Response to:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Degarelix for treating advanced hormone-dependent prostate cancer

APPENDIX A

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3 February 2014

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Section 1: PSA progression data

1.1. Mechanism of action

This section aims to address the uncertainty that the AC panel voiced with respect to the PSA progression results for degarelix: *'The Committee concluded that the results for PSA progression and long-term PSA progression benefit for degarelix compared with LHRH agonists were highly uncertain and therefore no PSA progression benefit from degarelix compared with LHRH agonists could be assumed'* **[page 30, section 4.7]**.

The AC meeting discussions did not cover the full details of the differential mechanism of action of degarelix versus LHRH agonists and the subsequent impact this is likely to have on

PSA progression. Although degarelix and LHRH agonists act on the same receptor (gonadotrophin-releasing hormone [GnRH] receptor) their modes of action are very different. LHRH agonists stimulate the GnRH receptor, leading to an initial surge in follicle-stimulating hormone [FSH], luteinsing hormone (LH) and testosterone.[1] It is only after prolonged continuous stimulation by LHRH agonists that a down regulation of the pituitary GnRH receptors occur. Conversely, GnRH antagonists block the receptor immediately leading to a rapid and sustained inhibition of FSH, LH and testosterone.[2] As a result, the following pharmacokinetic profiles are seen (see **Table A1**):[2]

Table A1. LH, FSH and testosterone profiles of LHRH agonists versus GnRH antagonists

LHRH agonists	**GnRH antagonists (degarelix)**
Surge in FSH, LH and testosterone[1]	Immediate suppression of FSH, LH and testosterone
Microsurges in LH and testosterone on repeat injection[3]	No microsurges[2]
FSH suppression, but not maintained to the same extent as degarelix in the long term[2]	Prolonged suppression of FSH, LH and testosterone[2]

Although the mechanism by which degarelix improves PSA PFS relative to LHRH agonists is not fully established, it is likely down to these differential hormonal effects both in the short- and long-term. One hypothesis to explain why there are longer-term differences in agonist and antagonist effects is that the initial testosterone surge, which has acute consequences in terms of exacerbating clinical symptoms (clinical flare), might also have longer-term effects on tumour control.[4] The presence of microsurges following LHRH agonist re-administration may also have long-term detrimental effects, and it has been shown that breakthrough increases in testosterone can adversely affect PFS.[5] Another potential factor is the differential effect on FSH levels (both in the short- and long-term), with FSH receptors shown to be present in the endothelium cells prostate cancer cells of all tumour grades.[6] Furthermore, preclinical evidence suggests that FSH signalling contributes to the progression of castration-resistant prostate cancer.[7] Thus, the increases in hormone levels in the form of short-term flare surges, medium- to long-term microsurges and poorer long-term FSH control may all contribute to a faster PSA progression when comparing LHRH agonists to degarelix.

1.2. PSA progression efficacy data

1.2.1. CS21A extension study

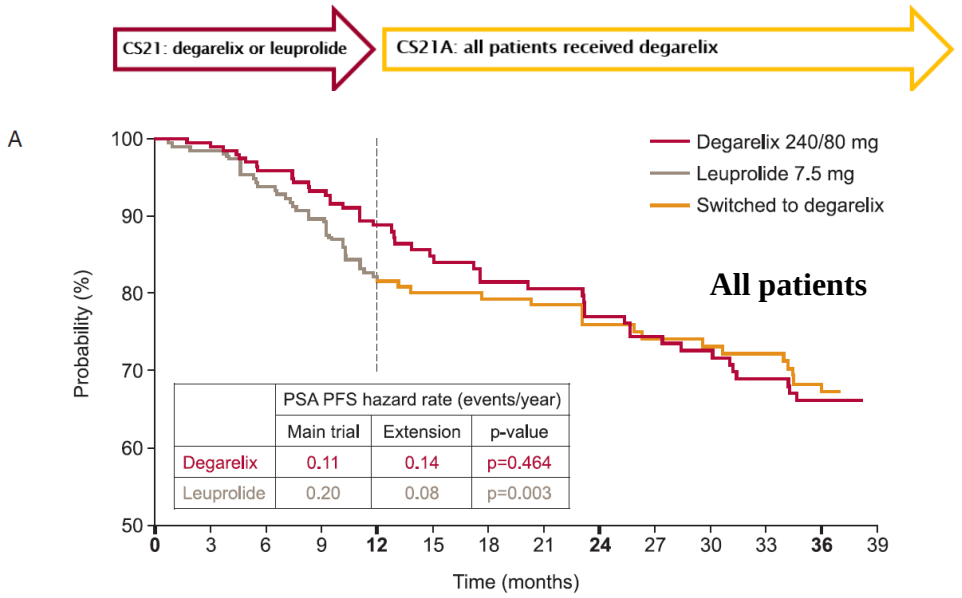
The CS21A extension study[8] provides further evidence, as described within the original submission, that supports the PSA PFS survival benefit for degarelix over leuprorelin which

