease progression prior to radiation therapy, respectively. If radiation therapy date is the same as SRE date, the patient will be censored for SRE only and this censoring rule will only apply to bone disease progression
Patients whose new antineoplastic treatment started before study treatment discontinuation and before objective evidence of disease progression or prior to confirmatory scan for bone disease progression	Date of last soft tissue or bone radiographic assessment without evidence of soft tissue or bone disease progression prior to initiation of new antineoplastic treatment
Patients with study treatment discontinuation prior to first evidence of disease progression	Date of last radiographic assessment without evidence of disease progression prior to treatment discontinuation
Patients with 2 or more consecutive missed tumour assessments	Date of last radiographic assessment without evidence of disease progression prior to missed tumour assessments

PD, progressive disease; SRE, skeletal-related event.

B. What events were treated as events and what were treated as censoring events within the Kaplan Meier curves that underlie the TTD curves of the electronic model.

Time to treatment discontinuation was the time from randomisation to the date of last dose of study medication or analysis data cut-off date of

30June2014, whichever was first. Patients not known to have discontinued the study treatment at the data analysis cut-off date were censored at the date of the data analysis cut-off of 30June2014.

Section B: Clarification on cost-effectiveness data

Quality of life

B1. PRIORITY Please submit the full utility report underlying the values of table B64. As a minimum, or if a utility report is not available:

A. Please provide a full set of coefficients for the predictors that were examined coupled with confidence intervals. These data should be presented for all the model forms that were explored and not just for the model form (mixed-effects model for repeated measures) that underlies the values of table B64, coupled with goodness of fit statistics suitable for distinguishing between the models.

B. Please also provide summary statistics by arm for all the predictors examined within the various models.

C. Please also provide an outline of the arithmetic that underlies the central estimates of table B64: for example the sumproduct of the mean values of the predictors and their coefficients.

What was the rationale for preferring the model form (mixed-effects model for repeated measures) that underlies the values of table B64 over the other models that were explored?

We would like to clarify that we have not examined multiple models for the on-treatment benefit analysis presented in table B64. We further would like to clarify that in addition to the pre-specified analyses in the protocol, a separate statistical analysis plan was developed prior to database lock for the analyses of the HRQoL outcomes in PREVAIL (Appendix I from reference 53 [Quintiles report for the analysis of PRO data collected in the PREVAIL study], which we supply herewith). To estimate longitudinal changes from baseline in HRQoL scores, the primary analysis used a mixed-effects model for repeated measures (MMRM), controlling for baseline covariates and a pattern-mixture model (PMM) with placebo-based pattern imputation was used in a sensitivity analysis. The primary hypothesis tested the difference between least square means at week 61 change from baseline.

The on-treatment utility benefit incorporated in the economic model slightly differs from the model defined in the pre-planned SAP in that we are looking at the treatment effect during the study (i.e. over all the visits).

For this analysis we have used the MMRM model only, given the similar results from the sensitivity analysis with PMM.

As requested, additional details on the MMRM model used to obtain the values in table B64 of the submission are provided below.

The outcome was change from baseline in utility value (CHG), and the predictors were:

- treatment (ARMN :enzalutamide or placebo),
- time (treated as a categorical variable, AVISITN: week 13, week 25, week 37, week 49, week 61 and week 73),
- baseline score (BASE: continuous),
- site (SITEIDGR: 80 levels),
- ECOG performance status at baseline (ECOGBLGR: 0 or 1),
- fatigue severity using question #3 of the Brief Fatigue Inventory (BFI) at baseline (FATSEVBL: < 7 or ≥ 7),
- pain at baseline (PAINBGRN: asymptomatic and symptomatic),
- age (AGEGR1N: < 65 or ≥ 65 years),
- time by treatment arm interaction, and
- time by baseline value interaction.

All predictors were included in the model, even if they were not statistically significant. As per the SAP, data from a limited number of visits was used in case of substantial dropout (i.e. analysis was limited to time points at which at least 10% of patients in each treatment group have non-missing data). This time point was week 73 for the EQ-5D data.

