NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Astellas' Response to NICE Final Appraisal Determination (FAD)**

3. **ERG critique of Astellas' revised Patient Access Scheme Submission**
   - **ERG critique**
   - **Further scenario analyses**
   - **Equalising the PAS between 1st line and 3rd line enzalutamide**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SingleTechnology Appraisal

Enzalutamide for metastatic hormone-relapsed prostate cancer when chemotherapy when chemotherapy is not yet clinically indicated

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Astellas	Executive Summary Astellas contest NICE's position regarding the cost-effectiveness of enzalutamide in chemo-naive mHRPC. The main points we wish to make are: Abiraterone is the most appropriate comparator in this appraisal, as the majority of patients in England are already receiving active treatment (either enzalutamide or abiraterone), as opposed to being observed until their health declines sufficiently to receive docetaxel. This committee has previously endorsed abiraterone as established practice in the NHS. Data show that patients receiving enzalutamide have an improvement in their quality of life, and this justifies the use of an 'on-treatment' utility gain in our model. The use of an 'on-treatment' utility has previously been accepted by this committee in the enzalutamide post-chemotherapy appraisal (TA316)with agreement that this reflected the patient experience. Astellas recognises the difficulty of capturing the benefit of delaying chemotherapy perceived by the patients in the utility values included in the modelling and considers that a stable utility value (including the small utility gain) is the best approach to capture the benefit of delaying chemotherapy in the cost-effectiveness analysis. Enzalutamide provides a cost-effective treatment alternative for all patients with chemo-naïve mHRPC.	Comments noted. The points summarized by the company in its executive summary are addressed below as they are raised in the main body of Astella's response.

Consultee	Comment [sic]	Response
Astellas	The economic model upon which this appraisal is based is robust with respect to face validity and uncertainty and is consistent with the economic model submitted for the post-chemotherapy indication. Face validity within the model is achieved by ensuring balance between the flow of patients through the model and the experience of patients whose survival data is used to inform the model outcomes. In addition, the adjustment of survival data to better reflect the UK treatment pathway ensures the model results are generalisable. Whilst, there is uncertainty inherent in economic modelling, the uncertainty associated with the current model has been mitigated as far as possible by strict adherence to DSU guidance for data adjustment and extrapolation. Moreover, there is a clear upper bound on the impact of uncertainty around the benefit of enzalutamide on estimates of cost-effectiveness available from use of the ITT data within the model.	Comments noted. Comments noted. Responses to these points are given below, where they are further elaborated on by the company.
Astellas	There is a clinical differentiation between the patient population assessed in the post-chemotherapy indication and those patients in the chemo-naive setting that progress beyond chemotherapy. Given this difference, the current model shows a high level of consistency in terms of the extrapolated survival benefit. The response to the ACD is structured in three sections. Firstly, Astellas provide the evidence to justify and support the contention that abiraterone is the most relevant comparator for the purpose of evaluating the cost-effectiveness of enzalutamide in chemo-naïve patients. Secondly, we will address the ERG and Committee concerns on the face validity and uncertainty of the economic model. Finally, the third section discusses those changes that have been applied to the economic base case and with which Astellas disagree.	Comments noted. Responses to these points are given below, where they are elaborated on further by the company.

Consultee	Comment [sic]	Response
Astelllas	Choice of abiraterone as a comparator In reliance on the position set out in the draft[i] and final scope[ii], and other communications during the scoping period, Astellas considers that abiraterone remains the most appropriate comparator to inform the cost-effectiveness assessment of enzalutamide in chemo-naïve mHRPC patients, and for this reason, properly included it in the model as per direction from the scoping committee. However, despite being included in the final scope the Committee considers abiraterone no longer a relevant comparator for the purpose of this health technology assessment. On pages 24-25, the ACD states: "*The Committee concluded that because NICE has not issued technology appraisal guidance on abiraterone and has not recommended sipuleucel-T taken before cytotoxic chemotherapy, because access to abiraterone through the Cancer Drugs Fund varies, and because there are some people who cannot have abiraterone but can take enzalutamide or best supportive care, the main comparator for enzalutamide is best supportive care.*" Astellas disagrees with the validity of this statement that abiraterone cannot be considered the most appropriate comparator. We will address the points made above and present further arguments that abiraterone is the most appropriate treatment comparator.	Comment noted. The scope identifies relevant 'potential' comparator technologies and the Appraisal Committee determines the appropriate comparators given the evidence presented during the appraisal. The text has been updated to read: the Committee concluded that all people have access to best supportive care and some people have access to abiraterone through the Cancer Drugs Fund (FAD 4.1)

Consultee	Comment [sic]	Response
Astellas	*"Access to abiraterone through the Cancer Drugs Fund varies"* While use of abiraterone through the Cancer Drug Fund (CDF) may vary to a small degree as with many drugs, Astellas contends that the impression given by the clinical experts invited to the Appraisal Committee hearing, though experts in their field, did not give a fair view of the widespread access to abiraterone and enzalutamide nor their place as standard of care in chemo-naïve patients. Access to enzalutamide is equitable across the whole of England to any oncologist who treats prostate cancer for any patient who meets the criteria laid down in the CDF listing. Although it is true that urologists in the main cannot access enzalutamide or abiraterone, this is not due to a lack of desire and has in many cases fuelled referral of patients to oncologists in order to access these drugs. The clinical experts, a urologist practising in England and an oncologist practicing in Northern Ireland where neither drug is accessible through CDF, were commenting from a standpoint where they personally cannot commonly prescribe either drug. Clinical opinion should not take precedence over real world evidence. In reality, that abiraterone and enzalutamide are now the standard of care for chemo-naïve mCRPC patients in England is clearly demonstrated by CDF data. These data show that the majority (53%) of all eligible chemo-naïve mCRPC patients received abiraterone in England through this fund 12 months prior to the availability of enzalutamide on CDF[iii]. Since the availability of enzalutamide on CDF the proportion of eligible patients receiving either drug has increased further to 71%[iv].	Comments noted. The sections of the ACD relating to Committee's discussion on access to abiraterone have been removed. The data relating to abiraterone/ enzalutamide prescribing through the Cancer Drugs Fund (CDF) was discussed at the second committee meeting. Section 4.2 of the FAD states: although people currently have abiraterone through the Cancer Drugs Fund, the current funding arrangements within the Cancer Drugs Fund will come to an end in April 2016. The Committee was aware that abiraterone is currently being appraised by NICE and that preliminary recommendations had not recommended abiraterone. The Committee agreed that because abiraterone was not embedded in the NHS, it should not be considered as a comparator.

Consultee	Comment [sic]	Response
Astellas	*"There are some people who cannot have abiraterone but can take enzalutamide or best supportive care"* The ACD also comments *"The Committee noted that people with visceral disease cannot have abiraterone, but can have enzalutamide through the Cancer Drugs Fund and people with liver dysfunction cannot have abiraterone, but can take enzalutamide. Additionally because abiraterone is taken with corticosteroids, (prednisone or prednisolone) enzalutamide is more suitable for people who cannot take corticosteroids"* The NICE committee correctly identifies small groups of patients in whom enzalutamide offers a treatment advantage. However, abiraterone is not contraindicated in patients with visceral disease according to the SPC, although these patients were excluded from the COU-AA-302 trial. It is also important to note that abitaterone is not contraindicated in all patients with liver dysfunction, only those with severe hepatic dysfunction. The only other absolute contraindication is hypersensitivity to abiraterone. Additionally, abiraterone plus prednisolone is generally well tolerated with only 10% of patients discontinuing treatment in COU-AA-302 due to adverse events. Enzalutamide has advantages over abiraterone in terms of liver toxicity, mineralcorticoid related adverse events, requirement for coadministration of steroids and having data in chemo-naïve patients with visceral disease. However, in the absence of enzalutamide, abiraterone, as a generally well tolerated treatment with few absolute contraindications would be used in a large majority of patients. When comparing two drugs in a HTA there are inevitably differences in the safety profiles and contraindications associated with each drug (for example sipuleucel T and abiraterone). In this case as in most, these small differences do not form a basis for abiraterone to be ruled out as the main comparator. For the minority of patients who cannot receive abiraterone, access to enzalutamide ensures equitable access to a life extending therapy which improves quality of life.	Comments noted.

Consultee	Comment [sic]	Response
Astellas	Furthermore, the clinical argument that abiraterone is the most appropriate comparator cannot be ignored. When both the PREVAIL and COU-AA-302 trials were designed, there were no proven active therapies available for these patients, hence BSC/placebo was an ethical comparator. This is confirmed in current clinical trials for this indication where BSC/placebo is no longer acceptable as a control. The licensing of abiraterone and now enzalutamide gives treatment options which both prolong life and improve quality of life meaning that conservative management with BSC would not be an ethical choice for most patients and hence should not be included as the main comparator. Therefore, abiraterone and not BSC is the most appropriate comparator. In the absence of enzalutamide, abiraterone alone would be prescribed in a significant majority of these patients. It is generally well tolerated with few contraindications and as a treatment option which prolongs life and improves quality of life, BSC would not be an ethical option	Comments noted. Section 4.2 of the FAD states: although people currently have abiraterone through the Cancer Drugs Fund, the current funding arrangements within the Cancer Drugs Fund will come to an end in April 2016. The Committee was aware that abiraterone is currently being appraised by NICE and that preliminary recommendations had not recommended abiraterone. The Committee agreed that because abiraterone was not embedded in the NHS, it should not be considered as a comparator.

Consultee	Comment [sic]	Response
Astellas	*"NICE has not issued technology appraisal guidance on abiraterone and has not recommended sipuleucel-T taken before cytotoxic chemotherapy"* Astellas is mindful that NICE has not yet issued the technology appraisal guidance on abiraterone and that currently this drug is only available through the CDF in the chemo-naïve setting. This does not detract from the fact, that there is an established precedent by NICE where abiraterone was considered a relevant comparator in the chemo-naïve mCRPC setting. Based on the FAD of the sipuleucel-T submission in a comparable population, the Committee considered abiraterone as established practice - although through CDF - in England. Indeed, on page 24 of the FAD for sipuleucel-T[v] it is stated: "*The Committee noted that people in England with prostate cancer that is not yet suitable for chemotherapy may have abiraterone through the Cancer Drugs Fund. Although the Committee was aware that the use of abiraterone in this setting is currently being appraised by NICE, and that the Cancer Drugs Fund is a special funding arrangement that is not guaranteed after 2016, it was satisfied that abiraterone is currently part of established practice in the NHS.*" Astellas is not aware of any factors that would have changed the statement in the sipuleucel-T FAD regarding abiraterone being part of the standard of care for asymptomatic or mildly symptomatic patients for which chemotherapy is not yet clinically indicated. And thus, Astellas consider it unreasonable for NICE to consider abiraterone as an inappropriate comparator in the cost-effectiveness assessment of enzalutamide in a clinical setting given the similarities to that of sipuleucel-T. Furthermore, an intervention being available through the CDF has not been the basis for it to be excluded from being considered a relevant comparator in submissions in other diseases eg. trastuzumab (example provided in Appendix).	Section 4.2 of the FAD states: although people currently have abiraterone through the Cancer Drugs Fund, the current funding arrangements within the Cancer Drugs Fund will come to an end in April 2016. The Committee was aware that abiraterone is currently being appraised by NICE and that preliminary recommendations had not recommended abiraterone. The Committee agreed that because abiraterone was not embedded in the NHS, it should not be considered as a comparator.

Consultee	Comment [sic]	Response
Astellas	In conclusion Astellas considers that abiraterone is the most appropriate comparator and that BSC is no longer a valid clinical comparator. The safety and efficacy profile of abiraterone support its use in the vast majority of the patient population assessed in this appraisal. That active treatment of this patient population is now standard of care is demonstrated by CDF data and the clinical argument for withholding treatment for this patient population, reducing overall survival and hastening deterioration in quality of life does not exist. The ACD issued by NICE contains unreasonable and erroneous statements around current access to abiraterone and its safety profile which cannot form the basis of excluding it as a comparator, as well as considering that BSC can no longer be regarded an ethical standard of care.	Comments noted. The sections of the ACD relating to Committee's discussion on access to abiraterone have been removed.
Astellas	Validity of model results Within the ACD, the Committee raised several concerns around the structure of and data used to inform the economic model, which can be categorised as follows: Adjustment for treatment switching; Model face validity; Extrapolation of OS; Model bias against abiraterone.	Comments noted. Responses are given below.

Consultee	Comment [sic]	Response
Astellas	Adjustment for treatment switching Astellas would like to reiterate the purpose of the OS adjustment and what exactly it corrected for. The OS adjustment carried out on PREVAIL data intended to correct for the receipt of treatments outside of the current UK treatment pathway; that is, treatments such as pre-chemo abiraterone. Treatments considered within the current treatment pathway, such as docetaxel were not adjusted for. Additionally, as a result of missing data, it was not possible to adjust for treatments received 3rd line. The Committee have expressed concerns about the uncertainty of the real treatment benefit of enzalutamide over BSC: The ACD states (page 19): "*The Committee noted that both methods [IPCW and the two stage method] used to adjust the OS estimates for the effect of subsequent treatments that are not used in England decreased the hazard ratio (that is, it resulted in a larger difference) for enzalutamide compared with placebo, but that the IPCW method reduced it more. The Committee was aware that the IPCW method assumed that there were no unmeasured confounders affecting the association between moving onto another treatment and mortality. However, the company was not able to tell the Committee during the Committee meeting which confounders the company had included in its models.* Astellas wishes to clarify that a thorough list of possible baseline and time-dependent confounders were included as predictors for treatment switch and survival in the IPCW method. The table below provides the complete list of covariates included in the IPCW method.	Comments noted. NICE appreciates the company providing further information about the potential confounders tested by the company. Section 4.7 of the FAD has been updated to include the Committee's discussion of the company's comments on the IPCW methodology.

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td>Astellas</td><td>Table 1 Covariates included in the IPCW method
<table>
<tr><th>Baseline covariates</th><th>Time dependent covariates</th></tr>
<tr><td>Age (years, continuous)
Time since diagnosis (categorical; <5 years / ≥5 years)
Number of bone metastases at screening (categorical; ≤5 / >5)
Presence of visceral disease at baseline (categorical; yes / no)
Type of disease progression at study entry (categorical; PSA progression only / radiographic progression with or without PSA / no disease progression at study entry); two dummy variables were computed (PSA progression / otherwise; and radiographic progression with or without PSA / otherwise)
Baseline EQ-5D utility index (continuous)
Baseline FACT-P total score (continuous)
Disease progression (categorical; Yes/No)
Time to study treatment discontinuation (continuous).</td><td>ECOG performance status (categorical; 0 / otherwise)
PSA level (continuous)
Laboratory tests: LDH (categorical; ≤240 IU/mL / >240 IU/mL)
History of grade 3/4/5 adverse events (AEs) since randomization (categorical; yes / no)
Occurrence of grade 3/4/5 AEs since last (categorical; yes / no)
Corticosteroid use (categorical; yes / no)
EQ-5D utility index (continuous)
FACT-P total score (continuous)
Time since the date of study treatment discontinuation (days; continuous)</td></tr>
</table></td><td>Table noted.</td></tr>
</table>

Consultee	Comment [sic]	Response
Astellas	*The Committee agreed that it was appropriate to adjust OS for subsequent active treatments not used in the NHS, that might prolong life. However, it was not clear which of the 2 methods used by the company (or indeed other possible methods, including marginal structural models and rank preserving structural nested failure time models) would give the most appropriate adjustment and capture the true treatment effect of enzalutamide over best supportive care. The Committee concluded that enzalutamide increased OS compared with placebo, but the extent of the difference was uncertain, and the Committee was unclear whether the company's choice of adjustment method provided estimates that represented the true difference in survival between enzalutamide and placebo.*" As mentioned in the ACD, in line with the NICE DSU guidance[vi] Astellas conducted specific analysis to adjust the PREVAIL OS data. Astellas was offered advice on the application of the methods and interpretation of results by one of the lead experts in this field, Dr. Nicholas Latimer, in order to select the most appropriate method and ensure proper treatment of the data.	Comment noted.

Consultee	Comment [sic]	Response
Astellas	In the case of PREVAIL, in addition to placebo patients receiving enzalutamide after study treatment discontinuation, patients in both arms (experimental and control) moved to several second-line treatments with life extending capacity which differed from the treatment these patients would have received in clinical practice (i.e., were switchers). In this context where switching is allowed in both treatment arms to several second line treatments, RPSFT and IPE are not recommended[vii]. This is because their standard forms can only deal with a situation where patients are either 'on' treatment or 'off' treatment. Multivariate versions of the RPSFT, which could incorporate more than one treatment exposure, have been tried several times in the literature and have failed to work[viii,ix,x]. Under these circumstances, observational-based methods, such as the IPCW, Marginal Structural Models (MSM) and two-stage method, are more appropriate as these can be adapted to adjust for switching in any direction and to any treatment, with models being applied to different groups as appropriate[xi]. As a note, the IPCW and MSM are essentially the same thing in this case. An MSM is a model weighted using the IPCW weights. In PREVAIL, the IPCW weights have been used within a Cox model to get an adjusted HR. While both the IPCW and two-stage methods were deemed suitable for the adjustment of OS data in PREVAIL, the simple two-stage method is theoretically inferior to the IPCW method which adjusts for time-dependent confounding. The IPCW method has a solid methodological background and was originally developed for use with observational data. Both the IPCW and the two-stage method have limitations. The limitations were detailed in reference number 37 from the manufacturer submission and an overview is provided in the table below.	Comments noted. Section 4.7 of the FAD has been updated to include the Committee's discussion of the company's comments on the IPCW methodology.