is seen during the first year of treatment in CS21.[4] Upon completion of CS21, patients were switched from leuprorelin to degarelix. Notably, the PSA PFS hazard rate was decreased significantly after the switch in the leuprorelin/degarelix group, while the rate in those who continued on degarelix was consistent with the rate in treatment Year 1: at a median follow-up of 27.5 months, the PSA PFS hazard rate decreased significantly from 0.20 events annually in Year 1 to 0.08 events annually after the switch in the leuprorelin/degarelix group (p=0.003).[8] The corresponding hazard rate in the continuous degarelix (240 mg/80 mg) group was 0.11 and 0.14 events annually (p=0.464), showing a consistent effect of degarelix with time.[8] As shown in **Figure A1, A,** PSA PFS is significantly improved after crossover from leuprorelin to degarelix**.** The same hazard rate change pattern occurred in the group with baseline PSA >20 ng/ml: the PSA PFS hazard rate decreased significantly from 0.38 events annually in Year 1 to 0.19 events annually after the switch in patients on leuprorelin (chi-square test p=0.031) (see **Figure A1, B**).

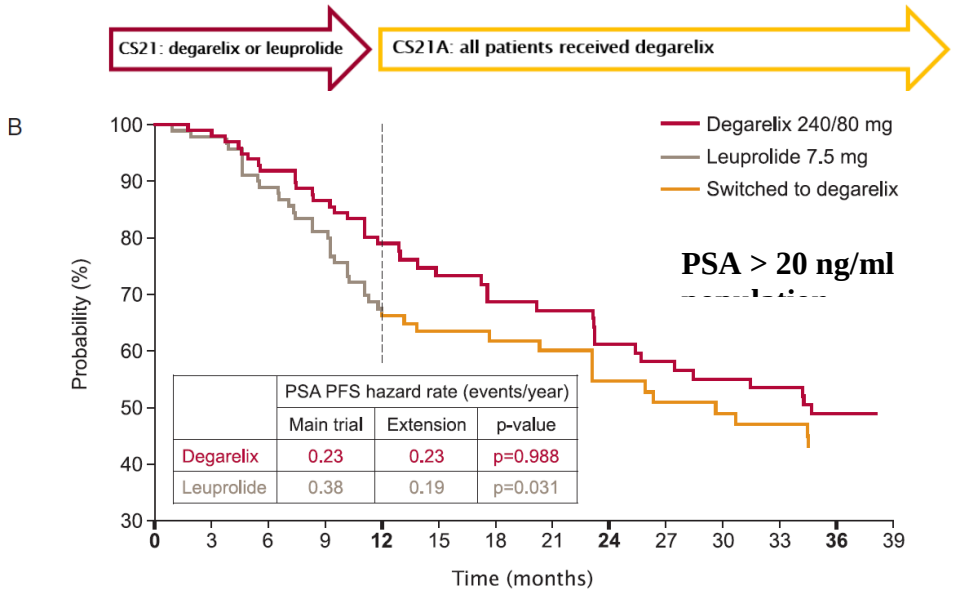
This significant change in pattern at crossover was also observed for FSH levels: at Year 1 (Day 364), median FSH was 1.20 and 4.40 IU/l in the degarelix (240 mg/80 mg) and leuprorelin groups, respectively (p<0.0001). In CS21A, at three months, FSH continued to be suppressed in patients who continued on degarelix (240 mg/80 mg) (median 1.30 IU/l at day 448). In contrast, FSH was further suppressed in patients who switched from leuprorelin to degarelix (240 mg/ 80 mg) until levels were similar to those observed during continuous degarelix treatment (median 1.60 IU/l at day 448), as seen in **Figure A2**.

These results from the crossover population in the CS21A extension study clearly show that degarelix is providing an improved, differential effect in terms of PSA PFS compared with leuprorelin in the longer term.