In scalar notation, the model estimate for an observed value y_{ij} can be written as follows:

$$
\begin{aligned}
y_{ij} = \beta_0 + \beta_b * x_b & \\
& + \sum_{t=1}^{2} \beta_t * x_t + \sum_{k=1}^{6} \beta_k * x_k \\
& + \sum_{s=1}^{80} \beta_s * x_s \\
& + \sum_{e=1}^{2} \beta_e * x_e \\
& + \sum_{f=1}^{2} \beta_f * x_f + \sum_{p=1}^{2} \beta_p * x_p + \sum_{a=1}^{2} \beta_a * x_a + \sum_{t=1}^{2} \sum_{k=1}^{6} \beta_{tk} * x_{tk} \\
& + \sum_{k=1}^{6} \beta_{bk} * x_k * x_b
\end{aligned}
$$

where β_0 is the intercept, x_b is the baseline value, x_t, x_k, x_s, x_e, x_f, x_p, x_a, x_{tk} are indicators for the 2 treatments, 6 visits, 80 sites, 2 ECOG, 2 fatigues severity, 2 pain, 2 age categories and 12 treatment x visit combinations

respectively, and β_t, β_k, β_s, β_e, β_f, β_a, and β_{tk} are the corresponding coefficients.

The analysis was conducted using PROC MIXED in SAS. The model assumed an unstructured covariance pattern of the repeated visits per patient. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

The summary statistics of the predictors used in the model on the patients included in the MMRM analysis are presented in table below.

Summary statistics of the predictors used in the MMRM model

	Statistic	**Placebo**	**Enzalutamide**
		(N=600)	**(N=805)**
Age group (yrs)			
Total non-missing	N	600	805
< 65	N (%)	122 (20.3%)	165 (20.5%)
>=65	N (%)	478 (79.7%)	640 (79.5%)
ECOG			
Total non-missing	N	600	805
0	N (%)	434 (72.3%)	552 (68.6%)
1	N (%)	166 (27.7%)	253 (31.4%)
Pain at baseline (a)			
Total non-missing	N	598	794
Asymptomatic	N (%)	418 (69.9%)	534 (67.3%)
Symptomatic	N (%)	180 (30.1%)	260 (32.7%)
Missing	N	2	11
Fatigue severity			
Total non-missing	N	587	779
< 7 in question #3 of the BFI	N (%)	552 (94.0%)	730 (93.7%)
>=7 in question #3 of the BFI	N (%)	35 (6.0%)	49 (6.3%)
Missing	N	13	26

The complete set of coefficients can be find in the SAS output which is provided as Appendix to this response document.

B2. PRIORITY Please submit the full utility report underlying the values of table B65 and explanations of the values within it on the same basis as question B1 above concerning table B64.

The impact of SREs on quality of life was included in the pre-planned SAP mentioned above. In summary, the SRE disutilities presented in table B65 are obtained using the following steps.

Step 1: Model each patient's longitudinal trajectory of the EQ-5D utility values over time before the SRE

All patients included in PREVAIL who were alive and experienced an SRE of any type (pathologic bone fracture, spinal cord compression, and the need for radiotherapy or surgery to bone) during the study were identified. Next, all EQ-5D assessments of these patients with an assessment date prior to the first SRE were retrieved and included in the analysis.

To model the longitudinal trajectory of the EQ-5D utility, a linear random coefficients analysis model with a random intercept was performed. The corresponding statistical model is as follows:

$$Y_{it} = \beta_{0i} + \beta_1 * t + \sum_{j=1}^{5} \beta_{2j} * X_i + \varepsilon_{it}$$

Y_{it}= utility value for patient i at time t; β_{0i}=random intercept; β_1=coefficient for time; t= time; X_i=predictor j for patient I; β_{2j}=coefficient for predictor j.

The predictors (fixed effects) used in the longitudinal model are the following: time (continuous), age (< 65 or ≥ 65 years), region (Europe, North America and rest of the world), ECOG performance status at baseline (0 or 1), pain at baseline (asymptomatic and symptomatic), fatigue severity at baseline (question #3 of the Brief Fatigue Inventory (BFI) score < 7 or ≥ 7). Variable TIME was coded to take value 0 for baseline assessment, 12 for Week 13 visit assessment, 24 for Week 25 visit assessment, etc. Please note that the SAP indicates investigator site as one of the fixed effects, but this predictor could not be included in the model due to convergence issues. Therefore, geographic region was used instead. Similar to the MMRM model, all predictors were included in the random coefficients analysis model and no selection of predictors was performed.

It is important to note that in the impact of SREs on QoL analysis, the data from the two treatment arms is combined, and treatment was not a predictor. The summary statistics of the predictors on the patient population included in the analysis (i.e. with ≥1 SRE during the study) is presented in the table below.