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td>Astellas</td><td>Table 2 Key limitations associated with IPCW and the two-stage method
<table>
<tr><th>Method</th><th>Key limitations</th></tr>
<tr><td>IPCW</td><td>No unmeasured confounders assumption; that is, data must be available on all baseline and time dependent prognostic factors for mortality that independently predict informative censoring (switching).
Method does not provide a counterfactual dataset to which parametric models can be fitted for extrapolation purposes.
Method is prone to error if switching proportions are very high, particularly if sample sizes are also small</td></tr>
<tr><td>Two-stage method</td><td>It can only be applied if an appropriate secondary baseline exists.
No unmeasured confounders assumption to hold at the point of the secondary baseline.
Switching must occur soon after secondary baseline time-point, otherwise the method is prone to time-depending confounding.
Bias may be introduced when recensoring</td></tr>
</table></td><td>Comments noted. Section 4.7 of the FAD has been updated to include the Committee’s discussion of the company’s comments on the IPCW methodology.</td></tr>
</table>

Consultee	Comment [sic]	Response
Astellas	Taking into account the theoretical and practical limitations, the size of the study, the proportion of patients switching in both arms and the data on confounding factors, Astellas concluded that the IPCW is a more appropriate method than the two-stage method. Moreover, the ERG agreed that the IPCW method is appropriate for estimating the true effect of treatment on survival. One of the Committee's concerns was the "no unmeasured confounders" assumption, which is indeed a limitation of IPCW, but also of the two-stage method. In practice, it is unlikely that this assumption will perfectly hold true, but the IPCW method is likely to work adequately if the ''no unmeasured confounders'' assumption is approximately true; that is, there are no important independent predictors missing[xi]. Moreover, if a confounder was missing, but was correlated with a confounder that was measured, its absence may lead to only minimal bias. Given the number of covariates included here, it seems quite unlikely that there will be important missing covariates that are not in some way correlated with covariates that were included. As shown in Table 1, a thorough list of possible confounders were incorporated based on variables collected during the PREVAIL study. Astellas further reviewed previous studies in order to determine whether any important covariates were excluded from the PREVAIL study and clinical expert opinion was sought in order to determine whether any indicators of switching may not have been collected in the PREVAIL study. Although there is no certainty that all important predictors were measured, all covariates measured during the trial which were considered by clinical experts to be potentially prognostic for switching and survival have been included.	Comments noted. In response to the list of potential confounders provided by the company, the FAD states: The Committee appreciated that the company provided the list of covariates that the company had identified as potential confounders in response to the appraisal consultation document and considered the list to be generally appropriate (FAD section 4.7).

Consultee	Comment [sic]	Response
Astellas	The Committee also raised a concern that the OS data for abiraterone were not adjusted (page 29): "*The Committee further noted that the company had not presented an estimate for OS for abiraterone that had been adjusted for the active treatments people had after abiraterone that are not available on the NHS and that may prolong life, as it had done for enzalutamide (see section 4.4). It considered that it was not unreasonable to expect the effect of enzalutamide and abiraterone on survival to be similar. However, by adjusting for the effects of subsequent therapy not available on the NHS on the effect of enzalutamide, but not on abiraterone, survival estimates from the company inappropriately favoured enzalutamide*." Astellas would like to clarify that the third interim analysis, used to inform the OS of abiraterone within the base case economic model, was in proximity to the date of unblinding[xii]. As stated in the manufacturer's submission for Abiraterone on pre-chemo patients (page 61): "*Cross-over from PP to AAP occurred following unblinding (02.04.12) for three patients by the third interim analysis (22.05.12). Any effect on the third interim analysis results is expected to be minimal due to the few patients involved and the short time between unblinding and the third interim analysis.* xiii" In addition, neither enzalutamide nor sipuleucel-T were available at this time, hence patients who progressed were given docetaxel which is in line with the current treatment pathway or palliative treatments that have no impact on survival. Therefore, any effect of switching on survival estimates taken from the third interim analysis results is expected to be minimal.	Comment noted. This text has been removed from the FAD because section 4 now only describes the Appraisal Committee's consideration of the comparison of enzalutamide with best supportive care.
Astellas	In conclusion, Astellas considers that all important predictors have been incorporated (either directly or indirectly) into the IPCW adjustment and that this method provides a more accurate estimate of the true survival benefit conferred by enzalutamide treatment than the two-stage or ITT approach. Furthermore, cost-effectiveness estimates from the ITT approach provide an upper bound on the impact of the survival benefit with enzalutamide on the cost-effectiveness results. Astellas contend that the data used to inform the survival of patients on abiraterone is largely unaffected by bias from the effects of subsequent therapy not available on the NHS.	Comments noted.

Consultee	Comment [sic]	Response
Astellas	Model face validity Patient flow and OS data used On page 20 of the ACD it is stated "*The ERG commented that in the model, a patient's probability of dying per cycle was the same in each health state. The ERG considered this to be implausible because it meant that people with stable, asymptomatic or mildly symptomatic disease on their first treatment had the same risk of dying as people with progressive disease on palliative care after up to 3 lines of active treatment had failed.*" Astellas would like to highlight that the model characteristic described in the ACD does not affect survival for the total model population. The key aim of any Markov cohort model is to calculate the outcomes for the entire model population over the time horizon rather than for an individual patient in a specific health state. However, as highlighted by the ERG, the independence of the survival curve from patient flow through the model has the potential to produce a model that lacks face validity. This independence is a result of using one curve (per arm) to model overall survival for the time horizon of the model.	Comments noted.

Consultee	Comment [sic]	Response
Astellas	The decision to use one curve was based on the selection of PREVAIL data to inform OS. PREVAIL was selected as a result of an absence of suitable OS data to inform each step of the model. Furthermore, as patients in PREVAIL were followed from first-line treatment, through to 2nd line and then 3rd line treatment/palliative care, these data were considered to capture OS over the patient journey. Moreover, separating the events for the individual health states may lead to increased uncertainty, as survival probabilities would be based on small numbers of events. Therefore, the one curve approach was preferred to minimise uncertainty. The independence of OS data and patient flow elevates the importance of balance between the costs and benefits modelled. That is, for a "fair" assessment of relative cost-effectiveness, the flow of patients through the model should represent as closely as possible the journey of patients whose data is used to inform the OS. The decision problem specified by NICE requires an assessment of the cost-effectiveness of enzalutamide in the UK clinical pathway. However, as is common within the clinical trial environment, the patient journey in PREVAIL is not an accurate representation of the patient journey in the NHS. Therefore, Astellas sought to produce a model that: Reflected the decision problem as relevant to the UK NHS; Provided balance between the flow of patients through the model and the journey of patients whose data is used to inform the OS.	Comments noted.

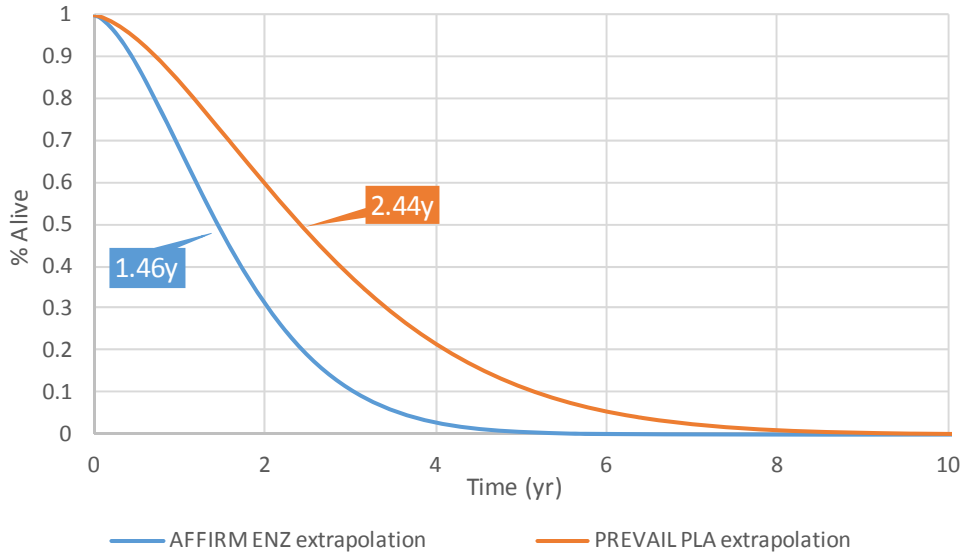
Consultee	Comment [sic]	Response
Astellas	The model submitted by Astellas matches the flow of patients through the cost-effectiveness model with that experienced by patients whose data is used to inform OS and with patients in UK clinical practice, as closely as possible, by: Adjusting (as far as possible) for patients following a treatment pathway outside of that seen in the UK; Using TTD data from the same data cut-off as that used for OS; Using the percentage of patients moving from 1st-line treatment to 2nd-line treatment and the percentage of patients moving from 2nd-line treatment to 3rd-line treatment seen in PREVAIL to inform model transitions. An alternative approach to handling the probability of dying would include a micro-simulation approach, which has been criticised as complex and not transparent in abiraterone's chemo-naïve evaluation. Another approach could be to estimate separate mortality probabilities for the individual Markov health states; however, the level of time-dependency that would be required to be introduced into the Markov model would result in a model that was largely intractable.	Comments noted.
Astellas	Within the ACD, the Committee expresses concern that the time on 2nd line docetaxel and 3rd line enzalutamide (in patients who had not previously received enzalutamide) may not align with clinical practice. For clarification, Astellas used median time on treatment from TAX 327 and from AFFIRM to model the time on treatment with 2nd line docetaxel and 3rd line enza, respectively. Unfortunately, it is not possible to compare these durations with the period of time spent on treatment in PREVAIL; however, it is reasonable to assume that patients receiving enzalutamide following docetaxel may have a similar median treatment duration to that of the enzalutamide arm of AFFIRM. Similarly it is reasonable to assume, that time on treatment with docetaxel would be similar to that seen in TAX 327. These assumptions were validated with UK clinical experts, who fed back that the most likely deviation from these assumptions would be patients previously treated with enzalutamide spending less time on docetaxel than patients previously treated with BSC. If this is the case in PREVAIL, then the model will over-estimate the cost and to a lesser extent the QALYs in the enzalutamide arm.	Comments noted.

Consultee	Comment [sic]	Response
Astellas	Time to treatment discontinuation (TTD) used in the model First of all, Astellas wishes to rectify the statement on page 28 that TTD does not take into account discontinuation of treatment as a result of side effects; this statement is incorrect. In PREVAIL, the TTD definition includes all patients who discontinued the study treatment due to any cause including adverse events. Therefore, the TTD calculations do take into account those patients who discontinued treatment due to toxicity. One of the concerns mentioned in the ACD is the use of June 2014 TTD rather than the September 2013 TTD. On page 11 of the ACD, it is stated that "*The ERG commented that the company had used data up to June 2014 for TTD in its modelling, but that the earlier unblinding of the data in December 2013 may have influenced the decision on whether to continue or stop study treatment.*" Astellas disagrees with assertion made in the ACD that the use of September 2013 TTD is more appropriate than using June 2014 TTD data. At the time of database lock only 61 patients (7.2%) were still on placebo treatment, hence the potential bias for introducing unblinding would be minimal. Moreover, the June 2014 TTD data cut-off includes 1,483 events versus 1,287 events in September 2013, thus the June 2014 data provides more mature data.	Comments noted. Section 4.8 of the FAD states: although a TTD estimate includes people who stop treatment before disease progression, because enzalutamide is well-tolerated, the number of people stopping before progression would be low. Section 4.12 of the FAD states: The Committee preferred the use of the September 2013 data for TTD data because the reduced potential for bias outweighed the benefit of the additional data provided by the June 2014 data.

Consultee	Comment [sic]	Response
Astellas	Proportion of patients moving to docetaxel In the ACD it is stated (page 30): "*It further noted that in the model it was assumed that more than 80% of people would go on to have docetaxel, but in clinical practice in England that figure would be around 40%.*" In line with PREVAIL where 84% of discontinuing patients received second-line treatment, Astellas' model also assumes that 84% of patients move to second-line therapy (i.e., to docetaxel). This value was discussed with clinicians who considered it to reflect clinical practice. The Committee refers to a study by Harris et al[xiv] that would suggest the percentage of patients receiving docetaxel to be lower, however the population in this study and the population moving to chemotherapy in PREVAIL differ. In PREVAIL patients have progressed either on chemo-naïve enzalutamide or BSC, while the population in Harris et al is broader and also includes non-castration-resistant as well as non-metastatic patients, many of whom may not develop metastatic disease and therefore never be suitable for chemotherapy. Summarising the three points above, face validity within the model is achieved by ensuring balance between the flow of patients through the model and the experience of patients whose survival data is used to inform the model outcomes. Therefore, use of June TTD data (which is associated with minimal risk of bias from unblinding) and the proportion of patients moving onto chemotherapy observed in PREVAIL (considered reflective of clinical practice by UK oncologists) should be used to ensure said balance.	Comment noted. The discussion of this in the ACD did not reference Harris et al. Section 4.10 of the FAD states that the 40% estimate came from clinical experts.

Consultee	Comment [sic]	Response
Astellas	External validity of extrapolation of OS On page 31-32 of the ACD the "*Committee also queried why the company had chosen the same parametric curves to reflect both enzalutamide and best supportive care, when the company's own statistical analyses suggested that different curves better reflected the course of the disease.*" Astellas would like to clarify that the approach taken followed the guidance included in the NICE DSU technical support document[xv] which suggests that "*where parametric models are fitted separately to individual treatment arms it is sensible to use the same 'type' of model, that is if a Weibull model is fitted to one treatment arm a Weibull should also be fitted to the other treatment arm*". This avoids fitting vastly different functional forms to patients who have the same underlying disease. On page 31 of the ACD the "*Committee considered that the company had selected the parametric curve based on the predicted survival rates rather than the curve with the best statistical fit to the trial data and was concerned that the company had not done further checks of the face validity of the extrapolated data. For example,* the *Committee queried why the manufacturer had not compared the modelled results with data from trials assessing treatments later in the treatment pathway than PREVAIL or COU-AA-302. The Committee was aware that the company would have had access to the individual patient-level data from the AFFIRM trial of enzalutamide after docetaxel, which could inform the course of patients on first-line best supportive care in this appraisal*".	Comments noted. NICE appreciates this clarification. Section 4.11 of the FAD states: The Committee recognised that the company had selected the parametric curve based on the predicted survival rates and statistical fit to the trial data, rather than the curve with the best statistical fit alone.

Consultee	Comment [sic]	Response
Astellas	Astellas would like to highlight that the fit of alternative models was assessed systematically following the recommendations of the NICE DSU guidance on survival modelling[xv]. Log-cumulative hazard plots, AIC/BIC tests, and clinical plausibility based upon expert judgement were presented and assessed. No external data sources on survival in mCRPC could be identified to externally validate the extrapolation estimates for OS. The use of AFFIRM trial data to inform the course of patients on first-line BSC was considered by Astellas during model development; however, this approach did not provide any additional data. Patients in the PREVAIL study stayed on BSC for a median of 4.55 months (TTD in the placebo arm), subsequently received docetaxel for an assumed median of 9.5 cycles (6.58 months) and then started a next antineoplastic therapy. Thus patients would have been in the study for approximately 12 months before they could be considered comparable to the baseline population in AFFIRM. Median follow-up in PREVAIL was 30 months (June 2014) versus 15 months in AFFIRM (at database lock), thus AFFIRM follow-up is not long enough to validate the extrapolation of the OS curve in PREVAIL. **The Committee questioned the consistency of the chemo-naïve economic model and the post-chemo model (technology appraisal TA316). To assuage these concerns, Astellas has assessed the consistency of the extrapolated survival curves and the consistency of outcomes from the BSC arm of the chemo-naïve model (from 3rd line treatment with enzalutamide until death) with that of the enzalutamide arm of the post-chemo model.**	Comments noted. 4.11 of the FAD states: [the company] had stated that it could not use data from AFFIRM to validate the modelled post-docetaxel survival estimates for enzalutamide because the follow-up period in AFFIRM was not long enough.

Consultee	Comment [sic]	Response
Astellas	Figure 1 Comparison of survival curve extrapolations (PREVAIL and AFFIRM)  Comparison of the survival curves indicate a broadly similar pattern, with the median OS in PREVAIL approximately 1 year greater than that of AFFIRM. This is as expected since the median duration of BSC and chemotherapy for patients in PREVAIL was approximately 12 months (4.55 months plus 6.58 months).	Comments noted.

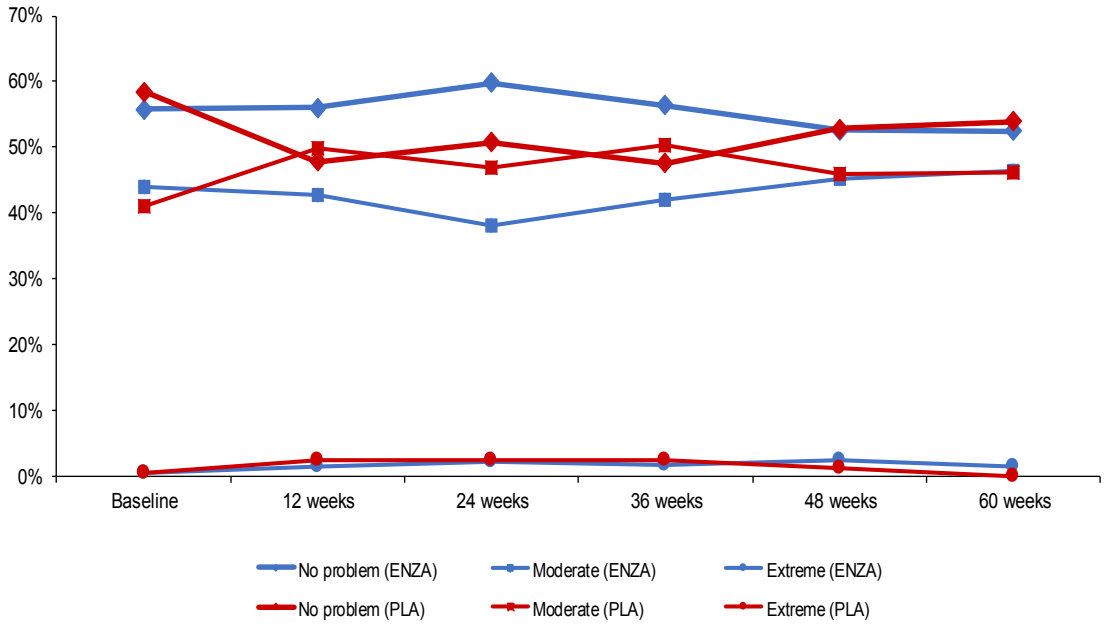
<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td>Astellas</td><td>Table 3 Scenario analysis comparing outcomes of pre-chemo and post-chemo models
<table>
<tr><th>Measure</th><th>PP2 and Palliative, Chemo-naïve model</th><th>Post-chemo model</th></tr>
<tr><td>Cost of treatment (per patient, incl. PAS)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>QALYs on enzalutamide (per patient)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>QALYs palliative</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Total QALYS</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>LYs on enzalutamide (per patient)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>LYs palliative</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Total LYs</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td><td>Comments noted.</td></tr>
</table>

Consultee	Comment [sic]	Response
Astellas	As expected because of the clinical differentiation of patients in PREVAIL and AFFIRM (patients in AFFIRM were permitted to have had more than one chemotherapy treatment, the outcomes of the pre- and post-chemo models are not 100% consistent. However, a reasonable degree of consistency can be seen suggesting that the current model is broadly aligned with the post-chemo model previously accepted by NICE. Finally the Committee criticised the assumed continued treatment effect, and mentioned that sensitivity analyses should have been included to test the impact of this assumption. There is no evidence that indicates that the treatment effect diminishes over time, and the application of individual curves, rather than hazard ratios would already account for this. However, to validate the extrapolation of the OS curve, we have performed an additional analysis representing an extreme scenario where there would be no OS benefit after the trial horizon. In this scenario all patients have an equal probability of dying as observed in the BSC arm after 38 months (approximately the last observation from the PREVAIL study). This modification was applied to the Committee preferred scenario and only had a small impact on the ICER vs BSC (increase by 2.4%). In conclusion, whilst there is uncertainty inherent in economic modelling, the uncertainty associated with the current model has been mitigated as far as possible by strict adherence to DSU guidance and extrapolation. Moreover, the current model displays a high level of consistency with the economic approach taken in the post-chemotherapy indication.	Comments noted.