Figure A1. PSA PFS probability in all patients (*A*), and those with baseline PSA > 20 ng/ml (B) when switched from leuprorelin to degarelix (240 mg/80 mg) and those continuing degarelix (240 mg/80 mg) using original CS21 criteria for PSA progression[8]

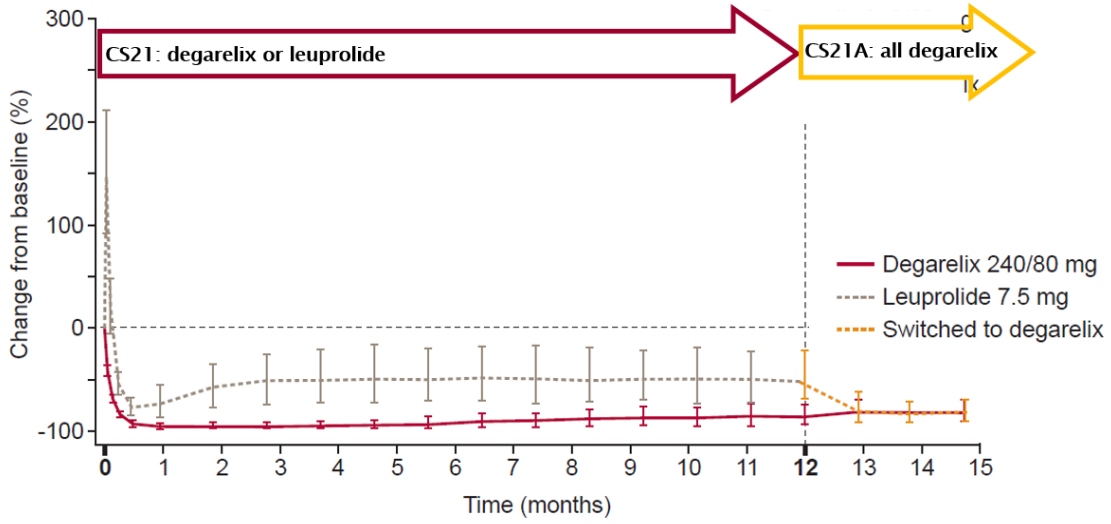


Time (days)	*0*	*84*	*168*	*252*	*336*	*420*	*504*	*588*	*672*	*756*	*840*	*924*	*1008*	*1092*	*1176*
Number of patients at risk															
Degarelix	207	200	187	176	162	109	101	93	91	87	83	79	75	71	67
Leuprolide	201	193	182	174	157	110	102	98	93	85	81	78	74	68	66



Time (days)	*0*	*84*	*168*	*252*	*336*	*420*	*504*	*588*	*672*	*756*	*840*	*924*	*1008*	*1092*	*1176*
Number of patients at risk															
Degarelix	100	97	91	84	77	53	50	45	44	40	37	36	35	32	31
Leuprolide	93	90	81	75	63	43	40	37	35	29	27	26	23	23	21

Figure A2. Results from CS21A to show further FSH suppression after crossover from leuprorelin to degarelix. Median percent change from baseline and quartiles in FSH in patients switched from leuprorelin to degarelix (240 mg / 80 mg) and those continuing on degarelix (240 mg / 80 mg)[8]



Time (days)	0	28	56	84	112	140	168	196	224	252	280	308	336	364	392	420	448
Number of patients																	
Degarelix	206	206	201	195	193	186	187	188	183	179	173	172	166	167	40	13	112
Leuprolide	199	196	195	191	190	190	185	188	183	181	178	179	172	171	124	120	113

The results from the CS21A study were described within the original submission. Further analyses over five years has recently been completed and demonstrates the significant PSA PFS benefit established for degarelix over leuprorelin during year one remained consistent at 5 years.[9]

1.2.2. PSA progression as a marker for disease progression

Ferring also notes within the ACD that '*The ERG heard from its clinical specialists that PSA progression should not be used as a universal predictor of mortality and noted that, because of their short duration, the clinical trials were not appropriate for demonstrating a difference in overall survival'* **[page 22, section 3.29]**. We would like to clarify that the link between PSA progression and overall survival has only been applied in the model prior to progression to castration-resistant prostate cancer (CRPC) (please see **Section 3** of this Appendix for further details). This decision is in line with the published evidence,[10] clearly showing that PSA progression is much more highly correlated with survival in patients with hormone-dependent prostate cancer than in CRPC patients. This observation from the literature was

based on trial data using a comparable time duration as the RCTs presented used to inform PSA efficacy data for degarelix within the submission.