Baseline demographic and disease characteristics - Patients with ≥1 SRE during the study

	Statistic	Placebo (N=309)	Enzalutamide (N=278)	Total cohort (N=587)
Age group (yrs)				
Total non-missing	[redacted]	[redacted]	[redacted]	[redacted]
< 65	[redacted]	[redacted]	[redacted]	[redacted]
>=65	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Geographic region				
Total non-missing	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the world	[redacted]	[redacted]	[redacted]	[redacted]
ECOG				
Total non-missing	[redacted]	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
Pain at baseline (a)				
Total non-missing	[redacted]	[redacted]	[redacted]	[redacted]
Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue severity				
Total non-missing	[redacted]	[redacted]	[redacted]	[redacted]
< 7 in question #3 of the BFI	[redacted]	[redacted]	[redacted]	[redacted]
>=7 in question #3 of the BFI	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]

(a) Defined using Brief Pain Inventory – Short Form Question #3: asymptomatic=score 0 or 1; symptomatic=score >2.

The model assumed an unstructured specification for the variance-covariance matrix. The coefficients for each predictor, including their 95% CI are provided in table 3.6.1 of Appendix II of reference 53 (Quintiles report for the analysis of PRO data collected in the PREVAIL study) and in the table below.

Complete set of coefficients from the random coefficients analysis model

Type of SRE	Parameter estimates	SE	95% CI	p-value
Radiation or surgery to bone				
Intercept	0.66	0.04	(0.59, 0.73)	<.0001
Time	-0.00	0.00	(-0.00, -0.00)	<.0001
ECOG at baseline (0 vs 1)	0.07	0.02	(0.03, 0.10)	0.0002
Pain at baseline (asymptomatic vs symptomatic)	0.09	0.02	(0.05, 0.12)	<.0001
Fatigue severity at baseline (<7 vs >=7)	0.02	0.03	(-0.03, 0.08)	0.4118
Age (<65 vs >=65)	0.03	0.02	(-0.01, 0.06)	0.1510
Region - Europe	0.04	0.02	(-0.01, 0.08)	0.1038
Region - North America	0.03	0.02	(-0.01, 0.08)	0.1544
Pathologic bone fractures				
Intercept	0.72	0.10	(0.53, 0.91)	<.0001
Time	-0.00	0.00	(-0.00, -0.00)	0.0023
ECOG at baseline (0 vs 1)	0.04	0.03	(-0.02, 0.10)	0.2064
Pain at baseline (asymptomatic vs symptomatic)	0.07	0.03	(0.01, 0.13)	0.0189
Fatigue severity at baseline (<7 vs >=7)	0.05	0.09	(-0.12, 0.23)	0.5670
Age (<65 vs >=65)	0.01	0.04	(-0.07, 0.09)	0.7848
Region - Europe	-0.02	0.03	(-0.08, 0.05)	0.6120
Region - North America	-0.05	0.04	(-0.13, 0.03)	0.2070
Spinal cord compression				
Intercept	0.73	0.08	(0.56, 0.90)	<.0001
Time	-0.00	0.00	(-0.00, -0.00)	0.0003
ECOG at baseline (0 vs 1)	0.09	0.04	(0.02, 0.16)	0.0122
Pain at baseline (asymptomatic vs symptomatic)	0.09	0.04	(0.02, 0.16)	0.0166
Fatigue severity at baseline (<7 vs >=7)	0.01	0.08	(-0.14, 0.17)	0.8511
Age (<65 vs >=65)	0.06	0.04	(-0.03, 0.14)	0.1797
Region - Europe	-0.05	0.04	(-0.14, 0.03)	0.1905
Region - North America	-0.04	0.05	(-0.13, 0.06)	0.4682

It should be noted that, in addition to the impact of the first SRE on QoL, reference 53 also reports the impact of the most severe SRE on QoL, for those patients who experienced multiple SREs. For the purpose of the cost-effectiveness model, we included the disutility using the first SRE analysis as this was considered more reliable. The alternative analysis (most severe SRE), does not account for the impact of any previous SRE on QoL. However, as could be seen from table 3.6.4 of Appendix II from reference 53, the results are very similar and confirm the analysis of the first SRE.