Consultee	Comment [sic]	Response
Astellas	Model bias against abiraterone On page 19 of the ACD "*For abiraterone, the ERG noted that in the model the TTD curve (extrapolated with a gamma distribution) crossed the OS curve (extrapolated with a Weibull distribution) (…) The ERG noted that although the enzalutamide TTD and OS curves also crossed, this occurred later and had less of an effect on the ICER estimates than did abiraterone's earlier-crossing curves.* " The crossing of the curves is likely to be an artefact of the curve fitting. Although the crossing does not affect survival, it may have a small impact on the number of patients moving to subsequent lines of treatment. In the model, subsequent lines of treatment are associated with both costs and quality of life (but not survival). For PFS with abiraterone the parametric model with the best statistical fit (Gamma) is used in the base case model and is of the same functional form as the curves used for BSC and enzalutamide. For OS the choice of Weibull curve was based on achieving alignment with the curves fitted to the BSC and enzalutamide arm; as per DSU guidance. When the parametric function with the best statistical fit is used to inform OS with abiraterone (Gamma curve), the crossing of the curves is delayed by 16 weeks. This 16 week delay in the crossing of the curves has minimal impact on the proportion of patients moving on to chemotherapy. More importantly, it should be noted that the due to the use of the naïve comparison the model does not adjust for differences in the PREVAIL and COU-AA-302 trial populations. Therefore, since PREVAIL enrolled more severe patients than COU-AA-302 this is likely to lead to bias against enzalutamide.	Comments noted.

Consultee	Comment [sic]	Response
Astellas	Updated base case analysis As stated on page 34 and 35 of the ACD, "*The Committee considered the key modelling assumptions that differed in the company's base case and the ERG's exploratory base case and concluded that the following modelling assumptions were the most plausible:* *The company's assumption that people who had enzalutamide or abiraterone before docetaxel would not have an active treatment after docetaxel.* *The ERG's assumptions on utility values for the stable disease health state and for people having enzalutamide post-docetaxel.* *The ERG's assumption that data from September 2013 rather than June 2014 should be used to model TTD.* *The ERG's assumptions on how to determine the number of people having drugs per model cycle and that drugs are prescribed every 4 weeks, rather than weekly.* *The company's assumptions on the frequency of monitoring visits a person has while on enzalutamide and abiraterone.*" Astellas disagrees with a number of the modifications to the base scenario discussed below.	Comments noted. Since these comments on the ACD the company submitted a revised base case with its revised patient access scheme.

Consultee	Comment [sic]	Response
Astellas	Utility values Stable disease The ERG argued that the change from baseline for the stable disease utility health state should have been included rather than the on-treatment gain. Astellas wishes to highlight that evidence suggests that the health state utility remains stable for patients who have not yet progressed and that the utility gain for patients on enzalutamide is justified as follows. As demonstrated in PREVAIL, enzalutamide significantly improved HRQL compared to placebo, with a least squares (LS) mean estimate for mean changes from baseline for enzalutamide versus placebo of 0.022 (95% CI: 0.003 – 0.041, p=0.021)[xvi]. Moreover, enzalutamide also led to a significantly higher proportion of patients with clinically meaningful improvement on QoL based on EQ-5D index and VAS (p<0.001 for both measures)[xvi]. This improvement in HRQL has been implemented as a utility gain. This approach is in line with the use of an on-treatment utility gain in post-chemotherapy enzalutamide submission which this Committee has previously accepted, agreeing that this reflected the patient experience.[xvii] In addition, the manufacturer submission for abiraterone also used a similar approach of applying on-treatment utility gain for chemo-naïve patients on abiraterone, which was also accepted by NICE.[13]	Comments noted. Since these comments on the ACD the company submitted a revised base case with its revised patient access scheme. In this submission the company used the ERG's approach for determining utility values from AFFIRM.

Consultee	Comment [sic]	Response
Astellas	Figure 2 Time-course of EQ-5D-3L “Pain/Discomfort” dimension by treatment arm 	Figure noted.

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td>Astellas</td><td>When change from baseline was assessed for this item, results indicate that the difference was not clinically meaningful at any time point up to week 61, i.e. for patients while on treatment, according to published minimum important differences (MID)[xvii] Pain is the item having the greatest impact on the utility index according to the time-trade-off algorithm used to calculate it[xvii], and it is widely accepted as being one of the key domains driving patient's QoL[xvii].

Finally enzalutamide significantly delays time to chemotherapy initiation. Unlike in PREVAIL where patients and investigators were blinded to the treatment, in clinical practice patients will know that they have been prescribed a treatment that has shown to significantly delay initiation of chemotherapy (and corresponding toxicity) equating to gain in time spent in good health with its concomitant effects on patient's physical and psychological well-being. This is in addition to enazalutamide significantly delaying disease progression and significantly increasing overall survival. In clinical practice, patients will no longer have the uncertainty whether they are being treated with the new intervention or not, and whether the new intervention has any treatment benefit over BSC. Astellas recognises the difficulty of capturing the benefit of delaying chemotherapy perceived by the patients in the utility values included in the modelling and considers that a stable utility value (including the small utility gain) is the best approach to capture the benefit of delaying chemotherapy in the cost-effectiveness analysis.

Astellas believe based on the points highlighted above that the on treatment utility gain for patients on enzalutamide implemented in the model is justified.</td><td>Comments noted see response above.</td></tr>
<tr><td>Astellas</td><td>PP2

In addition, the ERG had argued that the use of the AFFIRM baseline EQ-5D should have been used to represent the PP2 health state. With this in mind other sources of evidence were taken into account and the weighted average of the available values was deemed more appropriate. The value proposed by Astellas for the PP2 utility and the method used to estimate it are provided in Table 4.

Table 4 Calculation of the utility for PP2
<table><tr><td></td><td>n</td><td>utility</td></tr><tr><td>Wolff[xviii]</td><td>37</td><td>0.66</td></tr><tr><td>Diels[xviii]</td><td>143</td><td>0.60</td></tr><tr><td>AFFIRM</td><td>209</td><td>0.688</td></tr><tr><td>Weighted average</td><td></td><td>0.653</td></tr></table></td><td>Since these comments on the ACD the company submitted a revised base case with its revised patient access scheme. In this revised submission the company proposed a new utility value for people having enzalutamide after docetaxel (the PP2 health state). This was based on data from AFFIRM.</td></tr>
</table>

Consultee	Comment [sic]	Response
Astellas	Palliative care As stated on page 33 of the ACD, "*The Committee also noted that the utility assumed by the company for people having palliative care did not match the value reported in the reference (Sandblom et al. 2004) cited by the company. The Company stated at the meeting that it had rounded down the utility value from 0.526 to 0.500*". Astellas wishes to clarify that the utility value was not taken directly from the Sandblom paper and hence not rounded. This utility value was estimated by calculating the average observed over the last 8 months of life. Utilities from this study ranged from 0.58 (patients with 8–12 months of remaining survival) to 0.46 (patients with <4 months survival remaining). Given that mCRPC patients are likely to spend their last 6–8 months of life in the progressed health state, the average utility of 0.50 was used with a standard error of 0.08. This approach was previously used by Janssen and accepted for the post-chemotherapy abiraterone NICE submission[xviii]. This value has also been used by Janssen in the chemo-naïve abiraterone submission, and no comments were made by the Committee on the calculation[13].	Coment noted. Section 4.13 of the FAD states: The Company clarified in its response to the appraisal consultation document that it had used a weighted average of utility values reported in Sandblom to estimate utility values for people with a similar life expectancy to people modelled to be having palliative care in its model. The Committee noted that the company did not provide the formula it used to get the weighted value.
Astellas	TTD As discussed above Astellas regards the use of June TTD data as more appropriate than the September data (see section 2.2.2).	Comment noted.

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td>Astellas</td><td>Revised ICER
The revised base case scenario taking into account the June TTD data, Astellas' approach to the baseline utility value and the weighted average utility for PP2 is presented in Table 6 and Table 5. The ICER versus the main comparator abiraterone is £[redacted].
Table 5 Revised base case vs the most appropriate comparator abiraterone
<table>
<tr><th></th><th>Enzalutamide</th><th>Abiraterone</th></tr>
<tr><td>Technology acquisition cost</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Other costs</td><td>£16,625</td><td>£17,468</td></tr>
<tr><td>Total costs</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Incremental costs</td><td>-</td><td>£1,408</td></tr>
<tr><td>LYG undisc</td><td>3.238</td><td>3.003</td></tr>
<tr><td>LYG undisc difference</td><td></td><td>0.24</td></tr>
<tr><td>QALYS</td><td>2.28</td><td>2.13</td></tr>
<tr><td>QALY difference</td><td></td><td>0.155</td></tr>
<tr><td>ICER (Cost/QALY gained)</td><td></td><td>[redacted]</td></tr>
</table>
Table 6 Revised base case vs BSC for minority of patient not eligible for abiraterone
<table>
<tr><th></th><th>Enzalutamide</th><th>BSC</th></tr>
<tr><td>Technology acquisition cost</td><td>[redacted]</td><td>£0</td></tr>
<tr><td>Other costs</td><td>£16,625</td><td>£27,700</td></tr>
<tr><td>Total costs</td><td>[redacted]</td><td>£27,700</td></tr>
<tr><td>Incremental costs</td><td>-</td><td>£20,354</td></tr>
<tr><td>LYG undisc</td><td>3.238</td><td>2.745</td></tr>
<tr><td>LYG undisc difference</td><td></td><td>0.493</td></tr>
<tr><td>QALYS</td><td>2.28</td><td>1.69</td></tr>
<tr><td>QALY difference</td><td></td><td>0.598</td></tr>
<tr><td>ICER (Cost/QALY gained)</td><td></td><td>[redacted]</td></tr>
</table></td><td>Comments and revised ICERs noted. Since these comments on the ACD the company submitted a revised base case with its revised patient access scheme.</td></tr>
</table>

Consultee	Comment [sic]	Response
Astellas	PPRS Finally on page 33 of the ACD it is stated "*The Committee agreed that without detailed and transparent justification of how the PPRS would affect enzalutamide, it could not include a rebate in the modelling*." Astellas note there has been a positioning statement produced by NICE which concludes 'NICE consider it reasonable to conclude that the 2014 PPRS Payment Mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines.' Astellas contend this is unreasonable, and will respond to the two major considerations discussed in the document 'PPRS 2014 - NICE Positioning Statement'. The first such consideration is NICE's opinion regarding whether or not PPRS payments can be linked to the price or cost of an individual product under consideration. It is very clear which products are included in the PPRS agreement, and which are not, as laid out in section 4 of the NICE Positioning Statement. The repayment is calculated on the inclusion and exclusion criteria agreed through PPRS, and is paid by each company as a single payment based on a single percentage rebate. It is therefore extremely simple to understand how the PPRS repayment affects each individual product, put simply, the same effect on price as the percentage rebate. The second consideration relates to how such an impact actually affects the opportunity cost of acquiring the product. Astellas believe that there is a positive impact to the NHS. It may indeed be the case that individual commissioners do not receive a portion of the rebate, however, this is a result of the process as agreed with Department of Health. It has been agreed that such repayments are made to the DoH to a 'Health General Cash' account. It is clear therefore that the DoH do indeed benefit from this rebate. Since NHS and each individual trust reporting to NHS ultimately receive budget from the Department of Health, and because the repayment is set up in the manner it is, Astellas believe companies cannot be held responsible for the fact that repayments are not returned to the individual commissioner groups, and indeed this is simply a facet of financial control outside the control of the pharmaceutical industry, but directly in the control of DoH.	Comments noted. The Committee discussion of these comments is reported in section 4.16 of the FAD.

Consultee	Comment [sic]	Response
Astellas	Other points for clarification are as follows. In response to the query regarding where the 10.36% was derived, Astellas wish to clarify that the repayment calculation is undertaken by DoH and shared with companies (details of this can be found on the following link) https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385782/2014_pprs_revised_forecasts_profile_payment_percentages.pdf This is then allocated as standard across members, and calculated according to which products are included. Clearly each relevant product will be subject to the same proportional repayment. Any other methodology would be unreasonable. NICE may also be aware that the 2015 repayment percentage of 10.36% as calculated by DoH is currently in place as the active repayment. Indeed companies have already made one payment to this level. It is also shown on the link that the expectation is that the calculated repayment percentages are likely to continue to increase over the remainder of the PPRS period. NICE comment that there is no certainty that members will remain in the PPRS scheme, and could opt out. It is clear, as NICE have stated in the positioning statement (section 20) that should a member follow this route, they will automatically move under the statutory scheme, which would result in a 15% reduction in their maximum price.	Comments noted. The Committee discussion of these comments is reported in section 4.16 of the FAD.

Consultee	Comment [sic]	Response
Astellas	Astellas would like to further comment that there is no desire to continually review such a discount, but use this time point for the remainder of the PPRS period, and for the 3 years under which the HTA would stand. This would be at a calculated percentage repayment of 10.36%, as per the calculations of DoH. Hence, the impact of the repayment would stand at this level for a known period. Additionally, Astellas would like to point out that repayment methods are indeed a valid and accepted method within Patient Access Schemes. The only difference here, is that the repayment is at a company level back to DoH level, but the impact on particular products is very easily calculable. In summary, Astellas contend DoH and NICE conclusion that the PPRS repayment should not be included in HTAs. This is a repayment methodology which is accepted within Patient Access Schemes, is a flat rate applicable to all members and all products within each company, will stand for the remainder of the PPRS agreement, and benefits DoH which govern overall funding of NHS, trusts and drugs budget within. Astellas cannot be responsible for DoH not making allowance for this repayment at commissioner level, and so also contend that this is a bone fide reason to exclude the repayment within HTAs. Applying the PPRS rebate to all treatments (i.e., enzalutamide as well as abiraterone and docetaxel) to the above described updated base case analysis would result in the ICERs presented in Table 7 and Table 8.	Comments noted. The Committee discussion of these comments is reported in section 4.16 of the FAD.

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td>Astellas</td><td>Table 7 Revised base case including PPRS rebate vs the key comparator abiraterone
<table>
<tr><th></th><th>Enzalutamide</th><th>Abiraterone</th></tr>
<tr><td>Technology acquisition cost</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Other costs</td><td>£16,403</td><td>£17,255</td></tr>
<tr><td>Total costs</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Incremental costs</td><td>-</td><td>£1,166</td></tr>
<tr><td>LYG undisc</td><td>3.238</td><td>3.003</td></tr>
<tr><td>LYG undisc difference</td><td></td><td>0.24</td></tr>
<tr><td>QALYS</td><td>2.28</td><td>2.13</td></tr>
<tr><td>QALY difference</td><td></td><td>0.155</td></tr>
<tr><td>ICER (Cost/QALY gained)</td><td></td><td>[redacted]</td></tr>
</table>
Table 8 Revised base case including PPRS rebate vs BSC
<table>
<tr><th></th><th>Enzalutamide</th><th>BSC</th></tr>
<tr><td>Technology acquisition cost</td><td>[redacted]</td><td>£0</td></tr>
<tr><td>Other costs</td><td>£16,403</td><td>£26,661</td></tr>
<tr><td>Total costs</td><td>[redacted]</td><td>£26,661</td></tr>
<tr><td>Incremental costs</td><td>-</td><td>£17,916</td></tr>
<tr><td>LYG undisc</td><td>3.238</td><td>2.745</td></tr>
<tr><td>LYG undisc difference</td><td></td><td>0.493</td></tr>
<tr><td>QALYS</td><td>2.28</td><td>1.69</td></tr>
<tr><td>QALY difference</td><td></td><td>0.598</td></tr>
<tr><td>ICER (Cost/QALY gained)</td><td></td><td>[redacted]</td></tr>
</table></td><td>Results including the PPRS noted. Section 4.16 of the FAD states: [the Committee] concluded that the PPRS mechanism was irrelevant when considering the cost effectiveness of enzalutamide.</td></tr>
</table>

Consultee	Comment [sic]	Response
Astellas	Summary Enzalutamide is an innovative medicine for the treatment of men with metastatic hormone relapsed prostate cancer who are not yet suitable for docetaxel. Until the licensing of enzalutamide and abiraterone for this indication, there was an unmet need. mHRPC patients were observed with supportive treatment until their disease progressed sufficiently to warrant cytotoxic chemotherapy. Enzalutamide delays the use of cytotoxic chemotherapy, which men with mHRPC identify as being important to them. Abiraterone is the most relevant comparator in this evaluation because it is the standard of care in England, and has previously been identified by this committee as established practice in the NHS. While any model has uncertainty, Astellas has performed extensive analyses that show the face validity of the model results. Astellas recognises the difficulty of capturing the benefit of delaying chemotherapy perceived by the patients in the utility values included in the modelling and considers that a stable utility value (including the small utility gain) is the best approach to capture the benefit of delaying chemotherapy in the cost-effectiveness analysis. Enzalutamide provides a cost-effective treatment alternative for all patients with chemo-naïve mHRPC, with the most plausible estimate of the ICER vs abiraterone is [redacted] (£[redacted] when the additional discount received by the DoH from PPRS is taken into account.)	Summary noted. The responses to the company's comments are given in the preceding sections of this table.
Astellas	Appendix One example of an intervention being available only through the CDF and was considered a relevant comparator in submissions in other diseases is the trastuzumab emtansine submission in breast cancer. In the corresponding FAD[xviii] it is stated: "*(page 28) The Committee noted that continued trastuzumab therapy was not offered by all cancer centres, and that lapatinib plus capecitabine was available in England through the Cancer Drugs Fund… (page 29*) The Committee concluded that local access to treatments and the availability of treatments through the Cancer Drugs Fund led to some variation in clinical practice so that no single pathway of care could be defined… (*page 37*) *After further consideration, the Committee did not change its view that the evaluation of expected survival with current standard of care should be based on that of patients receiving lapatinib plus*." In this particular case, NICE correctly concluded that CDF drugs can be considered comparators if they are considered as standard practice.	Comment noted.