It is established that PSA levels are routinely measured to assess disease control and to inform treatment decisions in the treatment of prostate cancer. Degarelix was associated with a significantly longer PSA PFS than leuprorelin and this effect was confirmed by the significant improvement in PSA PFS when patients were crossed over to degarelix in the longer-term extension study. These findings are particularly prominent in those with PSA >20 ng/ml. Those with PSA >20 ng/ml represent an important patient subgroup, since they are deemed to be at high risk of disease recurrence or progression, as described in NICE clinical prostate cancer guidelines. An improvement in the time to progression, which can trigger the use of chemotherapy and/or more aggressive later-line hormonal therapies (eg, abiraterone and enzalutamide) and their associated toxicity, or death is clearly of both clinical and cost value to the patient and NHS, respectively.

2. Section 2: Meta-regression analyses

To address the AC's concerns with respect to the pooled analyses: *'It considered this* [use of pooled analyses] *to be inappropriate because such pooling ignores the characteristics of individual studies and relies on the assumption that there is no difference between individual trials. The ERG suggested that meta-analyses would have been more appropriate to maintain the effects of randomisation and ensure that each study acts independently, minimising the impact of potential confounding variables. Therefore, the ERG considered that the results presented in pooled analyses in the manufacturer's submission (see section 3.11) were inappropriate and should be interpreted with caution.'* **[page 20, section 3.2.4]**, this response details meta-regression analyses, as detailed in **Table 1** of the ACD response**,** since this method of analysis is preferred by the ERG. The analyses are performed in order to assess trial heterogeneity.

2.1. Outcome definitions

The same outcome definitions used in the submitted pooled analyses have been used within the meta-regression analyses presented here.

2.1.1. PSA PFS

Disease progression is defined as PSA failure or death from any cause, whichever is first.

PSA failure is defined as the days from first dosing (scheduled trial days) where an increase in serum PSA of ≥ 50% from nadir and at least 5 ng/ml measured on two consecutive occasions at least two weeks apart is noted.

The analysis of hazard ratios between degarelix and an LHRH agonist in time to PSA PFS are adjusted for Gleason score, disease stage, and baseline PSA.

2.1.2. Fractures and Joint-Related Signs and Symptoms (JSS)

These endpoints constitute a collection of SMQ terms, used to combine AEs into one composite endpoint (fracture or JSS); see **Supplementary Information 1** for a list of included terms using standardised MedDRA queries.[11] Estimates of hazard ratios are adjusted for treatment group, Gleason score, disease stage and baseline PSA.

2.1.3. CV serious adverse events

CV serious AEs (SAE) are defined as any severe AE falling within any of the following five SMQ terms:

- Myocardial infarction
- Ischaemic cerebrovascular conditions
- Haemorrhagic cerebrovascular conditions
- Embolic and thrombotic events, arterial
- Other ischaemic heart disease.

The analysis of hazard ratios between degarelix and an LHRH agonist in time to a CV event (both with and without death) is adjusted for baseline CV risk factors which are: alcohol consumption, blood pressure (diastolic >90 or systolic >140 mmHg), serum cholesterol >6.2 mmol/l, smoking, usage of statins, treated for hyperlipidaemia, hypertension, or diabetes, all coded as 'Yes/No' variables. Adjustments were also made for age, BMI, and testosterone.

2.2. Assessment of trial heterogeneity using individual patient data

In this analysis we applied a one-step fixed-effects meta-regression model. A one-step procedure is where (all) individual patient data are used in one regression model and used to assess the combined result. We will consider the significance of the trial-treatment interaction term as a measure of heterogeneity between the trials. This follows the approach in Tudur-Smith *et al,*[12] and it is assumed that hazard functions are proportional across the trials. Software for random effects models in the framework of Cox-proportional hazards model are still at a developing stage;[13] thus, we have chosen a fixed effects model.

The non-stratified one-step fixed effect meta-regression model:

The hazard function for patient *i,* participating in trial *j,* is defined as:

$$\lambda_{ij}(t) = \lambda_0(t)\exp\left(\beta_0 x_{0ij} + \beta_1 x_{1ij} + \beta_{2j} + \beta_{3j} x_{3ij}\right)$$

Where:

$\beta_0 x_{0ij}$ adjusts for baseline covariates

$\beta_1 x_{1ij}$ for treatment

β_{2j} adjusts for trial participation

$\beta_{3j} x_{3ij}$ adjusts for interaction between trial and treatment.