Step 2: Derive utility decrement

The utility decrement was derived by calculating the trajectory adjusted mean change (TAMC). TAMC was defined as the mean deviation of the post-SRE utility value from the expected value based on the model above (predicted value). EQ-5D assessments were scheduled every 12 weeks, so we coded the first assessment made <84 days after an SRE as the 'post-SRE assessment'.

B3. Please provide Appendices I, II and III from reference 53 (Quintiles report for the analysis of PRO data collected in the PREVAIL study).

The requested appendices have been attached to this response.

B4. Please clarify if within section 7.4.3 remaining on treatment is synonymous with Stable Disease (1st paragraph page 170).

This is correct, and matches the definition of stable disease in the model (patients who are alive and have not yet progressed according to the time to treatment discontinuation endpoint).

B5. What were the mean (s.d.) quality of life values that were used for TA316 (ref 32) for baseline, treatment effects change from baseline and disease progression? Please confirm that a parallel approach to the TA316 calculation of the quality of life impact of disease progression could not be calculated due to a lack of data within PREVAIL.

The base case values from TA316 are described in the table below. It should be noted that the base case quality of life impact of disease progression in TA316 was not based on the AFFIRM study. Similar to PREVAIL, quality of life (EQ-5D and FACT-P) was only collected in AFFIRM for patients on treatment.

For a scenario analysis TA316 also presented the quality of life impact of progression according to modified PFS criteria (radiographic progression, first SRE or death). As this analysis only represented the impact of the start of progression (as all measurements were taken for patients with radiographic progression or a first SRE, but who were still on treatment) the analysis was not used in the base case. For the same reason, this analysis was not performed on the PREVAIL data.

State	Utility value	CI / SE	Reference in TA316	Justification
Stable Disease	[redacted]	SE = [redacted]	7.4.3	The baseline utility (EQ-5D) values in AFFIRM represent patients in SDis.
Disutility progression	-0.085	SE assumed 20% of mean = 0.017	7.4.7	As no QoL data was collected beyond progression, only the utility decrease upon the first sign of progression could be calculated, and not the utility while in progressive disease. Therefore literature data were preferred: Decrease in utility from 16-8 months before death to 8-0 months before death in Sandblom study (122) was assumed to represent utility decrement for progression.
On treatment benefit for enzalutamide	[redacted]	[redacted]	7.4.3	Enzalutamide showed a significant effect on pain, resulting in a significant utility gain over placebo in AFFIRM based on mapped FACT-P utilities.

B6. What were the mean (s.d.) QALY decrements, or QoL decrements coupled with their assumed durations, that were applied for each SRE within TA316? Please clarify why decrements for SREs based upon a trajectory adjusted mean change as in TA316 were not calculated or not calculable from the PREVAIL EQ-5D data?

The QALY decrements used in TA316 for the SREs are described in the table below. As described on page 170 of the submission, the same approach was used for the PREVAIL EQ-5D data in this submission.

SRE disutilities	Utility value	CI / SE	Reference in TA316	Justification
Radiation or surgery to bone	[redacted]	95% CI [redacted]	7.4.3	SREs in AFFIRM were associated with a significant decline in utility (MMRM analysis based on mapped FACT-P values).
Pathologic bone fractures	[redacted]	95% CI [redacted]	7.4.3	
Spinal cord compression	[redacted]	95% CI [redacted]	7.4.3	
Duration of SRE disutility	1 month		Botteman 2011 (ref. 121 in TA316)	Duration was based on literature data. No other sources were identified.

B7. Please provide non-redacted tables 46, 49 and 51 of the TA316 enzalutamide post docetaxel company submission, ref 32 (table 46: maximum likelihood parameter estimates for AFFIRM placebo overall survival; table 49: maximum likelihood parameter estimates for AFFIRM placebo time to treatment discontinuation; table 51: number of events and rates for SREs used in the model).