Consultee	Comment [sic]	Response
Astellas	References cited [1] Draft scope of Enzalutamide for treating metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy. Available at: http://www.nice.org.uk/guidance/gid-tag457/documents/prostate-cancer-metastatic-hormonerelapsed-enzalutamide-id683-draft-scope-for-consultation-prereferral-october-2013-2 [1] Final scope of Enzalutamide for treating metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy. Available at: http://www.nice.org.uk/guidance/gid-tag457/documents/prostate-cancer-metastatic-hormonerelapsed-enzalutamide-id683-final-scope2 [1] NHS England, Quarterly figures – including notifications and Individual Cancer Drug Fund Requests (Reporting Period: April 2013 - March 2014). Available at: http://www.england.nhs.uk/wp-content/uploads/2014/04/cdf-m12-report.xlsx [1] NHS England, Quarterly figures – including notifications and Individual Cancer Drug Fund Requests (Reporting Period: April 2014 - March 2015). Available at: http://www.england.nhs.uk/wp-content/uploads/2015/05/cdf-m12-report-2014-15.xlsx [1] Final appraisal determination. Sipuleucel-T for treating asymptomatic or minimally symptomatic metastatic hormone-relapsed prostate cancer. NICE January 2015. Available at: http://www.nice.org.uk/guidance/ta332/documents/prostate-cancer-metastatic-hormone-relapsed-sipuleucelt-1st-line-id573-final-appraisal-determination-document2. [1] NICE DSU Technical support document 16: Adjusting survival time estimates in the presence of treatment switching. Available at: http://www.nicedsu.org.uk/TSD16_Treatment_Switching.pdf [1] Morden JP, et al. Assessing methods for dealing with treatment switching in randomised controlled trials: a simulation study. BMC Medical Research Methodology 2011, 11:4. [1] White IR et al (1999). Randomisation-based methods for correcting for treatment changes: examples from the Concorde trial. Statistics in Medicine; 18: 2617–2634 [1] Yamaguchi T, Ohashi Y. Adjusting for differential proportions of second-line treatment in cancer clinical trials. Part I: Structural nested models and marginal structural models to test and estimate treatment arm effects. Statistics in Medicine 2004; 23(13):1991-2003 [1] Robins JM, Greenland S. Adjusting for Differential Rates of Prophylaxis Therapy for PCP in High-Dose Versus Low-Dose AZT Treatment Arms in An AIDS Randomized Trial. J Am Statist Assoc. 1994; 89(427):737-749	References noted.

Consultee	Comment [sic]	Response
Astellas	[1] Latimer NR, Abrams K, Lambert P, Crowther M, Wailoo A, Morden J, Akehurst R, Campbell M. Adjusting Survival Time Estimates to Account for Treatment Switching in Randomized Controlled Trials—an Economic Evaluation Context: Methods, Limitations, and Recommendations. Medical Decision Making 2014; DOI: 10.1177/0272989X13520192. [1] Rathkopf DE, Smith MR, de Bono JS, Logothetis CJ, Shore ND, de Souza P, Fizazi K, Mulders PF, Mainwaring P, Hainsworth JD, Beer TM, North S, Fradet Y, Van Poppel H, Carles J, Flaig TW, Efstathiou E, Yu EY, Higano CS, Taplin ME, Griffin TW, Todd MB, Yu MK, Park YC, Kheoh T, Small EJ, Scher HI, Molina A, Ryan CJ, Saad F. Updated Interim Efficacy Analysis and Long-term Safety of Abiraterone Acetate in Metastatic Castration-resistant Prostate Cancer Patients Without Prior Chemotherapy (COU-AA-302). Eur Urol. 2014 Mar 6. pii: S0302-2838(14)00185-7. [1] Appraisal Consultation Document for Prostate cancer (metastatic, hormone relapsed, not treated with chemotherapy) - abiraterone acetate (with prednisolone) [ID503]. Available at: http://www.nice.org.uk/guidance/gid-tag434/documents/prostate-cancer-metastatic-hormone-relapsed-not-treated-with-chemotherapy-abiraterone-acetate-with-prednisolone-id503-appraisal-consultation-document [1] Harris V, Lloyd K, Forsey S, Rogers P, Roche M, Parker C. A population-based Study of prostate cancer chemotherapy. Clin Oncology. 2011; 23; 706-708. [1] NICE DSU Technical support document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. [1] Astellas' submission for Prostate cancer (metastatic, hormone-relapsed) - enzalutamide [ID683]. [1] Report for the Analysis of PRO Data Collected in the PREVAIL Study. Dated 19 September 2014. [1] Appraisal Consultation Document for Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen. Available at: http://www.nice.org.uk/guidance/ta316/documents/prostate-cancer-hormone-relapsed-metastatic-enzalutamide-after-docetaxel-appraisal-consultation-document.	References noted.

Consultee	Comment [sic]	Response
Astellas	[1] Pickard AS, Neary MP, Cella D Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer; Health and Quality of Life Outcomes 2007, **5**:70 [1] Dolan P (1997). Modeling valuations for EuroQol health states. Medical Care 35: 1095-1108 [1] McCarberg BH et al. The Impact of Pain on Quality of Life and the Unmet Needs of Pain Management: Results From Pain Sufferers and Physicians Participating in an Internet Survey; American Journal of Therapeutics 2008; 15, 312–320. [1] Wolff JM, Donatz V, Klier J, Erhardt W, Dass RN, Geiges G. Quality of life among German patients with metastatic castration-resistant prostate cancer. Value Health. 2012;15 (7):A431. [1] Diels J, Hamberg P, Ford D, Price PW, Spencer M, Dass RN. Mapping FACT-P to EQ-5D in a large cross-sectional study of metastatic castration-resistant prostate cancer patients. Qual Life Res. 2014. DOI: 10.1007/s11136-014-0794-5. [1] Single Technology Appraisal for “Abiraterone Acetate (Zytiga®) for the Treatment of metastatic castration resistant prostate cancer following previous cytotoxic therapy”. Available at: http://www.nice.org.uk/guidance/ta259/documents/prostate-cancer-metastatic-castration-resistant-abiraterone-following-cytoxic-therapy-manufacturers-submission2 [1] Final appraisal determination for Trastuzumab emtansine for treating HER2- positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane. Available at: http://www.nice.org.uk/guidance/gid-tag350/documents/breast-cancer-her2-positive-unresectable-trastuzumab-emtansine-after-trastuzumab-taxane-final-appraisal-determination-document2.	References noted.

Consultee	Comment [sic]	Response
British Association of Urological Surgeons (BAUS)	***Has all of the relevant evidence been taken into account?*** BAUS feels strongly that urologists, who are the clinicians who predominately diagnose and treat the very many sufferers of prostate cancer, should be in a position to treat them with the innovative androgen receptor blocker enzalutamide when castration resistance develops. NICE states urologists cannot currently access enzalutamide. Although this is true, it is not because urologists do not wish to, but instead because of the SOP (1) governing access to medicines through the Cancer Drugs Fund. If this restriction were not in place, many more urologists would be in a position to prescribe enzalutamide for their patients, jointly with oncologists, in accordance with decisions stemming from their Multidisciplinary Team meeting (MDT). 1. NHS England, Standard Operating Procedures: The Cancer Drugs Fund (CDF), November 2014. Available at: http://www.england.nhs.uk/wp-content/uploads/2014/11/sop-cdf-1114.pdf	Comments noted.

Consultee	Comment [sic]	Response
British Association of Urological Surgeons (BAUS)	***Are the provisional recommendations sound and a suitable basis for guidance to the NHS?*** NICE has recognised that the ability to delay or avoid chemotherapy is highly valued by patients, so much so that some patients would prefer to delay chemotherapy, even if this means that they might not be eligible for chemotherapy in the future (2). However, this is not fully reflected in the recommendations of the ACD. As a natural course of the disease, patients experience significant worsening quality of life. New treatments like enzalutamide may help improve quality of life in many men, allowing them to return to or carry on with day to day activities (3,4). This has not been adequately recognised and endorsed in the ACD. If a solution cannot be found, a negative decision by NICE would mean that 5000 men in England and Wales would potentially miss out on routine access to the treatment on the NHS. This is particularly pertinent when considering patients in whom administration of cytotoxic chemotherapy would be clinically inappropriate. 2. NICE, Enzalutamide for treating metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy – Appraisal Consultation Document, 11 June 2015, accessed on 23 June 2015. Available at:https://www.nice.org.uk/guidance/gid-tag457/resources/prostate-cancer-metastatic-hormonerelapsed-enzalutamide-id683-appraisal-consultation-document 3. Loriot Y. et al, Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial, Lancet Oncology, 2015:16: 509;521 4. Prostate Cancer UK, Consultee submission – Prostate Cancer UK. Available at:http://www.nice.org.uk/guidance/gid-inconsultation/resources/prostate-cancer-metastatic-hormonerelapsed-enzalutamide-id683-committee-papers-2	Comments noted. Section 4.18 of the FAD reports that the Committee considered the benefits associated with enzalutamide to be innovative, and that not all of these benefits were captured in the QALY calculation.

Consultee	Comment [sic]	Response
British Association of Urological Surgeons (BAUS)	***Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?*** Restrictions on access to enzalutamide would further exacerbate the disadvantage faced by men living with cancer who experience poorer access to cancer treatments than women (5), and considerably poorer survival rates compared with men across Europe(6)." 5.Cancer Research UK, Global cancer death toll 50 per cent higher in men than women, 14 February 2014. Available at: http://www.cancerresearchuk.org/about-us/cancer-news/press-release/2014-02-14-global-cancer-death-toll-50-per-cent-higher-in-men-than-women 6.WHO, International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), 2015. Available at: http://apps.who.int/classifications/icd10/browse/2015/en	Comment noted.

Consultee	Comment [sic]	Response
British Uro-oncology Group (BUG)	Men with metastatic Castration Resistant Prostate Cancer (mCRPC), whose disease is asymptomatic or mildly symptomatic, and for whom chemotherapy may not be immediately appropriate or necessary, have limited treatment options. The British Uro-oncology Group (BUG) fails to understand NICE's preliminary recommendation that: *1.1 Enzalutamide is not recommended for treating metastatic hormone relapsed prostate cancer in people who have no or mild symptoms after androgen deprivation therapy has failed, and when chemotherapy is not yet clinically indicated.* BUG urges NICE to re-consider its ACD recommendation on the basis that enzalutamide in the pre-chemotherapy setting has the potential to prolong survival, palliate symptoms, and improve quality of life for men suffering from prostate cancer. In the UK, responsibility for initiating treatment and managing patients will most likely lie with the oncologist and their team. As experts in their field oncologists recognise that there are patients who will respond very well to enzalutamide which is an oral and well tolerated and easily accessible treatment which allows them to delay time to chemotherapy. There are also patients who chose to avoid chemotherapy, even if it means that they may then not be eligible for chemotherapy at a later date.	Comments noted. Since this comment on the ACD was made, the company agreed a revised patient access scheme with the Department of Health and enzalutamide has now been recommended for this indication

Consultee	Comment [sic]	Response
British Uro-oncology Group (BUG)	The data relating to enzalutamide and the fact that it can be accessed by the CDF in the pre-chemotherapy setting, strongly support a positive NICE appraisal: Enzalutamide met both its primary endpoints of overall survival (OS) and radiographic progression free survival (rPFS) in the PREVAIL study. The PREVAIL results were reviewed by the independent Data Monitoring Committee after 540 deaths and in light of statistically significant benefits in OS and rPFS in favour of enzalutamide, the PREVAIL trial was stopped and unblinded. The time on the study drug was more than three times longer for enzalutamide than placebo with a median treatment duration of 16.6 months versus 4.6 months. At the time of the data cut-off 42.1% of men continued on enzalutamide versus only 7.2% of the placebo group continuing. At the point of analysis, 72% of patients in the enzalutamide group were alive, compared to 63% in the placebo group (HR, 0.71; 95% CI, 0.60 to 0.84; P<0.001). Enzalutamide reduced the risk of death by 29%. This survival benefit was reported across all subgroups including those with European Co-operative Group (ECOG) performance status 0 or 1, ages above or below 75, different geographical locations and those men with or without visceral disease. A significant difference in the rate of rPFS was also reported, with no progression in 65% of subjects in the enzalutamide group compared to 14% in the placebo group (HR, 0.19; 95% CI, 0.15 to 0.23; P<0.001). This 81% reduction in the risk of radiographic progression is both statistically and clinically significant, and applies to all subgroups including those with visceral metastases.	Comments noted. These data were presented in the company's submission and have been considered by the Committee.

Consultee	Comment [sic]	Response
British Uro-oncology Group	Enzalutamide also showed benefits with regard to secondary endpoints, which are of critical importance for patients. Other treatments in this setting have shown tumour activity and this will often improve quality of life (QOL) by reducing the cancer disease burden and consequently the complications of prostate cancer. However there is a balance between this efficacy and the tolerability and ease of access to drugs which is important to maintain the optimal quality of life for our patients. In the PREVAIL study, there was a significant delay in the time to QOL deterioration as measured by the validated FACT-P scoring tool. The time to FACT-P global score decline was 11.3 months for enzalutamide and 5.6 months for placebo patients respectively (HR, 0.169; p<0.0001). Enzalutamide also significantly delayed the median time to cytotoxic chemotherapy by 17 months. A 28 month delay was seen in enzalutamide patients compared to 10.8 months for placebo (HR, 0.35 95% CI: 0.30–0.40; p<0.0001. Other secondary endpoints which showed significant benefit for enzalutamide included the time to first skeletal-related event (HR, 0.72), time to PSA progression (HR, 0.17), and the number of subjects experiencing a PSA drop of at least 50% (78% vs. 3%) (P<0.001 for all comparisons).	Comments noted. These data were presented in the company's submission and have been considered by the Committee.

Consultee	Comment [sic]	Response
British Uro-oncology Group	The excellent tolerability of enzalutamide previously demonstrated in the earlier AFFIRM study was confirmed in the PREVAIL study. Adverse events were similar in both arms of the trial and reported for 96.9% of men receiving enzalutamide and 93.2% for placebo. It is important to note the difference in duration of study drug which was longer for enzalutamide (16.6 vs 4.6 months for placebo). Study discontinuation due to an adverse event occurred in 5.6% of the enzalutamide group and 6.0% of placebo patients. The most common clinically relevant adverse events associated with enzalutamide were fatigue (35.6% vs 25.8%) and hypertension (13.4% vs 4.1%). There was a very low risk of abnormalities in liver function tests in both groups (0.9% vs 0.6%) with no need for routine monitoring of patients on enzalutamide. There was no increase in the seizure risk with one seizure reported in the placebo group during the monitoring period and one seizure in the enzalutamide group after the data cut-off period. An updated analysis of the overall survival data from PREVAIL was conducted at 784 deaths and presented at the EAU in March 2015. The data confirmed a statistically significant overall survival benefit for enzalutamide with a 23% reduction in risk of death (OS: HR 0.77; 95% CI 0.67–0.88; p=0.0002) and a 4-month improvement in median survival with enzalutamide (35.3 months [95% CI 32.2 – not yet reached]) over placebo (31.3 months [95% CI 28.8 – 34.2]). This analysis further demonstrates the anti-tumour efficacy of enzalutamide and a delayed need for chemotherapy, an objective response rate of 59%, and a quality of life response rate of 40%.	Comments noted.

Consultee	Comment [sic]	Response
British Uro-oncology Group	In summary, enzalutamide demonstrates excellent efficacy and tolerability with meaningful endpoints and maintenance of QOL for men with mCRPC. The importance of enzalutamide in daily clinical practice has been demonstrated by the number of applications by oncologists to the Cancer Drugs Fund (CDF). Requests for enzalutamide have steadily increased since it became available on the CDF in March 2014. The last recorded data for March 2015 documents 244 new applications for enzalutamide in total for hormone relapsed prostate cancer. This highlights the importance of enzalutamide in the prostate cancer treatment pathway and the strong preference of patients to receive enzalutamide instead of chemotherapy in this setting and the support for this approach by their oncologists.	Comments noted.
British Uro-oncology Group	We are disappointed that despite applications to attend the NICE appraisal, English oncology representatives, including from BUG, were not able to attend the meeting, to put the patients' and clinicians' point of view directly and support the committee. We believe that oncologists in England have developed extensive experience of prescribing enzalutamide in the chemotherapy naïve setting and would be able to give first hand experience of the benefits of prescribing enzalutamide to the committee to enable an informed and balanced decision to be given. Restrictions on access to enzalutamide in the pre-chemotherapy setting of metastatic hormone refractory prostate cancer would exacerbate the poorer survival rates faced by men living with prostate cancer in UK compared to survival rates across Europe and this is of greater importance particularly the initiatives taken by NICE to improve the survival rates including the early referral guidelines. The British Uro-oncology Group urges NICE to make an accommodation with the manufacturer and review its ACD so as to allow continued prescribing of enzalutamide in chemotherapy naïve patients. The addition of enzalutamide at progression provides meaningful clinical benefit to men with metastatic castration resistant prostate cancer and it is very well tolerated, providing patients with optimal, productive quality of life.	Comments noted. Many thanks for your nominations. It is part of the technology appraisals process that the Appraisal Committee Chair decides the clinical experts from those nominated by consultees.