For example, the interaction variable x_{3ij} is equal to 1 if patient *i* belongs to the degarelix group in trial *j,* and 0 otherwise. The formal test of trial-treatment interaction is based on the likelihood ratio test, as suggested by Tudur-Smith *et al.*[12] That is, the –2 log likelihood difference between the model not containing the interaction term, and the one including it.

Hazard ratios and statistical inferences are computed using PROC PHREG, in SAS software. Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

2.1. Results

The six trials included in the combined data analysis do not all contribute to the mere count of events; see Tables 1.1 to 1.5 in **Supplementary Information 2**. If a trial does not contribute to any events in any of the arms it will be excluded from the sensitivity analysis of trial heterogeneity since hazards ratios are non-estimable for that particular trial.

Results of sensitivity analysis by means of the non-stratified one-step fixed effect meta-regression model are found in in forest plots **(Supplementary Information 3)**, in Tables 2.1 to 2.9 in **Supplementary Information 2**, and are summarised in **Table A1 (Column E)** below. The interaction term was non-significant, thus there is no suggestion of any trial heterogeneity or 'between-trial effect' and hence not included in producing the final HR estimates, see Tables 3.1 to 3.9 in **Supplementary Information 2,** and **Table A1 (Column F).** The final model used adjusts for baseline covariates and factors, and does not exclude any trials under consideration. As shown in **Table A1**, there are marginal quantitative

differences between the non-stratified one-step fixed effect meta-regression model and the final model in terms of adjusted HR estimates for PSA PFS or CV SAEs (with or without death). The adjusted HR for fractures and joint related signs and symptoms (JSS) is more sensitive and closer to 1 when data from all six trials are included in the final model **Table A1 (Column F)**, as compared to the adjusted HR that includes the non-significant trial-treatment interaction term **Table A1 (Column E).**

A full summary of the results (including the number of event counts) compared with previously presented information within the original submission and model is provided in **Tables A2 and A3** for PSA progression and AEs, respectively.

Table A2. Top-line results

Column A	Column B	Column C	One-step fixed effect meta-regression results		Column F
			Column D	Column E	
Endpoint	Studies included***	Group	p-value of LR test for study-treatment interaction and study terms	Adjusted HR (95 % CI; p-value)***	Final adjusted ACD response HR (95 % CI; p-value)
PSA PFS	CS21 and CS35	Overall – FAS	[redacted]	[redacted]	[redacted]
PSA PFS	CS21 and CS35	Baseline PSA > 20 ng/ml - FAS	[redacted]	[redacted]	[redacted]
PSA PFS	CS21 and CS35	Locally advanced or metastatic patients - FAS	[redacted]	[redacted]	[redacted]
Joint Related Signs and Symptoms	CS21, (CS28), CS30, (CS31) CS35 and CS37*	Overall – Safety Analysis Set	[redacted]	[redacted]	[redacted]
Joint Related Signs and Symptoms	CS21, (CS28, CS30, CS31), CS35 (and CS37*)	Baseline PSA > 20 ng/ml – Safety Analysis Set	[redacted]	[redacted]	[redacted]
Fractures	CS21, (CS28, CS30, CS31), CS35 and CS37*	Overall – Safety Analysis Set	[redacted]	[redacted]	[redacted]
Fractures	CS21, (CS28, CS30, CS31), CS35 and (CS37*)	Baseline PSA > 20 ng/ml – Safety Analysis Set	[redacted]	[redacted]	[redacted]
CV SAE excluding death	CS21, (CS28, CS30, CS31), CS35 and CS37*	CVD population – Safety Analysis Set	[redacted]	[redacted]	[redacted]
CV SAE including death	CS21, (CS28, CS30, CS31), CS35 and CS37*	CVD population – Safety Analysis Set	[redacted]	[redacted]	[redacted]

*All data from the intermittent degarelix arm in CS37 is censored at month 7, i.e. the data from CS37 used within meta-regression analyses only included patients with a continuous therapy.
** Significant at the p=0.05 level

*** Studies within parenthesis were not used in the non-stratified one-step fixed effects meta-regression model since they did not contribute with events in one, or both arms

Abbreviations: FAS: Full analysis set; CVD: Cardiovascular disease; SAE: serious adverse event; HR; hazard ratio