Table 46: Maximum likelihood parameter estimates for AFFIRM placebo overall survival

Parameter	Exponential	Weibull	Log-Normal	Log-Logistic	Gamma
Intercept (SE)	2.93 (0.07)*	**2.79 (0.04)***	2.54 (0.05)*	2.53 (0.05)*	2.65 (0.07)*
Scale (SE)	1.00 (0.00)	**0.62 (0.04)**	0.89 (0.04)	0.50 (0.03)	0.78 (0.07)
Shape (SE)	1.00 (0.00)	**1.00 (0.00)**			0.42 (0.21)

*Parameter met the 0.05 criterion for statistical significance.
Abbreviations: SE=standard error; Numbers in bold indicate the final model chosen

Table 49: Maximum likelihood parameter estimates for AFFIRM placebo time to treatment discontinuation

Parameter	Exponential	Weibull	Log-Normal	Log-Logistic	Gamma
Intercept (SE)	1.52 (0.05)*	**1.59 (0.04)***	1.21 (0.04)*	1.22 (0.04)*	1.27 (0.06)*
Scale (SE)	1.00 (0.00)	**0.75 0.03)**	0.79 (0.03)	0.42 (0.02)	0.78 (0.03)
Shape (SE)	1.00 (0.00)	1.00 (0.00)			0.15 (0.10)

*Parameter met the 0.05 criterion for statistical significance.
Abbreviation: SE: standard error; Numbers in bold indicate the final model chosen

Table 51: Number of events and rates for SREs used in the model

	AFFIRM (IA) (Ref. 15 in TA316)				**COU-AA-301 (Logothetis 2012) (Ref. 67 in TA316)**						**ITC**
	ENZ		**PLA**		**ABI**		**PLA**		**ABI-PLA**		**ABI**
SREs	**n (events)**	**Rate**	**n (events)**	**Rate**	**n (events)**	**Rate**	**n (events)**	**Rate**	**RD**	**SE RD**	**Indirect rate**
Spinal cord compression	72	**0.12**	31	**0.19**	45	0.07	28	0.14	-0.07	0.03	**0.12**
Pathologic bone fractures	41	**0.07**	15	**0.09**	36	0.06	8	0.04	0.02	0.02	**0.11**
Radiation to bone	238	**0.39**	111	**0.67**	145	0.24	92	0.46	-0.22	0.05	**0.45**
Surgery to bone	24	**0.04**	3	**0.02**	10	0.02	2	0.01	0.01	0.01	**0.02**
Total	375	0.62	160	0.97	236	0.39	130	0.65	-0.26	0.06	0.71

Abbreviations: ABI: abiraterone; ENZ: enzalutamide; PLA: placebo; RD: rate difference; SE: standard error

B8. Please confirm whether the functions of tables 46 and 49 of the TA316 enzalutamide post docetaxel submission, ref 32 apply to time measured in months or some other time span, the implied means for OS and TTD for placebo, and, the implied means for OS and TTD for enzalutamide and abiraterone given the estimated hazard ratios

The parametric functions of Table 46 and 49 in TA316 refer to time in months. The mean time in TTD and OS from the model is presented in the table below.

Means discounted life years	**PLA**	**Enz**	**Abi**
OS	[redacted]	[redacted]	[redacted]
TTD	[redacted]	[redacted]	[redacted]
Means undiscounted life years			
OS	[redacted]	[redacted]	[redacted]
TTD	[redacted]	[redacted]	[redacted]

Model inputs and structure

B9. **The modelling contains a large number of possible scenarios in terms of the OS curves that can be applied. There is no easy read across between these and the clinical effectiveness tables in the submission and extrapolation report (81_Extrapolation report_Appendix A_14JAN2015.pdf). Please provide table references from both the written submission and the extrapolation report, as available, for the parameters underlying the curves referred to in the *Overall_Survival* worksheet cells M100:M114 for enzalutamide, cells M119:M130 for BSC and cells M135:M138 for abiraterone.**

	Submission clinical effectiveness section		**Extrapolation report**	
Cell	Table	Page	Table	Page
Enzalutamide				
M100	N/A*	N/A*	Table 5	Page 14
M101	N/A*	N/A*	HR: Table 3 Reference curve: Table 5	HR: Page 12 Reference curve: Page 14
M102	N/A*	N/A*	Table 11**	Page 23
M103	N/A*	N/A*	Table 11**	Page 23
M104	N/A*	N/A*	Table 11**	Page 23
M105	N/A*	N/A*	Table 17	Page 31
M106	N/A*	N/A*	Table 5	Page 14
M107	N/A*	N/A*	Table 5	Page 14
M108	N/A*	N/A*	HR: Table 3 Reference curve: Table 5	HR: Page 12 Reference curve: Page 14
M109	N/A*	N/A*	Table 5	Page 14
M110	N/A*	N/A*	Table 12**	Page 24