Consultee	Comment [sic]	Response
Prostate Cancer UK	Thank you for giving Prostate Cancer UK the opportunity to respond to NICE's appraisal consultation document (ACD) on enzalutamide for metastatic hormone-relapsed prostate cancer when chemotherapy is not yet clinically indicated. **About us** Prostate Cancer UK is the UK's leading charity for men with prostate cancer and prostate problems. We support men and provide information, find answers through funding research and lead change to raise awareness and improve care. The charity is committed to ensuring the voice of people affected by prostate disease is at the heart of all we do.	Comments noted.

Consultee	Comment [sic]	Response
Prostate Cancer UK	**Consultation response** **Has all of the relevant evidence been taken into account?** Yes. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** No. The subgroup of patients for whom enzalutamide would be the only active treatment option was not considered as part of the economic modelling scenarios. This subgroup pertains to those with visceral disease and liver dysfunction, for whom abiraterone is contraindicated, or those who cannot take corticosteroids. There was also no consideration given in the economic modelling to the subgroup of patients who will never receive chemotherapy. We recommend for these patient subgroups to be considered by the Evidence Review Group (ERG) in its economic modelling scenarios. In addition, the ERG calculated the cost of enzalutamide based on the number of patients at the start of a treatment cycle, whereas the company based costs on the number of patients on treatment at the end. We would like clarity about why the ERG did not consider a costing scenario based on the average time to treatment discontinuation (TTD). We believe this may provide a useful estimate for the real-world usage of enzalutamide.	Comments noted. No evidence for the clinical and cost effectiveness of enzalutamide in the subgroup of people for whom enzalutamide is the only active treatment was presented to Committee. The appraisal Committee can only appraise enzalutamide within its marketing authorisation. The marketing authorisation does not cover the use of enzalutamide at the position in the treatment pathway where people need chemotherapy but do not receive it. It is the Company's responsibility to provide the evidence on which Committee makes its decision. The ERG critique and explore uncertainties in the company's data but do not independently provide new data.

Consultee	Comment [sic]	Response
Prostate Cancer UK	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No, we do not believe that the Appraisal Committee's preliminary recommendation 1.1 constitutes a suitable basis for guidance to the NHS. Enzalutamide is the only treatment option for men with visceral disease and liver dysfunction, for whom abiraterone is contraindicated, and for men who cannot take corticosteroids. We cannot support a decision that will leave these men without active treatment for their disease. In addition, enzalutamide is an important treatment option for those men who are unable to receive, or who do not wish to receive, chemotherapy. At least 20 to 40% of patients with metastatic prostate cancer never receive chemotherapy (1–3). Again, without a positive recommendation from NICE, these men will be left without an active treatment option. Of these men, those who are unsuitable for abiraterone also will be denied their only active treatment option. We are also in disagreement with the Appraisal Committee's preliminary recommendation 1.1 owing to the clinical benefits associated with enzalutamide when used to treat metastatic, hormone-relapsed prostate cancer in the chemotherapy naïve setting. Enzalutamide is well tolerated and can delay chemotherapy, and its side-effects, by an average of 17 months (4). We know from men with prostate cancer that delaying the initiation of cytotoxic chemotherapy is a valuable option in the treatment pathway, owing to the quality of life benefits gained (5). It is also an important treatment option for those men who have tried treatment with abiraterone, but have been unable to complete treatment with it because the side-effects they experienced were too severe. There will be some men for whom enzalutamide is their last remaining active treatment option at this stage of the treatment pathway and it is crucial for enzalutamide to be made available to these men.	Comments noted.

Consultee	Comment [sic]	Response
Prostate Cancer UK	The Appraisal Committee's preliminary recommendation is particularly concerning given the uncertainties around the future availability of enzalutamide in England via the Cancer Drugs Fund (CDF). Enzalutamide is currently available via the CDF for men with hormone-relapsed prostate cancer who have not received previous treatment with chemotherapy (6), and 807 men have accessed the drug for this indication since it became available on the Fund in September 2014 (7). Hundreds of men will be left without enzalutamide if it does not move into baseline commissioning and is no longer available via the CDF We believe that, as an absolute minimum, the Appraisal Committee should consider a positive recommendation for the subgroups of patients for whom enzalutamide is their only active treatment option. As an ideal, and if cost-effective, we would like for enzalutamide to be recommended within its licensed indication so that all men at this stage of the prostate cancer treatment pathway can benefit from it, if they and their clinician believe it is the best treatment option for them. If a positive recommendation cannot be reached, we agree with the Appraisal Committee's preliminary recommendation 1.2.	Comments noted.
Prostate Cancer UK	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** No. Thank you again for this opportunity to respond to NICE's ACD on enzalutamide for metastatic hormone-relapsed prostate cancer when chemotherapy is not yet clinically indicated.	Comments noted.

Consultee	Comment [sic]	Response
Prostate Cancer UK	1. Harris V, Lloyd K, Forsey S, Rogers P, Roche M, Parker C. A population-based study of prostate cancer chemotherapy. Clin Oncol R Coll Radiol G B. 2011 Dec;23(10):706–8. 2. Perlroth DJ, Luna Y, Goldman D, Thompson SF, Mozaffari E, Lakdawalla D. Treating people right: who goes untreated with systemic therapy for metastatic prostate cancer (mPC)? F1000Posters [Internet]. 2012 Mar 13 [cited 2014 Sep 17];3(153). Available from: http://f1000.com/posters/browse/summary/1089934 3. Perlroth DJ, Thompson SF, Luna Y, Goldman D, Mozaffari E, Lakdawalla D. Timing is everything: time to ADT and chemotherapy initiation for treatment of metastatic prostate cancer. F1000Posters [Internet]. 2012 Mar 13 [cited 2014 Sep 17];3(152). Available from: http://f1000.com/posters/browse/summary/1089933 4. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014 Jul 31;371(5):424–33. 5. Prostate Cancer UK. “A survey of the public’s views on Xtandi® (enzalutamide) becoming a treatment option for men with advanced prostate cancer, who have not previously received chemotherapy”. Total sample size was 267 UK adults which included men with prostate cancer and friends/family of men with prostate cancer. Fieldwork was undertaken between 7th January and 1st February 2015. The survey was carried out online. 2015. 6. NHS England. National Cancer Drugs Fund List Ver 4.2 [Internet]. 2015. Available from: http://www.england.nhs.uk/wp-content/uploads/2015/05/ncdf-list-may15-upd.pdf 7. NHS England. Cancer Drugs Fund Reporting Template. Reporting Period: April 2014 - March 2015 [Internet]. 2015. Available from: http://www.england.nhs.uk/wp-content/uploads/2015/05/cdf-m12-report-2014-15.xlsx	References noted.
NHS England	Please find NHS England’s response to the ACD – enzalutamide which has been reviewed by the Chemotherapy CRG Has all of the relevant evidence been taken into account? Yes Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Possibly- see below	Comments noted.

Consultee	Comment [sic]	Response
NHS England	Any other comments? NHS England would like to make two comments: Section 4.1 – it is our belief that no systemic anti-cancer therapy should be prescribed by urologists. All forms for access to drugs via the CDF contain the following criteria “Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy”. Whilst this is documented for CDF drugs we would consider the same rule should apply to all SACT including both abiraterone and enzalutamide. Therefore urologists should not have access to prescribing these drugs. Section 4.1 – both abiraterone and enzalutamide are available in this indication via the CDF. There is no limitation imposed on their access based on whether the prescriber is based in a larger or smaller centre. Therefore we are concerned that the statement that access to abiraterone varies due to this factor is based on a statement without evidence and that if access is limited in this way then it would, by default, be limited for enzalutamide and potentially many other cancer drugs. Clearly we believe that as a result the wording of section 4.1 should be reviewed and, possibly, that abiraterone should perhaps be considered as a comparator.	Comments noted. The discussions on variability of access to abiraterone in section 4.1 of the ACD have been removed from the FAD.

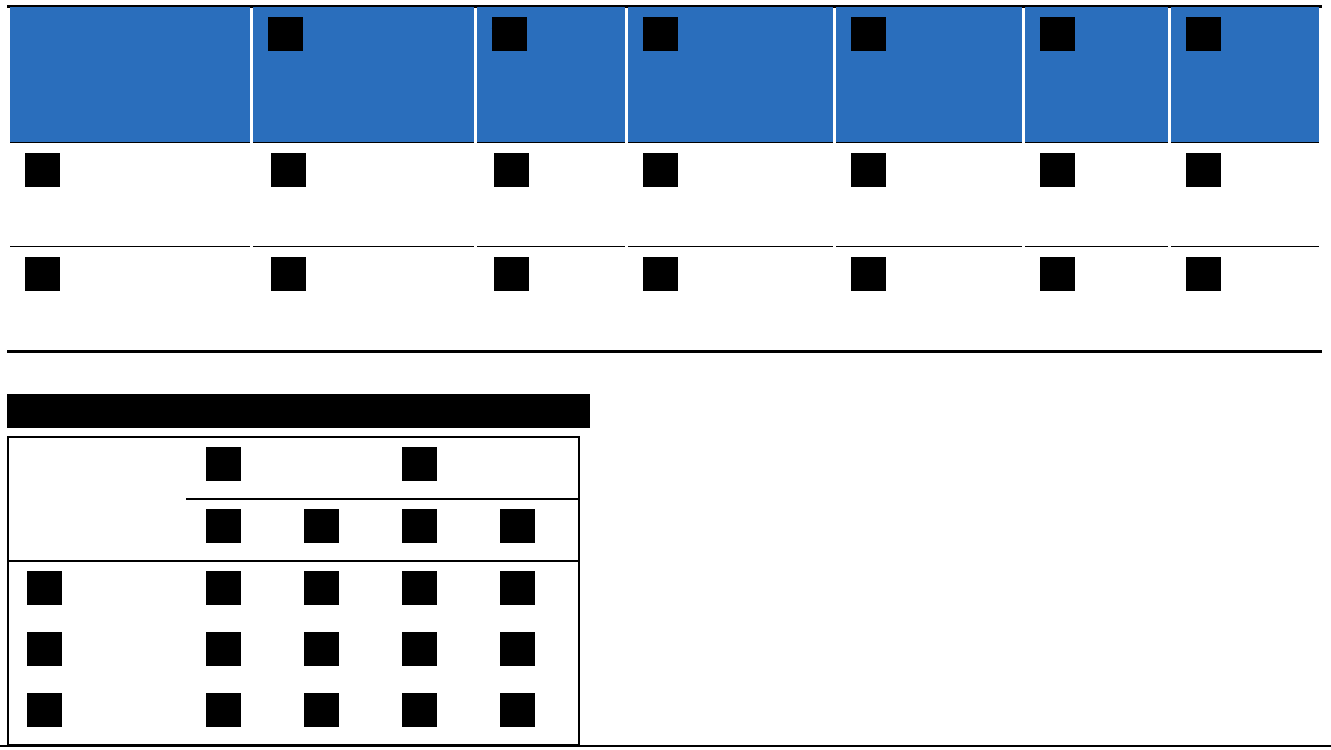
Comments received from clinical experts and patient experts: None

Nominating organisation	Comment [sic]	Response

Comments received from commentators

Commentator	Comment [sic]	Response
Janssen	Please find below Janssen's response to the second Appraisal Consultation Document (ACD) for enzalutamide. We are pleased to have the opportunity to provide our comments on the ACD for enzalutamide for the management of metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy. We would like first to raise two points about some inaccurate statements presented in the ACD. **Patient population** The point 4.1 of the ACD regarding the restriction of the eligible population based on liver impairment is not accurate. Based on the Summary of Product Characteristics (SmPC) of both enzalutamide and abiraterone, both drugs can be used in patients with moderate liver impairment, although some caution should be exercised on how patients are assessed when on abiraterone. It should also be noted that both enzalutamide and abiraterone are not recommended for use in patients with severe hepatic impairment.	Comments noted. The manufacturer of enzalutamide told the Committee at the second meeting that the summary of product characteristics for enzalutamide has been recently updated to state that enzalutamide can be used by people who have severe liver dysfunction.
Janssen	**Statistically significant difference in OS in COU-AA-302** Point 3.10 stating that "As in PREVAIL, COU-AA-302 had interim and final analyses, but unlike PREVAIL, it was stopped early without the criterion for a statistically significant difference in OS being met" is inaccurate. The COU-AA-302 trial was not stopped early; the trial was only unblinded between the second interim analysis and the final analysis, however, patient follow-up continued post the second interim analysis and the co-primary endpoint of a statistically significant difference in median overall survival was met at the final analysis. Median overall survival was significantly longer in the abiraterone acetate group than in the placebo group at this analysis (34·7 months [95% CI 32·7–36·8] vs 30·3 months [28·7–33·3]; hazard ratio 0·81 [95% CI 0·70–0·93]; p=0·0033), at a median follow-up of 49·2 months (Ryan et al. 2015).	Comment noted: The FAD (section 3.10) has been updated to read: As in PREVAIL, COU-AA-302 had interim and final analyses, but unlike PREVAIL, it was unblinded early without the pre-specified criterion for a statistically significant difference in overall survival at an interim analysis being met.

Commentator	Comment [sic]	Response
Janssen	Has all of the relevant evidence been taken into account? **Indirect treatment comparison** We do not agree with the indirect comparison approach (point 3.10) chosen by the manufacturer who conducted a naïve-treatment comparison of enzalutamide versus abiraterone assuming that the treatment effect in the control arm of COU-AA-302 was the same as that in the control arm of PREVAIL. Standard of care in chemotherapy-naïve mHRPC patients is use of corticosteroids. The proportion of study participants receiving corticosteroids in the control arm of COU-AA-302 (100% receiving prednisone) differed to that in PREVAIL (30% receiving corticosteroids throughout the trial). In this context, the control arm of COU-AA-302 better reflects standard of care in the UK than the control arm of PREVAIL. Consequently, assuming that the treatment effect of the two treatment arms is the same is inaccurate, and the lack of adjustment biases the indirect comparison in favour of enzalutamide. A matching treatment comparison adjusted on these differences should have instead been conducted.	Comments noted.
Janssen	[redacted]	Comments noted. NICE are unable comment these on additional commercial in confidence analyses provided by Janssen.

Commentator	Comment [sic]	Response
Janssen	[redacted] 	Comments noted. NICE are unable comment these on additional commercial in confidence analyses provided by Janssen.
Janssen	[redacted]	Comments noted. NICE are unable comment these on additional commercial in confidence analyses provided by Janssen.

Commentator	Comment [sic]	Response
Janssen	**Time horizon** The time horizon of 10 years considered as part of the base case economic analysis (point 3.14) is too short to adequately capture the life time of the mHRPC patients who would respond well to enzalutamide (around 20-30% of the patients treated with enzalutamide had not progressed at 36 months; Beer et al, 2015, ASCO) and who would continue to receive enzalutamide until progression based upon data extrapolation. [redacted] In this context, a lifetime time horizon should have been considered as part of the base case.	Comments noted.
Janssen	Choice of data extrapolation Janssen agrees with the Committee that the extrapolation of the OS and TTP curves for abiraterone and enzalutamide should be revised as the extrapolated OS and TTD curves crossed, indicating that patients died before their disease had progressed. Furthermore, the extrapolation of the OS and TTD curves for abiraterone should also be reconsidered on the basis that the two curves crossed earlier for abiraterone than for enzalutamide, biasing the model in favour of enzalutamide. It should also be noted that the decision to use the rPFS data from COU-AA-302 to estimate the TTD for abiraterone has also created a bias in the analysis that is emphasized by the data extrapolation.	Comments noted.
Janssen	Utility The current disutility associated with skeletal related-events (SRE) was applied for one month only as part of the economic modelling. This underestimates the duration of effect and is not aligned with published literature. Oglesby et al. (2008) studied the hospital burden associated with metastatic bone disease and SREs in prostate cancer patients and reported an average length of stay of 43 days, to which the impact of such a long hospitalisation on patients' quality of life post their discharge should be added. It should also be noted that some SREs, such as spinal cord compression, are associated with a lifetime effect on patients (Matza et al, 2013).	Comments noted.

Commentator	Comment [sic]	Response
Janssen	**Treatment sequence** We agree with the ERG that a quality of life gain should be applied to post-docetaxel treatment as it is likely that patients treated with enzalutamide or best supportive care before docetaxel would be treated with abiraterone after docetaxel. However, it is unlikely that people who had abiraterone before docetaxel would be treated with enzalutamide after docetaxel based upon the NICE guidance of enzalutamide in post-chemotherapy patients (TA316). **Drug costs** We agree with the ERG (point 3.32) that clinicians prescribe one-pack of either enzalutamide or abiraterone at a time and not weekly as assumed by the manufacturer. It should be noted that a pack of abiraterone corresponds to 30 days of treatment, while a pack of enzalutamide corresponds to 28 days of treatment. **Monitoring costs** We agree with the clinical experts that the difference in assumptions used by the manufacturer regarding monitoring costs for abiraterone and for enzalutamide is not justified. The frequency of monitoring of people taking enzalutamide and abiraterone is expected to be the same with monitoring visits every month.	Comments noted.