Table A3. Summary of PSA progression hazard ratios

Column A	Column B	Column C	One-step fixed effect meta-regression results		Column F
			Column D	Column E	
Endpoint	Studies included***	Group	p-value of LR test for study-treatment interaction and study terms	Adjusted HR (95 % CI; p-value)***	Final adjusted ACD response HR (95 % CI; p-value)
PSA PFS	CS21 and CS35	Overall – FAS	[redacted]	[redacted]	[redacted]
PSA PFS	CS21 and CS35	Baseline PSA > 20 ng/ml - FAS	[redacted]	[redacted]	[redacted]
PSA PFS	CS21 and CS35	Locally advanced or metastatic patients - FAS	[redacted]	[redacted]	[redacted]
Joint Related Signs and Symptoms	CS21, (CS28), CS30, (CS31) CS35 and CS37*	Overall – Safety Analysis Set	[redacted]	[redacted]	[redacted]
Joint Related Signs and Symptoms	CS21, (CS28, CS30, CS31), CS35 (and CS37*)	Baseline PSA > 20 ng/ml – Safety Analysis Set	[redacted]	[redacted]	[redacted]
Fractures	CS21, (CS28, CS30, CS31), CS35 and CS37*	Overall – Safety Analysis Set	[redacted]	[redacted]	[redacted]
Fractures	CS21, (CS28, CS30, CS31), CS35 and (CS37*)	Baseline PSA > 20 ng/ml – Safety Analysis Set	[redacted]	[redacted]	[redacted]
CV SAE excluding death	CS21, (CS28, CS30, CS31), CS35 and CS37*	CVD population – Safety Analysis Set	[redacted]	[redacted]	[redacted]
CV SAE including death	CS21, (CS28, CS30, CS31), CS35 and CS37*	CVD population – Safety Analysis Set	[redacted]	[redacted]	[redacted]

*All data from the intermittent degarelix arm in CS37 is censored at month 7, i.e. the data from CS37 used within meta-regression analyses only included patients with a continuous therapy.
** Significant at the p=0.05 level

*** Studies within parenthesis were not used in the non-stratified one-step fixed effects meta-regression model since they did not contribute with events in one, or both arms

Abbreviations: FAS: Full analysis set; CVD: Cardiovascular disease; SAE: serious adverse event; HR; hazard ratio

Table A4. Summary of adverse events hazard ratios

Placement in NICE STA (original submission or ACD response)	Data source and population/subgroup	Unadjusted HR (95% CIs) (degarelix vs. leuprorelin)	Adjusted HR (95% CIs)** (degarelix vs. leuprorelin)	p-value for trial effects	p-value for trial/treatment interaction effects	p-value for adjusted hazard ratio	Events degarelix	Events LHRH agonists
Original submission	CS21 80mg – ITT	0.58 (0.34-0.99)	0.66 (0.39- 1.15)[4]	N/A	N/A	0.14	NR	NR
Original submission	CS21 80mg – PSA > 20ng/mL	0.57 (0.33-1.01)	0.68 (0.38-1.14)	N/A	N/A	0.19	NR	NR
Final adjusted ACD response	CS21 and CS35 all doses – FAS	N/A	[redacted]	[redacted]	[redacted]	[redacted]	119/ 974	77/ 483
Final adjusted ACD response	CS21 and CS35 all doses – PSA > 20ng/mL, FAS	N/A	[redacted]	[redacted]	[redacted]	[redacted]	105/ 475	66/ 231
Final adjusted ACD response	CS21 and CS35 all doses – locally advanced + metastatic, FAS	N/A	[redacted]	[redacted]	[redacted]	[redacted]	83/ 250	46/ 118
Original submission	CS21 and CS35 degarelix all doses vs LHRH + AA***, FAS	N/A	0.490[14]	N/A	N/A	0.003[14] *	NR	NR

* Significant at the p=0.05 level

**Includes CS21, CS28, CS30, CS31, CS35 and CS37 but all data from the intermittent degarelix arm in CS37 is censored at month 7, i.e. the data from CS37 used within meta-regression analyses only included patients with a continuous therapy.

***HR described in the original submission

Abbreviation: CVD: cardiovascular disease; SAE: serious adverse event; PSA; prostate specific antigen

In order to clarify and compare all of the analyses that have been presented in the initial submission within the published literature, **Table A5** below provides a detailed description of the methods and covariates used.