M111	N/A*	N/A*	Table 12**	Page 24
M112	N/A*	N/A*	Table 12**	Page 24
M113	Table B48	Page 146	Table 17	Page 31
M114	Table B48	Page 146	Table 17	Page 31
BSC				
M119	N/A*	N/A*	Table 5	Page 14
M120	N/A*	N/A*	Table 11**	Page 23
M121	N/A*	N/A*	Table 11**	Page 23
M122	N/A*	N/A*	Table 11**	Page 23
M123	N/A*	N/A*	Table 17	Page 31
M124	N/A*	N/A*	Table 5	Page 14
M125	N/A*	N/A*	Table 5	Page 14
M126	N/A*	N/A*	Table 12**	Page 24
M127	N/A*	N/A*	Table 12**	Page 24
M128	N/A*	N/A*	Table 12**	Page 24
M129	Table B48	Page 146	Table 17	Page 31
M130	Table B48	Page 146	Table 17	Page 31
Abiraterone				
M135	Table B30***	Page 107	N/A	N/A
M136	Table B51	Page 148	N/A	N/A
M137	Table B51	Page 148	N/A	N/A
M138	Table B51	Page 148	N/A	N/A

* Please note the parameters underlying these curves are not presented in the main body of the submission. They are presented in the extrapolation report.

** Please note, Table 11 and Table 12 have two parts: Gamma AF, with recensoring model and Gamma AF, without recensoring model. The parameters from Gamma AF, without recensoring model are used.

*** Please note, ABI vs PLA IA3 cut-off HR for OS is used.

B10. The modelling contains a large number of possible scenarios in terms of the PFS curves that can be applied. There is no easy read across between these and the clinical effectiveness tables in the submission and extrapolation report (81_Extrapolation report_Appendix A_14JAN2015.pdf). Please provide table references from both the written submission and the extrapolation report, as available, for the parameters underlying the curves referred to in the *PFS* worksheet cells M102:M111 for enzalutamide, cells M114:M120 for BSC and cells M124:M128 for abiraterone.

	Submission clinical effectiveness section		Extrapolation report	
Cell	Table	Page	Table	Page
Enzalutamide				
M102	N/A*	N/A*	Table 5	Page 14
M103	N/A*	N/A*	HR: Table 3 Reference curve: Table 5	HR: Page 12 Reference curve: Page 14
M104	N/A*	N/A*	Table 5	Page 14

M105	N/A*	N/A*	Table 5	Page 14
M106	N/A*	N/A*	HR: Table 3 Reference curve: Table 5	HR: Page 12 Reference curve: Page 14
M107	Table B53	Page 150	Table 5	Page 14
M108	Table B53	Page 150	Table 5	Page 14
M109			HR: Table 3 Reference curve: Table 5	HR: Page 12 Reference curve: Page 14
M110	Table B53	Page 150	Table 5	Page 14
M111	Table B53	Page 150	Table 5	Page 14
BSC				
M114	N/A*	N/A*	Table 5	Page 14
M115	N/A*	N/A*	Table 5	Page 14
M116	N/A*	N/A*	Table 5	Page 14
M117	Table B53	Page 150	Table 5	Page 14
M118	Table B53	Page 150	Table 5	Page 14
M119	Table B53	Page 150	Table 5	Page 14
M120	Table B53	Page 150	Table 5	Page 14
Abiraterone				
M124	Table B30	Page 107	N/A	N/A
M125	Table B56	Page 151	N/A	N/A
M126	Table B56	Page 151	N/A	N/A
M127	Table B56	Page 151	N/A	N/A
M128	Table B56	Page 151	N/A	N/A

* Please note the parameters underlying these curves are not presented in the main body of the submission. They are presented in the extrapolation report.

Please note, together with this document we provide the following documents/ references:

1. Question A12 response - distribution of patients
2. Question B1 response - coefficients MMRM analysis
3. Appendices to Systematic Review and Mixed Treatment Comparison of Enzalutamide for Chemotherapy Naïve Castration-Resistant Prostate Cancer (46_YHEC FINAL report_SR and NMA of Enzalutamide_Appendices (Feb 2015) v4.0)
4. Appendices to PREVAIL PRO report:
   53_Astellas_Prevail PRO Report_Final_19Sept2014_Appendix I_SAP
   53_Astellas_Prevail PRO Report_Final_19Sept2014_Appendix II_Tables
   53_Astellas_Prevail PRO Report_Final_19Sept2014_Appendix III_Graphs