Commentator	Comment [sic]	Response
Janssen	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? **Cost-effectiveness analysis versus abiraterone** In point 3.23, it is noted that in the company's deterministic base case, best supportive care was associated with 1.657 quality-adjusted life years (QALYs); abiraterone with 2.120 QALYs and enzalutamide with 2.274 QALYs, meaning that abiraterone would give more benefit than best supportive care. However, the conclusion of point 3.23 seems to imply that best supportive care provides more benefit than abiraterone and that abiraterone is extensively dominated by best supportive care. The interpretation of the relative cost effectiveness versus abiraterone needs to be revised. It should also be noted that the assumptions used to define the best supportive care comparator (control arm of PREVAIL) do not represent standard of care in the UK (where a large majority of patients receive corticosteroids as part of their pre-chemotherapy management), biasing the analyses in favour of enzalutamide. The OS and TTP data used to inform best supportive care should have been adjusted to the fact that only 30% of the patients in the PREVAIL control arm actually received corticosteroids.	Comment noted. Since this comment on the ACD was made Astelllas (the company that makes enzalutamide) agreed a new patient access scheme with the Department of Health. Because the Committee had agreed that best supportive care was the appropriate comparator to determine whether enzalutamide is cost effective, the company did not provide the incremental cost effectiveness ratio for enzalutamide compared with abiraterone in its revised submission incorporating the new patient access scheme.
Janssen	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Yes	Comment noted

Comments received from members of the public

Consultee	Comment [sic]	Response

Philip Cornford Consultant Urological Surgeon NHS Professional England Declared interest – none Disclosure: I have contributed advice boards for Astellas, Jansen, Ipsen and Ferring. In addition my wife works for AstraZeneca	Increasing evidence of the clinical value of novel hormone manipulations (including both enzalutamide and Abiraterone) has led to adoption of these innovative medicines as a management options in the EAU prostate cancer guidelines and increasing uptake across western Europe. The decision to not recommend use in UK appears to have the following issues 1) Enzalutamide when used to treat men with metastatic hormone-relapsed prostate cancer leads to a clinically and statistically significant improvement in overall survival. The effect will probably more marked in the UK where many of the confounding interventions are not licenced, However this divergence between UK medical practice and European practice because of different funding structures will need to be overcome if men in UK are to benefit from medical advances and narrow the divide in cancer outcomes 2) Monitoring of patients on Enzalutamide are significantly less intense than for Abiraterone. Men taking Enzalutamide can be reviewed every 2 months and when stable on medication this could be every 3 months as these men are likely to respond predictably to drug for a median of 30 months 3) Unless there is to be a change in the ruling that men can only have either Enzalutamide or Abiraterone modelling the costs associated with sequential use seems aimed to increase cost without any evidence of effectiveness. Although data may become available in the future currently there is a dearth of data show sequential use to be effective 4) STAMPEDE has shown Docetaxel combined with androgen deprivation to improve outcomes for men presenting with Hormone naive metastatic prostate cancer as a consequence many of the men presenting with metastatic hormone relapsed disease and presumably will be eligible for enzalutamide, The difficulty will be for those men who don't wish to have or can't cope with docetaxel. Prior to use via the CDF men were given a single cycle of docetaxel just to make the eligible for these novel androgen manipulations. As a consequence would it not be wiser to allow one novel androgen manipulation (either Enzalutamide or abiraterone currently) either before or after Docetaxel chemotherapy and allow patients and their clinicians to decide sequencing	Comments noted. Comment noted. At the second meeting the clinical experts stated that the sequential use of enzalutamide and abiraterone it is not supported in the UK. .

Fiona Sexton President British Association of Urological Nurses Declared interest – no Disclosure: n/a	As a natural course of the disease, patients experience worsening quality of life. New treatments like enzalutamide may help improve quality of life in many men, allowing them to return to or carry on with day to day activities[i, ii]. This has not been adequately recognised and endorsed in the ACD [i] Loriot Y. et al, Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial, Lancet Oncology, 2015:16: 509;521 NICE has recognised that the ability to delay or avoid chemotherapy is highly valued by patients, so much so that some patients would prefer to delay chemotherapy even if this means that they might not be eligible for chemotherapy in the future[iii] However, this is not fully reflected in the recommendations of the ACD If a solution cannot be found, Astellas Pharma Ltd estimates that a negative decision by NICE would mean that up to 5,500 men in England and Wales would potentially miss out on routine access to the treatment on the NHS. Restrictions on access to enzalutamide would further exacerbate the disadvantage faced by men living with cancer who experience poorer access to cancer treatments than women [iv], and poorer survival rates than men across Europe [v] [ii] Prostate Cancer UK, Consultee submission â€“ Prostate Cancer UK, accessed on 19 June 2015. Available at: http://www.nice.org.uk/guidance/gid-inconsultation/resources/prostate-cancer-metastatic-hormonerelapsed-enzalutamide-id683-committee-papers-2	Comment noted. The Committee considered the benefits of enzalutamide in terms of improved overall survival and quality of life

Astellas' Response to NICE Final Appraisal Determination (FAD) Enzalutamide for metastatic hormone-relapsed prostate cancer when chemotherapy is not yet clinically indicated – ID683

In response to the Final Appraisal Determination (FAD) document, Astellas would like to submit an additional analysis using a revised patient access scheme (PAS) for enzalutamide. The analysis described in this response document incorporates all of the assumptions preferred by the Committee, as listed in the FAD, with two modifications: 1) a revised PAS for enzalutamide and 2) revised calculation of the post progression 2 (PP2) utility. The additional analysis presented here shows that enzalutamide is a cost-effective treatment option at a WTP of £30,000 per QALY.

1 Revised patient access scheme

Astellas has agreed a revised PAS for enzalutamide with the Department of Health [redacted]. With the PAS, enzalutamide is available at a price of [redacted] per pack of 112 capsules. The revised PAS is used in the analysis presented here.

2 PP2 utility

In the FAD the Committee expresses their preference for the ERGs approach to the modelling of utility. However, there is an inconsistency in the ERGs approach to the calculation of utility between the stable disease and the PP2 health states.

In its revised analyses, the ERG had adjusted the stable disease baseline utility for the mean change from baseline in the placebo arm of PREVAIL before applying the on-treatment utility gain. However the same adjustment was not made to the PP2 on-treatment baseline utility, leading to an inconsistency in the model. In order to apply a consistent approach the mean change from baseline from the AFFIRM placebo arm (-0.05, standard deviation 0.02) has been applied to the baseline EQ-5D (0.688) before adding the on-treatment utility gain (0.04).

3 Revised analysis

The revised analysis consists of the following scenario:

- Stable disease utility as per the ERGs modification
- PP2 utility based on the AFFIRM baseline EQ-5D (0.688) corrected for the average change from baseline (0.05)
- September 2013 data to model TTD
- The ERG's assumptions on how to determine the number of people having drugs per model cycle and that drugs are prescribed every 4 weeks, rather than weekly
- The updated PAS is used for enzalutamide in the enzalutamide arm

In line with the Committee's recommendation only results against BSC are presented. The results of the revised base case are shown in Table 1 below; enzalutamide has an incremental cost effectiveness ratio against BSC of £27,036 per QALY gained.

Table 1 Revised base case

	Enzalutamide	BSC
Technology acquisition cost	[redacted]	[redacted]
Other costs	[redacted]	[redacted]
Total costs	[redacted]	[redacted]
Difference in total costs	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
ICER		£27,036

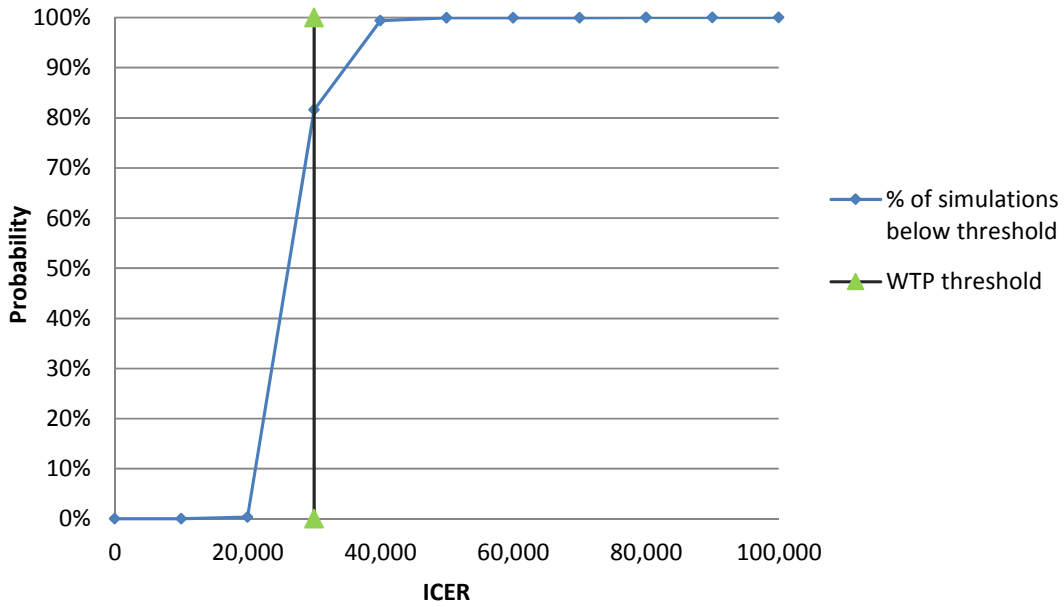
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

The probabilistic sensitivity analysis indicates that enzalutamide has an 81.6% probability of being cost-effective at a willingness to pay of £30,000. A scatter plot and cost-effectiveness acceptability curve (CEAC) are shown in Figure 1 and Figure 2 respectively. A summary of the PSA results, and a comparison with the deterministic results is provided in Table 2.

Figure 1 Results of 10,000 runs - enzalutamide vs BSC

Abbreviations: QALY: quality adjusted life year; WTP: willingness to pay

Figure 2 CEAC enzalutamide vs BSC



Abbreviations: ICER: incremental cost-effectiveness ratio; WTP: willingness to pay

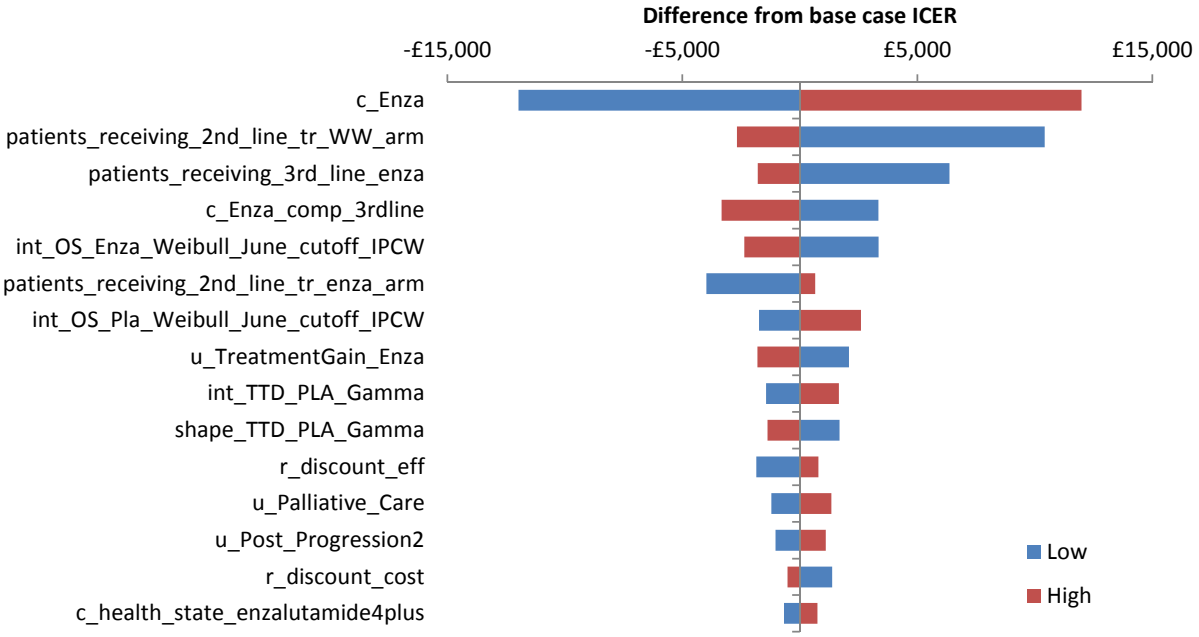
Table 2 Summary of probabilistic sensitivity analysis results – enzalutamide vs BSC

	Enzalutamide		BSC		Incremental		
	Costs	QALYs	Costs	QALYs	Costs	QALYs	CE ratio
Cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,036
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,066
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,243
95%LCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,936
95%UCL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	35,402

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

Results of the deterministic (one-way) sensitivity analysis are presented in Figure 3 below. Parameters are sorted from highest impact on ICER to lowest impact on ICER. The ten parameters with the biggest impact on the ICER are described in Table 3.

Figure 3 Tornado diagram for enzalutamide vs BSC



*It should be noted that the impact of correlated parameters (such as intercept and scale) should be interpreted with caution as only one parameter at a time is varied in this analysis, thus overestimating the actual impact

Table 3 Description of ten most influential parameters in model for comparison enzalutamide vs BSC

Name	Description	Model input (low; high)	ICER low; high (£/QALY)
Base case			**£27,036**
c_Enza	Daily drug costs for enzalutamide	[redacted]	15,057; 39,015
patients_receiving_2nd_line_tr_WW_arm	% of progressed patients who receive 2nd line treatment after 1st line WW	0.84 (0.00; 1.00)	37,453; 24,361
patients_receiving_3rd_line_enza	% of patients moving to 3rd line enzalutamide after progression of 2nd line treatment	0.81 (0.00; 1.00)	33,402; 25,247
c_Enza_comp_3rdline	Daily drug costs for enzalutamide in the comparator arm	[redacted]	30,369; 23,703
int_OS_Enza_Weibull_June_cutoff_IPCW	Intercept of OS Weibull model for enzalutamide June cutoff IPCW	[redacted]	30,393; 24,664
patients_receiving_2nd_line_tr_enza_arm	% of progressed patients who receive 2nd line treatment after 1st line enzalutamide	0.84 (0.00; 1.00)	23,059; 27,686
int_OS_Pla_Weibull_June_cutoff_IPCW	Intercept of OS Weibull model for placebo June cutoff IPCW	[redacted]	25,294; 29,638
u_TreatmentGain_Enza	Utility gain for patients on chemo-naïve enzalutamide over placebo	[redacted]	29,122; 25,229
int_TTD_PLA_Gamma	Intercept of TTD Gamma model for placebo	[redacted]	25,591; 28,700
shape_TTD_PLA_Gamma	Shape of TTD Gamma model for placebo	[redacted]	28,719; 25,657

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; IPCW: inverse probability of censoring weights; OS: overall survival; QALY: quality adjusted life year; TTD: time to treatment discontinuation

4 Requested sensitivity analysis: Committee scenario with revised patient access scheme

A sensitivity analysis with the revised patient access scheme, but without correction of the inconsistency in calculation of PP2 utility is shown in **Error! Not a valid bookmark self-reference.** below. This scenario is as described in section 3, but uses the AFFIRM baseline utility of 0.688 without any further modification.

Table 4 Sensitivity analysis with revised patient access scheme only

	Enzalutamide	BSC
Technology acquisition cost	[redacted]	[redacted]
Other costs	[redacted]	[redacted]
Total costs	[redacted]	[redacted]
Difference in total costs	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
ICER		£28,208

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

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

ERG CRITIQUE OF ASTELLAS REVISED PATIENT ACCESS SCHEME SUBMISSION

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Date completed: 23 October 2015

Version 0

This document contains a critique of the revised Patient Access Scheme for the single technology appraisal of Enzalutamide for treating metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy. The document is structured in the following manner:

Section 1	Summary
Section 2	The ERG interpretation of the ACD and FAD conclusions about the economics and the modelling
Section 3	Economic assumptions of the Astellas response to the FAD
Section 4	ERG revisions not applied by Astellas in response to the FAD
Section 5	Administration and monitoring visit frequency
Section 6	Administration and monitoring visit personnel
Section 7	Quality of life estimates pre-docetaxel and post-docetaxel
Section 8	Uncertainty around the extrapolated survival
Section 9	Implied cost effectiveness of 3rd line enzalutamide
Section 10	ERG revised base case and sensitivity analyses

1. Summary

Astellas submitted a revised base case analysis which increased the PAS from [redacted] to [redacted]. This also:

- Used the Sep 2013 data cut for the time to treatment discontinuation (TTD) curves;
- Applied the ERG interpretation of the PREVAIL QoL data; and,
- Introduced new data of a -0.050 QoL reduction from baseline in the AFFIRM BSC arm.

Astellas argued that consistency of approach between the pre-docetaxel health states and the post-docetaxel health states requires that the AFFIRM -0.050 QoL reduction be factored into the analysis.

These changes resulted in an Astellas cost effectiveness estimate for enzalutamide compared to BSC of £27,036 per QALY. Not including the AFFIRM -0.050 QoL reduction worsened the Astellas cost effectiveness estimate to £28,208 per QALY.

Astellas did not implement several other ERG changes such as including LHRH analogue costs. Including these changes worsens the Astellas £27,036 per QALY estimate to £28,339 per QALY. If 1st line enzalutamide and 1st line BSC are associated with the same monitoring frequency the cost effectiveness estimate worsens further to £31,579 per QALY.

It is unclear whether it is best to have the same approach for the pre-docetaxel and the post-docetaxel quality of life values. The ERG and AC have had reasonable access to the analyses of the PREVAIL

EQ-5D data that underlies the pre-docetaxel quality of life values. The same is not true of the revised post-docetaxel quality of life values which relies upon TA316 and the AFFIRM trial. The values are drawn from a combination of AFFIRM data and, for reasons that are not clear to the ERG, data from a submission for abiraterone to the Dutch Health Care Insurance Board.

TA316 had two estimates for the quality of life increments for enzalutamide and abiraterone over BSC in the post docetaxel setting:

- the [redacted] value from AFFIRM for enzalutamide; and,
- the 0.040 value of a submission for abiraterone to the Dutch Health Care Insurance Board.