Table A5. Cross-publication comparisons

Outcome	Population	Publication(s)	Method & covariates used in publication(s)	Result HR (95 %CI; p-value)
PSA PFS	CS21	Tombal et al 2010[4]	Treatment groups (160mg, 80mg, leuprolide), PCa stage, baseline PSA (<10, 10-20, 20-50)	0.66 ([0.39; 1.15]); NS) (80mg vs leuprolide)
PSA PFS	CS21 + CS35; degarelix vs LHRH agonists + antiandrogens	Iversen et al 2013[14]	Treatment group (degarelix vs LHRH agonist), baseline PSA, PCa stage and Gleason score	0.49 ([xx; xx]; p=0.0028)
PSA PFS	CS21, 28, 30, 31, and CS35	Klotz et al 2014[15]	Treatment group (degarelix vs LHRH agonist),testosterone, log PSA, PCa stage, age	0.71 ([0-54; 0.94]; 0.017)
PSA PFS	CS21, 28, 30, 31, and CS35, BL PSA > 20ng/mL	Klotz et al 2014[15]	Treatment group (degarelix vs LHRH agonist),testosterone, log PSA, PCa stage, age	0.74 ([0.55; 1.00]; 0.052)
Cardiovascular events (with death)	CS21, 28, 30, 31, 35 and CS37, CVD population	Albertsen et al 2013[16]	Treatment group (degarelix vs LHRH agonist), statin use, alcohol use, hypertension, smoker, serum cholesterol, Type 2 diabetes (treated), hypertension (treated), baseline age, testosterone and BMI	0.44 ([0.26; 0.74]; 0.002)
Joint related signs and symptoms	CS21, 28, 30, 31, and CS35	Klotz et al 2014[15]	Treatment group (degarelix vs LHRH agonist),testosterone, log PSA, PCa stage, age	0.64 ([0.42; 0.98]; 0.041)
Fractures	CS21, 28, 30, 31, and CS35	Klotz et al 2014[15]	Treatment group (degarelix vs LHRH agonist),testosterone, log PSA, PCa stage, age	0.42 ([0.16; 1.05]; 0.064)

2.2.1. PSA PFS

Table A2 shows that treatment with degarelix has a significant effect on PSA progression in overall population when analysis is conducted using both the CS21 and CS35 trials including all doses of degarelix and adjusting for baseline characteristics [redacted]. It is relevant to only combine CS21 and CS35 trials within the meta-regression analyses for purposes of evaluating PSA PFS, since only these two trials evaluated PSA failure using the same clinically relevant criterion, which is subsequently used to re-derive PSA PFS. Treatment with degarelix shows a trend towards significance within the PSA >20 ng/ml subgroup [redacted] and a similar magnitude of effect to the overall population, although sufficient power is lacking for significance within this subgroup alone.

The hazard ratio within the high-risk subgroup (PSA >20 ng/ml) in which clinicians at the AC meeting indicated degarelix is likely to be of most benefit in terms of reducing the risk of PSA progression is similar to the overall population. However, the underlying risk of progression is also greater in this population, leading to roughly equivalent or greater benefits from the use of degarelix to slow PSA progression.

2.2.2. CV risk

Treatment with degarelix was significant in the risk population defined as those with pre-existing CVD for the outcome of CV SAEs, both including [redacted] and excluding death [redacted] within one year of initiating therapy. As previously discussed in this response, such benefits can be put into context of other treatments used in a high-risk CVD population; for example, in those treated with a statin (simvastatin) versus placebo the relative risk observed was 0.66 (95% CI 0.59-0.75; p<0.00001) over a 5.4 year median follow-up period.[17]

2.2.2.1. Peer-reviewed, independent evidence of the CV risk benefit of degarelix

To ensure the AC is fully aware of the recent peer-reviewed, independently produced publication concerning the CV risk benefit of degarelix versus LHRH agonists in patients with CVD at baseline, please find below a summary of its main findings:[16]

1. The baseline incidence of CVD, i.e. those with pre-existing CVD, was approximately 30% in both treatment groups.
2. Patients with pre-existing CVD who were treated with degarelix had a significantly lower risk of experiencing a CV event or death when compared with patients receiving a LHRH agonist within one year of initiating androgen deprivation therapy. A Cox-proportional hazard model showed a 56% lower risk of a cardiac event or death during the initial year of treatment for men receiving the GnRH antagonist compared with men receiving a GnRH agonist (HR: 0.44; 95% CI, 0.26–0.74; p=0.002).
3. The absolute risk reduction during the first year was 8.2%, which yielded a number needed to treat of 12.

Individual patient level data was provided to this independent group, who did their own analysis and reporting of the results i.e. choice of model, covariates etc. Further evidence to support these findings is presented in the meta-regression analyses, as described above in this response.