The FAD for TA316 specified that the same increment should be used for enzalutamide and abiraterone but did not specify which. The ERG did not ask at clarification and Astellas has not stated what value it used in TA316 subsequent to the AC concluding that the increments for enzalutamide and abiraterone should be equal. For the current submission Astellas used the 0.040 increment rather than the AFFIRM [redacted] increment. The 0.040 increment improves the cost effectiveness estimate. It may have been the preferred value of the TA316 AC.
The TA316 AC reviewed the AFFIRM QoL data including the -0.050 change from baseline in the AFFIRM BSC arm, but apparently did not require this to be added to the AFFIRM baseline QoL value. Note that the baseline AFFIRM QoL value as a mean EQ-5D value was derived differently from the AFFIRM increments which were based upon mapping FACT-P to the EQ-5D.

It is not clear to the ERG that it is desirable to introduce the -0.050 decrement given that the ERG and the current AC have very much less information about the AFFIRM QoL data and analysis than the AC for TA316 which chose not to apply it. If it is introduced, ERG opinion is that this should be in the context of using AFFIRM values and so the AFFIRM [redacted] increment for enzalutamide over BSC.

The ERG remains concerned about the degree of extrapolation required in the OS curves, and the lack of any real exploration of the sensitivity of results to alternative assumptions around this as suggested by the NICE methods guide.

The ERG remains concerned that the implied cost effectiveness of 3rd line post-docetaxel enzalutamide is very much worse in the current submission than in TA316. This worsens the cost effectiveness of the BSC arm, and so improves the cost effectiveness of 1st line enzalutamide compared to 1st line BSC.

The ERG undertook four sets of analyses in order to reflect some of the decisions faced by the AC:

- Equalising the monitoring frequency between enzalutamide and BSC but not applying the AFFIRM -0.050 BSC change from baseline results in an ICER of £32,949 per QALY.
- Differentiating the monitoring frequency between enzalutamide and BSC but not applying the AFFIRM -0.050 BSC change from baseline results in an ICER of £29,586 per QALY.
- Equalising the monitoring frequency between enzalutamide and BSC and applying the AFFIRM -0.050 BSC change from baseline results in an ICER of £31,579 per QALY.
- Differentiating the monitoring frequency between enzalutamide and BSC and applying the AFFIRM -0.050 BSC change from baseline results in an ICER of £28,339 per QALY.

The unpublished FAD concluded that the best estimates for overall survival are likely to lie between the unadjusted and the IPCW adjusted estimates. Applying the Weibulls estimated from the unadjusted survival curves worsened the above cost effectiveness estimates to £41,103 per QALY, £36,341 per QALY, £38,652 per QALY and £34,174 per QALY respectively. The unpublished FAD also suggested that only 40% would receive docetaxel. Combining this 40% with the Weibulls estimated from the unadjusted survival curves further worsens the above cost effectiveness estimates to £45,465 per QALY, £41,543 per QALY, £44,367 per QALY and £40,540 per QALY respectively.

The PREVAIL EQ-5D data was only analysed up to week 61. Restricting the on treatment gain from treatment to the first 61 weeks of the model worsened the cost effectiveness estimates to £34,441 per QALY, £30,906 per QALY, £32,947 per QALY and £29,566 per QALY respectively.

Results were sensitive to the proportion of patients that were assumed to receive 2nd line docetaxel. The Astellas base case applied a rate of 84% as derived from PREVAIL. The ACD suggested that this was more likely to be 40% in current UK practice. Applying the 40% worsened the cost effectiveness estimates to £37,090 per QALY, £34,136 per QALY, £36,436 per QALY and £33,534 per QALY respectively.

2. The ERG interpretation of the ACD and FAD conclusions about the economics and the modelling

The ERG interpretation of the ACD and the FAD is that the AC concluded that:

- there was uncertainty around the most appropriate method for adjusting the overall survival (OS) curves
- the model having the same probability of death in each health state was implausible
- the degree of extrapolation required for OS meant that the modelled benefits had not been demonstrated and the uncertainties around this had been insufficiently explored

- The best estimate of survival gains probably lay somewhere between the unadjusted and the IPCW adjusted estimates
- for OS the June 2014 data cut should be used
- for time to treatment discontinuation (TTD) the September 2013 data cut should be used
- the Astellas modelling had assumed that 84% would receive 2nd line docetaxel when UK practice would be only 40%
- there was uncertainty as to whether the model reflected the survival benefits of 3rd line post-docetaxel enzalutamide use in the BSC arm
- the Astellas assumption that there would be no 3rd line treatment post-docetaxel in the enzalutamide arm was appropriate
- for stable disease on 1st line treatment the ERG approach to the PREVAIL QoL was appropriate
- for 3rd line post-docetaxel enzalutamide treatment the AFFIRM QoL values were appropriate
- for palliative care the ERG suggested QoL values were appropriate
- the ERG revisions to dosing were appropriate
- The clinical experts suggested more frequent monitoring requirements for abiraterone than for enzalutamide during the first three months of treatment, with the AC concluding that more frequent monitoring was required initially with abiraterone but that over the longer term the monitoring requirements for both drugs are similar
- The company assumptions for the frequency of monitoring while on enzalutamide and abiraterone were more plausible for the first 3 months than the ERG equalisation of these, but that thereafter the monitoring requirements would be similar for enzalutamide and abiraterone

3. Economic assumptions of the Astellas response to the FAD

The assumptions underlying the Astellas revised base case of table 1 of the Astellas response to the FAD are as below:

- The June 2014 IPCW OS Weibulls but little to no exploration of the uncertainty around the extrapolated OS
- The Sep 2013 TTD gamma
- 84% receive 2nd line treatment with docetaxel
- No 3rd line post-docetaxel treatment in the enzalutamide arm
- Include 3rd line post-docetaxel enzalutamide use in the BSC arm
- The ERG approach to the PREVAIL QoL data for 1st line treatment
- The use of AFFIRM data for the 3rd line enzalutamide QoL but with the introduction of new data in terms of a 0.050 reduction from baseline in the AFFIRM BSC arm

- Retention of the 0.500 quality of life value Astellas derived from rounding down Sandblom values
- The ERG revisions to dosing
- BSC requiring six weekly monitoring visits but enzalutamide only requiring eight weekly monitoring visits
- An increase in the PAS to [redacted] for enzalutamide when used 1st line pre-docetaxel

Note that the within the BSC arm for 3rd line post-docetaxel enzalutamide use the previous PAS of [redacted] is retained. This is justified provided that the revised PAS of [redacted] will only ever apply if 1st line pre-docetaxel enzalutamide use is approved.

4. ERG revisions not applied by Astellas

ERG revisions that have not been applied by Astellas are:

- Equalise administration and monitoring costs for enzalutamide and BSC in the pre-docetaxel setting
- Include an LHRH analogue cost
- Revise the LHRH analogue cost as previously suggested by Astellas
- Revise the outpatient cost to be an NHS reference cost
- Revise the docetaxel drug and administration cost

Each of these revisions individually worsens the cost effectiveness estimate[1] for enzalutamide compared to BSC. During the 2nd AC Astellas stated that it had not included the ERG changes to include LHRH analogue costs, reference costs rather than PSSRU costs for outpatient appointments and revisions to the docetaxel drug and administration costs because their impact was minor. The main sensitivity is to the administration and monitoring cost assumptions. Applying the additional ERG changes alters the Astellas revised base case as below.

Table 1 The effect of including the other ERG changes upon the ICER

	Astellas base case		Incl. other ERG changes	
	Enzalutamide	BSC	Enzalutamide	BSC
Technology acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs		[redacted]		[redacted]
QALYS	[redacted]	[redacted]	[redacted]	[redacted]
QALY difference		[redacted]		[redacted]

[1] Applying the Astellas suggested revision to the LHRH analogue cost only affects results if LHRH analogue costs are included.

ICER (Cost/QALY gained)		£27,036		£31,579

Astellas also submitted an analysis that retained the TA316 approach to the quality of life value for those receiving 3rd line enzalutamide treatment post-docetaxel. This worsened the Astellas cost effectiveness estimate from £27,036 per QALY to £28,208 per QALY.

Applying the other ERG revisions to the new Astellas base case results in a cost effectiveness estimate of £31,579 per QALY. This worsens to £32,949 per QALY if the TA316 approach to the quality of life value for those receiving 3rd line enzalutamide treatment post-docetaxel is retained.

5. Administration and monitoring visit frequency

The SmPC for abiraterone states that:

> *Serum transaminases should be measured prior to starting treatment, every two weeks for the first three months of treatment and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly. However, patients with a significant risk for congestive heart failure should be monitored every 2 weeks for the first three months of treatment and monthly thereafter (see section 4.4).*

The SmPC for enzalutamide notes that it is subject to additional monitoring, but does not appear to stipulate any particular monitoring frequency. In the light of the FAD this suggests that the monitoring frequency for enzalutamide should be four weekly.

The ACD did not comment upon the monitoring frequency that should be assumed for BSC compared to enzalutamide.

ERG expert opinion is that administration and monitoring costs would be broadly equal between the enzalutamide and BSC arms and that the introduction of enzalutamide would not reduce the frequency of monitoring.

Astellas assumed that after the first three months, for those remaining on 1st line enzalutamide treatment monitoring visits will be eight weekly compared to six weekly compared to those remaining on 1st line BSC. The number of CT scans required is also differentiated. Those receiving 1st line enzalutamide were assumed to require only one third the number of CT scan compared to those receiving 1st line BSC.

If monitoring for enzalutamide is eight weekly this may raise questions about how enzalutamide patients receive their medication. The frequency of prescribing may also be eight weekly. Since

enzalutamide packets are sufficient for only four weeks, two packets of enzalutamide may be required under each prescription. This could increase enzalutamide wastage, and so worsen the ICER.

6. Administration and monitoring visit personnel

Astellas assumed that monitoring visits would alternate between a consultant led outpatient visit and a nurse led outpatient visit; i.e. under BSC a patient would see a consultant only every 12 weeks and under enzalutamide a patient would see a consultant only every 16 weeks. Consultant led outpatient visits at £139 are more expensive than a nurse led outpatient visit at £42. As a consequence, this assumption has an impact upon monitoring costs.

Note that in the post-chemotherapy setting those receiving enzalutamide are still assumed to be monitored eight weekly but all these monitoring visits are assumed to be consultant led.

These elements were itemised by the ERG in the original ERG report, but were not further explored. ERG expert opinion suggests that in the pre-docetaxel setting monitoring may be mainly nurse led. A sensitivity analysis which assumes that all monitoring visits are nurse led may be warranted.

7. Quality of life estimates pre-docetaxel and post-docetaxel

The AC preferred the ERG interpretation of the PREVAIL quality of life data for the pre-docetaxel health states and that the estimated changes from baseline of -0.042 for enzalutamide and -0.064 for BSC should be added to the mean baseline value of 0.844.

Astellas argues that for the sake of consistency the same approach should be adopted for the post-docetaxel quality of life values as for the pre-docetaxel health states.

The Astellas approach for TA316 had some similarities with the current submission, but also some differences. It appears that the mean baseline EQ-5D quality of life value of AFFRIM was used: 0.688. But due to EQ-5D not being collected as frequently as FACT-P, for the changes from baseline the FACT-P data was mapped to the EQ-5D with a mixed model repeated measures analysis providing the net treatment effect estimate of [redacted] for enzalutamide over BSC. Astellas initially differentiated the treatment gain for enzalutamide of [redacted] from the treatment gain for abiraterone of 0.040, the latter being taken from a company submission for abiraterone to the Dutch Health Care Insurance Board.

Astellas added these increments to the 0.688 baseline utility to provide a quality of life value of [redacted] for those receiving enzalutamide post-docetaxel and [redacted] for those receiving post docetaxel

abiraterone. The TA316 FAD stated that the same increment should be applied for both enzalutamide and abiraterone, but it is not known which increment was preferred and was finally applied in TA316.

Astellas have now provided an estimate of -0.050 for the change from baseline for the BSC in AFFIRM.

The Astellas response to the ERG clarification question B5 itemised the AFFIRM TA316 quality of life values of a baseline utility of 0.688, the decrement of -0.085 for progression and a [redacted] increment for treatment with enzalutamide. The Astellas response to the ERG clarification question B5 did not itemise the -0.050 change from baseline that Astellas argues should now be included for consistency of approach.

Factoring in the -0.050 reduces the quality of life for those receiving enzalutamide post-docetaxel. Since this quality of life is only experienced in the BSC arm, reducing the value reduces the total QALYs in the BSC arm and so improves the quality of life estimate for enzalutamide. Without the additional -0.050 decrement the cost effectiveness estimate of table 1 of the Astellas response to the FAD worsens from £27,036 per QALY to £28,208 per QALY.

As far as the ERG can ascertain the -0.050 estimate for the change in the quality of life from baseline under AFFIRM is new data. In the light of this, the ERG cannot comment upon how the -0.050 change from baseline for the BSC in AFFIRM has been derived, the data that underlies it or the reliability of the estimate. As a corollary, it should be borne in mind that the analysis of the PREVAIL EQ-5D data was for no obviously justifiable reason restricted to the first 61 weeks of PREVAIL. It appears that the AFFIRM FACT-P data may have also been arbitrarily curtailed at 25 weeks. There may be any number of caveats to the AFFIRM quality of life data that the ERG has not been made aware of. It is consequently unreasonable for the ERG to speculate upon the reasonableness of these estimates. The ERG has little information available about the quality of life values used in TA316 and can only note the Astellas approach and the ERG and AC evaluations of this.

Astellas in response to the clarification questions of the ERG for TA316:

> *To derive the treatment arm effect for patients in stable disease, the individual patient changes from baseline utility as implied by the FACT-P mapping function are calculated. A mixed model repeated measure model (MMRM) was then fitted controlling for baseline covariates. The model included the following covariates: treatment (enzalutamide or placebo), time (week 13, week 17, week 21, etc.), baseline utility and ECOG status (0-1 or 2), prior chemotherapy regimens (1 or ≥2), pain (<4 or ≥4, assessed from question #3 of the BPI), age (< 65 or ≥ 65) and fatigue (<7 or ≥7, assessed from question #3 of the BFI). The*

model assumed unstructured covariance among the within subject repeated measurements. The analysis was conducted using PROC MIXED in SAS. With the exception of baseline utility variable, all variables listed above were included in the CLASS statement of the procedure. The unique subject identifier was also included as a class variable. A REPEATED statement over the visits was included with the unique subject identifier as the SUBJECT variable in the REPEATED statement.

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

The Evaluation Report for TA316 noted that:

The ERG has asked the manufacturer to provide the internal mapping algorithm and further details used to calculate the utility increments. In the response to the clarification letter (Response to the Clarification Letter, pg. 18) the manufacturer has repeated the same arguments and information as stated in the MS and did not provide the details on the calculation of the utility increments for on treatment benefits.

And:

However, in the absence of details on the calculation of the utility increments for the on treatment utility increment for enzalutamide versus BSC, together with the weak evidence on the on treatment utility increment for abiraterone versus BSC, the ERG prefers taking a conservative approach and disregarding the on treatment utility increments in the base case scenario.

The FAD for TA316 noted that:

The Committee concluded that it was appropriate for the manufacturer to have used the EQ-5D utility value from AFFIRM at baseline.

And:

The Committee discussed the increase in utility attributed to being 'on-treatment' with enzalutamide or abiraterone, noting that the manufacturer applied different values for the 2 treatments. It was aware that, to estimate the utility increase for enzalutamide, the manufacturer mapped FACT-P data onto EQ-5D using a mapping algorithm that it had not externally validated, and that the ERG could not verify. The Committee noted that the ERG considered that there was no evidence to assume different utility increases for enzalutamide and abiraterone, and that the ERG preferred excluding these estimates from the model. The

Committee, noting the patient experts' experience, agreed that including 'on-treatment' utility increases reflected patient experience, but that there is no evidence to assume different values for enzalutamide and abiraterone. The Committee concluded that the modelling should incorporate the same utility increase for both treatments.

As a consequence, the AC for TA316 appears to have reviewed:

- the AFFIRM baseline EQ-5D data;
- the MMRM analysis, the least squares mean QoL changes from baseline for enzalutamide and BSC within AFFIRM;
- the implied AFFIRM quality of life increment from enzalutamide treatment over BSC; and,
- the quality of life increment from abiraterone treatment over BSC that was within the submission for abiraterone to the Dutch Health Care Insurance Board.

The AC then concluded that the Astellas approach was appropriate for TA316, with the exception of differentiating the quality of life gain associated with treatment between enzalutamide and abiraterone.

But the TA316 FAD does not specify what the common increment for enzalutamide and abiraterone was:

- the [redacted] value from AFFIRM; or,
- the 0.040 value of the submission for abiraterone to the Dutch Health Care Insurance Board.

In response to the ERG clarification question B5 Astellas stated that for the [redacted] AFFIRM enzalutamide increment over BSC:

Enzalutamide showed a significant effect on pain, resulting in a significant utility gain over placebo in AFFIRM based on mapped FACT-P utilities.

For the current modelling Atellas has used the 0.040 value of the submission for abiraterone to the Dutch Health Care Insurance Board. The electronic model cites:

post-chemotherapy NICE appraisal for enzalutamide, FAD

as the source for the 0.040 estimate with the written submission stating that:

This on treatment utility gain ([redacted]) was based on the committee preferred scenario.

In the opinion of the ERG, the estimates for quality of life that should be applied are those that have been judged to be the most reasonable and that within this consistency of approach is not necessarily required. The AC agrees with the ERG approach for the pre-docetaxel health states. There is limited

information available about the AFFIRM quality of life data. The -0.050 estimate is new data to the current assessment but would seem to have been available to TA316, given the redacted adjusted LS mean changes from baseline of the TA316 FAD. For TA316 the ERG argued that the net treatment effect should not be added to the AFFIRM baseline. The FAD of TA316 concluded that the Astellas approach of adding a common net treatment effect to the AFFIRM baseline was appropriate for post-docetaxel enzalutamide and abiraterone use.

8. Uncertainty around the extrapolated survival

The original ERG report inferred the Kaplan Meier proportions remaining for the June 2014 data cut for both the unadjusted OS Kaplan Meier curve (KM1)[2] the IPCW adjusted OS Kaplan Meier curve (KM2) from the graphs of the submission. This data was tabulated against the numbers and proportions of patients remaining at risk and the weibull extrapolated OS curves of the model in table 60 of the original ERG report, and graphed as below. The numbers at baseline were [redacted] in the BSC arm and [redacted] in the enzalutamide arm.

Figure 1 OS KM, n at risk and weibull extrapolations

As the original ERG report noted, the OS Kaplan Meier curves are far from being complete. Even at the very tail of the OS Kaplan Meier curves when few remain at risk the percentages remaining alive in the adjusted Kaplan Meier curves at month 36 are roughly 56% for enzalutamide and 41% for placebo, compared to around 40% for both arms in the original Kaplan Meier curves.

The numbers at risk are reasonably in line with the OS Kaplan Meier curves up to around 24 months, but then begin to drop quite rapidly below them and tail off to close to zero between month 24 and month 36. At 24 months the proportions remaining alive within the OS Kaplan Meier curves are well above 50% in both arms.

[2] Taken from Figure 1 of the company extrapolation report.

The modelled survival gain from enzalutamide over BSC is the area between the two Weibulls. As can be seen from the above, the majority of this gain occurs after the numbers at risk has tailed off. There is also quite a considerable tail to both the Weibulls which is not obviously justified by a visual inspection of the IPCW adjusted Kaplan Meier curves. There is as a consequence considerable structural uncertainty about the gains in survival which have been extrapolated from the IPCW adjusted PREVAIL trial data.

Given the current modelling approach, it might be reasonable to explore the impact of less optimistic OS extrapolations in line with the NICE methods guide.

9. Implied cost effectiveness of 3rd line enzalutamide

It is possible that the incompleteness of the OS curves may mean that they do not entirely reflect the proportion modelled as receiving enzalutamide post-docetaxel and the possible impact of this upon survival.

As per the original ERG report, the ERG remains concerned about the implied cost effectiveness of 3rd line enzalutamide use in the BSC arm. Since this has no impact upon overall survival it increases patient quality of life but at a cost that suggests it has a very poor cost-effectiveness.

3rd line enzalutamide use prevents the patient moving into palliative care. The previous modelling applied quality of life values of a baseline of 0.688 and a treatment gain of 0.040 to result in a 3rd line quality of life value of 0.728 as compared with the 0.500 quality of life value for palliative care: and increment of 0.228. The revised Astellas approach reduces this by 0.050 to an increment of 0.178.

The weekly costs for 3rd line enzalutamide are direct drug costs of [redacted] with the [redacted] PAS, health state costs of £25.72, concomitant medication costs of £38.86 and adverse event costs of £1.54: a total 52 week cost of [redacted]. Palliative care is associated with a weekly health state cost of £103.82, so a 52 week cost of £5,399. 3rd line enzalutamide results in an annualised [redacted] cost increment over palliative care.

The current modelling seems to be including 3rd line enzalutamide with an implicit cost effectiveness of [redacted] per QALY if the 0.228 QoL increment is applied, or [redacted] per QALY if the Astellas revised 0.178 QoL increment is applied. The FAD for TA316 suggests in section 3.31 a PAS inclusive company estimate of £43,587 per QALY and in 3.47 an ERG estimate of £51,014 per QALY.

There is something of a disconnect between the Astellas estimate of the cost effectiveness of 3rd line enzalutamide as submitted for TA316 and the implied cost effectiveness and impact of 3rd line

enzalutamide within the current submission. The current cost effectiveness estimate for 1st line enzalutamide is in part driven by the poor implied cost effectiveness of 3rd line enzalutamide. Not applying 3rd line enzalutamide in the BSC arm worsens the revised Astellas cost effectiveness estimate of £27,036 per QALY to £33,402 per QALY.

The discrepancy may arise in part from the current modelling only extrapolating from the 1st line enzalutamide trial OS curves. An alternative modelling approach could have considered the OS curves for 3rd line enzalutamide and for BSC that were presented for TA316. The incompleteness of the PREVAIL June 2014 KM OS curves and degree of extrapolation required for the June 2014 IPCW OS Weibulls to fall to zero should be borne in mind when considering this point.

10. ERG revised base case and sensitivity analyses

Decisions about the most reasonable estimates for administration and monitoring visits and for quality of life post-docetaxel are required. In the light of this, four sets of analyses are presented:

- Equal administration and monitoring and the ERG post-docetaxel quality of life
- Unequal monitoring frequency and the ERG post-docetaxel quality of life
- Equal administration and monitoring and the Astellas revised post-docetaxel quality of life
- Unequal monitoring frequency and the revised Astellas revised post-docetaxel quality of life

These analyses apply the additional ERG revisions to LHRH analogue costs, outpatient costs and docetaxel drug and administration costs. All results include the revised PAS of [redacted] for 1st line pre-docetaxel enzalutamide use.

Note that the equalisation of administration and monitoring costs between BSC and enzalutamide has followed the previous ERG analyses, and equalises this to the BSC six weekly monitoring frequency rather than the four weekly monitoring frequency of the abiraterone SmPC. But as shown in table 37 of the original ERG report the weekly cost of monitoring is broadly that same after the first three months for six weekly BSC and four weekly abiraterone at £36.47 and £36.26 respectively. This is due to the tripling of the frequency of CT scans that Astellas assumed for BSC compared to abiraterone and enzalutamide.

The base cases are presented alongside a number of additional univariate sensitivity analyses:

- SA01: Applying the unadjusted June 2014 Weibull OS curves
- SA02: Applying the June 2014 2 stage adjusted Weibull OS curves
- SA03: Applying the June 2014 gamma TTD curves
- SA04: No 3rd line enzalutamide in the BSC arm
- SA05: Applying the AFFIRM [redacted] increment for 3rd line enzalutamide over BSC which it can be argued should be part of the base case[3]
- SA06: Applying the same quality of life for the pre-docetaxel health state in each arm subsequent to week 61 due to the PREVAIL quality of life data having been arbitrarily limited to that from baseline to week 61
- SA07: Applying the Sandblom mean of 0.538 for the palliative care QoL
- SA08: Only 40% of patients receive docetaxel[4] which given the ACD and the unpublished FAD can be argued should be part of the base case

[3] Implemented in the *Utilities* worksheet by setting cell D18=[redacted]
[4] Implemented within the *Second_line_treatment* worksheet by setting cell D25=40%

- SA09: Equalising administration and monitoring costs between BSC and enzalutamide using the Astellas estimate for enzalutamide monitoring rather than the Astellas estimate for BSC[5]
- SA10: Assuming that monitoring visits are all nurse led, rather than alternating between being consultant led and nurse led[6]

The implementation of these with the exceptions of SA05, SA08 and SA09 is as per section 5.4 of the original ERG report.

In the light of the FAD and the ERG critique multivariate sensitivity analyses that combine SA01 and SA08 and that combine SA01, SA05 and SA08 are also presented.

Table 2 ICERs for equal admin and monitoring and ERG post docetaxel QoL

		Δ Cost	Δ QALY	ICER
	Base case	[redacted]	[redacted]	£32,949
SA01	Unadjusted. June 2014 OS Weibulls	[redacted]	[redacted]	£41,103
SA02	June 2014 2-stage adjusted OS Weibulls	[redacted]	[redacted]	£36,540
SA03	June 2014 TTD gamma	[redacted]	[redacted]	£31,566
SA04	No 3rd line enzalutamide	[redacted]	[redacted]	£37,999
SA05	Applying the AFFIRM [redacted] QoL increment	[redacted]	[redacted]	£33,531
SA06	1st line QoL differentiated only to week 61	[redacted]	[redacted]	£34,441
SA07	Palliative care 0.538 QoL value	[redacted]	[redacted]	£33,350
SA08	Only 40% of patients receive docetaxel	[redacted]	[redacted]	£37,090
SA09	Monitoring costs equalised at enzalutamide rate	[redacted]	[redacted]	£30,831
SA10	All monitoring nurse led	[redacted]	[redacted]	£32,351
SA11	SA01 and SA08 combined	[redacted]	[redacted]	£45,465
SA12	SA01, SA05 and SA08 combined	[redacted]	[redacted]	£45,919

Table 3 ICERs for unequal admin and monitoring and ERG post docetaxel QoL

		Δ Cost	Δ QALY	ICER
	Base case	[redacted]	[redacted]	£29,568
SA01	Unadjusted. June 2014 OS Weibulls	[redacted]	[redacted]	£36,341
SA02	June 2014 2-stage adjusted OS Weibulls	[redacted]	[redacted]	£32,548
SA03	June 2014 TTD gamma	[redacted]	[redacted]	£28,248
SA04	No 3rd line enzalutamide	[redacted]	[redacted]	£35,174
SA05	Applying the AFFIRM [redacted] QoL increment	[redacted]	[redacted]	£30,090
SA06	1st line QoL differentiated only to week 61	[redacted]	[redacted]	£30,906
SA07	Palliative care 0.538 QoL value	[redacted]	[redacted]	£29,928

[5] Implemented in the Input_Parameters worksheet by setting cell F42=H34
[6] Implemented within the *MRU* worksheet by setting E18, L18, Z18, AG18 and BB18 equal to zero and cells E19, L19, Z19, AG19 and BB19 equal to one.

SA08	Only 40% of patients receive docetaxel	[redacted]		£34,136
SA09	Monitoring costs equalised at enzalutamide rate	n.a.	n.a.	n.a.
SA10	All monitoring nurse led	[redacted]		£29,122
SA11	SA01 and SA08 combined	[redacted]		£41,543
SA12	SA01, SA05 and SA08 combined	[redacted]		£41,958

Table 4 ICERs for equal admin and monitoring and revised post docetaxel QoL

		Δ Cost	Δ QALY	ICER
	Base case	[redacted]		£31,579
SA01	Unadjusted. June 2014 OS Weibulls			£38,652
SA02	June 2014 2-stage adjusted OS Weibulls			£34,759
SA03	June 2014 TTD gamma			£30,236
SA04	No 3rd line enzalutamide			£37,999
SA05	Applying the AFFIRM [redacted] QoL increment			£32,113
SA06	1st line QoL differentiated only to week 61			£32,947
SA07	Palliative care 0.538 QoL value			£31,948
SA08	Only 40% of patients receive docetaxel			£36,436
SA09	Monitoring costs equalised at enzalutamide rate			£29,549
SA10	All monitoring nurse led			£31,006
SA11	SA01 and SA08 combined			£44,367
SA12	SA01, SA05 and SA08 combined			£44,800

Table 5 ICERs for unequal admin and monitoring and revised post docetaxel QoL

		Δ Cost	Δ QALY	ICER
	Base case	[redacted]		£28,339
SA01	Unadjusted. June 2014 OS Weibulls			£34,174
SA02	June 2014 2-stage adjusted OS Weibulls			£30,962
SA03	June 2014 TTD gamma			£27,058
SA04	No 3rd line enzalutamide			£35,174
SA05	Applying the AFFIRM [redacted] QoL increment			£28,818
SA06	1st line QoL differentiated only to week 61			£29,566
SA07	Palliative care 0.538 QoL value			£28,669
SA08	Only 40% of patients receive docetaxel			£33,534
SA09	Monitoring costs equalised at enzalutamide rate	n.a.	n.a.	n.a.
SA10	All monitoring nurse led	[redacted]		£27,912
SA11	SA01 and SA08 combined			£40,540
SA12	SA01, SA05 and SA08 combined			£40,935

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

ERG CRITIQUE OF ASTELLAS REVISED PATIENT ACCESS SCHEME SUBMISSION- FURTHER SCENARIO ANALYSES.

This addendum contains the results of combining scenarios listed in tables 2 to 5 of the ERG critique of the revised Patient Access Scheme submission for enzalutamide. The new analyses are the last 2 rows in tables 2 to 5 below (SA13 and SA14).

Table 2 ICERs for equal admin and monitoring and ERG post docetaxel QoL

		Δ Cost	Δ QALY	ICER
	Base case	[redacted]	[redacted]	£32,949
SA01	Unadjusted. June 2014 OS Weibulls	[redacted]	[redacted]	£41,103
SA02	June 2014 2-stage adjusted OS Weibulls	[redacted]	[redacted]	£36,540
SA03	June 2014 TTD gamma	[redacted]	[redacted]	£31,566
SA04	No 3rd line enzalutamide	[redacted]	[redacted]	£37,999
SA05	Applying the AFFIRM [redacted] QoL increment	[redacted]	[redacted]	£33,531
SA06	1st line QoL differentiated only to week 61	[redacted]	[redacted]	£34,441
SA07	Palliative care 0.538 QoL value	[redacted]	[redacted]	£33,350
SA08	Only 40% of patients receive docetaxel	[redacted]	[redacted]	£37,090
SA09	Monitoring costs equalised at enzalutamide rate	[redacted]	[redacted]	£30,831
SA10	All monitoring nurse led	[redacted]	[redacted]	£32,351
SA11	SA01 and SA08 combined	[redacted]	[redacted]	£45,465
SA12	SA01, SA05 and SA08 combined	[redacted]	[redacted]	£45,919
SA13	SA05 and SA08 combined	[redacted]	[redacted]	£37,358
SA14	SA02, SA05 and SA08 combined	[redacted]	[redacted]	£41,264

Table 3 ICERs for unequal admin and monitoring and ERG post docetaxel QoL

		Δ Cost	Δ QALY	ICER
	Base case	[redacted]	[redacted]	£29,568
SA01	Unadjusted. June 2014 OS Weibulls	[redacted]	[redacted]	£36,341
SA02	June 2014 2-stage adjusted OS Weibulls	[redacted]	[redacted]	£32,548
SA03	June 2014 TTD gamma	[redacted]	[redacted]	£28,248
SA04	No 3rd line enzalutamide	[redacted]	[redacted]	£35,174
SA05	Applying the AFFIRM [redacted] QoL increment	[redacted]	[redacted]	£30,090
SA06	1st line QoL differentiated only to week 61	[redacted]	[redacted]	£30,906
SA07	Palliative care 0.538 QoL value	[redacted]	[redacted]	£29,928
SA08	Only 40% of patients receive docetaxel	[redacted]	[redacted]	£34,136
SA09	Monitoring costs equalised at enzalutamide rate	n.a.	n.a.	n.a.
SA10	All monitoring nurse led	[redacted]	[redacted]	£29,122
SA11	SA01 and SA08 combined	[redacted]	[redacted]	£41,543
SA12	SA01, SA05 and SA08 combined	[redacted]	[redacted]	£41,958
SA13	SA05 and SA08 combined	[redacted]	[redacted]	£34,383
SA14	SA02, SA05 and SA08 combined	[redacted]	[redacted]	£37,840

Table 4 ICERs for equal admin and monitoring and revised post docetaxel QoL

		Δ Cost	Δ QALY	ICER
	Base case	[redacted]		£31,579
SA01	Unadjusted. June 2014 OS Weibulls			£38,652
SA02	June 2014 2-stage adjusted OS Weibulls			£34,759
SA03	June 2014 TTD gamma			£30,236
SA04	No 3rd line enzalutamide			£37,999
SA05	Applying the AFFIRM [redacted] QoL increment			£32,113
SA06	1st line QoL differentiated only to week 61			£32,947
SA07	Palliative care 0.538 QoL value			£31,948
SA08	Only 40% of patients receive docetaxel			£36,436
SA09	Monitoring costs equalised at enzalutamide rate			£29,549
SA10	All monitoring nurse led			£31,006
SA11	SA01 and SA08 combined			£44,367
SA12	SA01, SA05 and SA08 combined			£44,800
SA13	SA05 and SA08 combined			£36,695
SA14	SA02, SA05 and SA08 combined			£40,423

Table 5 ICERs for unequal admin and monitoring and revised post docetaxel QoL

		Δ Cost	Δ QALY	ICER
	Base case	[redacted]		£28,339
SA01	Unadjusted. June 2014 OS Weibulls			£34,174
SA02	June 2014 2-stage adjusted OS Weibulls			£30,962
SA03	June 2014 TTD gamma			£27,058
SA04	No 3rd line enzalutamide			£35,174
SA05	Applying the AFFIRM [redacted] QoL increment			£28,818
SA06	1st line QoL differentiated only to week 61			£29,566
SA07	Palliative care 0.538 QoL value			£28,669
SA08	Only 40% of patients receive docetaxel			£33,534
SA09	Monitoring costs equalised at enzalutamide rate	n.a.	n.a.	n.a.
SA10	All monitoring nurse led	[redacted]		£27,912
SA11	SA01 and SA08 combined			£40,540
SA12	SA01, SA05 and SA08 combined			£40,935
SA13	SA05 and SA08 combined			£33,772
SA14	SA02, SA05 and SA08 combined			£37,069

Equalising the PAS between 1st line and 3rd line enzalutamide use at [redacted]

Table 1 ICERs for Astellas base case

		Δ Cost	Δ QALY	ICER
	Base case	[redacted]		£27,036
SA15	Equal 1st line and 3rd line PAS of [redacted]			£29,999

Table 2 ICERs for equal admin and monitoring and ERG post docetaxel QoL

		Δ Cost	Δ QALY	ICER
	Base case	[redacted]		£32,949
SA15	Equal 1st line and 3rd line PAS of [redacted]			£36,040

Table 3 ICERs for unequal admin and monitoring and ERG post docetaxel QoL

		Δ Cost	Δ QALY	ICER
	Base case	[redacted]		£29,568
SA15	Equal 1st line and 3rd line PAS of [redacted]			£32,659

Table 4 ICERs for equal admin and monitoring and revised post docetaxel QoL

		Δ Cost	Δ QALY	ICER
	Base case	[redacted]		£31,579
SA15	Equal 1st line and 3rd line PAS of [redacted]			£34,542

Table 5 ICERs for unequal admin and monitoring and revised post docetaxel QoL

		Δ Cost	Δ QALY	ICER
	Base case	[redacted]		£28,339
SA15	Equal 1st line and 3rd line PAS of [redacted]			£31,301