2.2.2.2. Potential mechanisms behind CV risk benefit

In light of the uncertainty documented in the ACD with respect to the CV safety data, Ferring has provided within this response an explanation of the potential molecular mechanisms to describe the CV risk difference when comparing degarelix with LHRH agonists in men with pre-existing CVD. The observation that the incidence of serious cardiac events differs dependent on whether a patient receives degarelix versus an LHRH agonist is strong evidence that there are other factors at play in the cause of CVD among patients undergoing ADT, opposed to simply lowering testosterone levels. This argument is further supported by findings from Keating *et al* 2006, which showed, based on a population-based cohort of 73,196 patients, that LHRH agonist use was associated with an increased risk of coronary heart disease (adjusted HR, 1.16; $p<0.001$), myocardial infarction (adjusted HR, 1.11; $p=0.03$) and sudden cardiac death (adjusted HR, 1.16; $p=0.004$), while those treated with orchiectomy did not exhibit a significant increased risk of these CVD outcomes (all $p>0.20$).[18] However, it is noted that there are conflicting studies within the literature with respect to the CV risk associated with orchiectomy.[19] As described within the discussion of the independent peer review paper produced by Albertsen *et al* 2013,[16] several molecular mechanisms are likely to be at play:

1. **Destabilisation of established vascular lesions.** Most acute CV events are caused by rupture of an atherosclerotic plaque. Plaques prone to rupture are characterised by a large core of lipids and necrotic debris covered by a thin cap of smooth muscle cells and connective tissue. The rupture is caused by a degradation of the cap connective tissue by infiltrating macrophages. Lymphocytes of the pro-inflammatory T helper (Th1) type are important macrophage activators and are the dominant T cell type in atherosclerotic plaques. GnRH receptors are expressed on T cells suggesting a potential auto- or paracrine role for the GnRH immune system. Activation of the GnRH receptors results in T cell activation, including increased proliferation and expression of the IL-2 receptor, thus suggesting that agonists may promote destabilisation of atherosclerotic plaques.
2. **Degarelix suppresses both LH and FSH, as opposed to LHRH agonists, which primarily suppress LH**. FSH receptors have been found on the luminal endothelial surface of proliferating tissue and may play a role in endothelial cell function, lipid metabolism and fat accumulation that may increase the risk of CVD in men on LHRH agonists. It is recognised from the literature that androgen deprivation therapy (ADT) – predominantly LHRH agonists – is associated with an increased risk of myocardial infarction and sudden cardiac death.[18,20,21] There have been recent changes to the wording within the summary of product characteristics (SPC) for degarelix, with respect

to special warnings of CVD, since EMA assessors considered the risk of CVD to be a potential risk that is it is inherent to all forms of androgen deprivation.[22] However, at the time of this EMA assessment the recent evidence (i.e. Albertsen *et al*[16] and the meta-regression results detailed within this response) were not available and therefore could not be taken into consideration during this SPC amendment. Thus, the SPC wording used does not take into account differences in the CV SAE risk incurred from ADT with a GnRH antagonist versus ADT with a LHRH agonist, which are presented in recent literature[16] and within this ACD response.

2.2.3. Fractures and joint-related signs and symptoms (JSS)

When adjusted for baseline disease characteristics, treatment with degarelix remained significant in the overall safety analysis set for JSS and was close to significance in the much smaller PSA >20 ng/ml population (21 events in 607 patients in the degarelix arms, 20 events in 305 patients in the LHRH arms). Treatment with degarelix is no longer significant when compared with treatment with LHRH for fractures. It should be noted that within the original analysis, presented in the manufacturer submission, the assumption of proportional hazards between the two treatment arms, does not appear to be valid (see Figure 29 of the submission). Therefore, a single hazard ratio cannot be accurately calculated. Clinicians at the advisory board confirmed that a proportional hazards assumption is unlikely to hold due to the nature of fracture events in prostate cancer with disease-related events (pathological fractures) more likely to be experienced early on and osteoporotic fractures becoming more common with advanced age. As degarelix is likely only to affect the rate of pathological fracture an assumption of proportional hazards is unlikely to hold. Thus, this analysis, for fracture events, should be viewed with caution.

3. Section 3: Additional modelling conducted

3.1. Summary

The meta-regressions presented with this response assessed the degree to which outcomes were influenced by characteristics of the patients (Gleason score, disease stage, baseline PSA and CV risk factors) and trials, by incorporating a study-treatment interaction term to account for heterogeneity between the studies. As no study-treatment interaction were found to be significant adjusted hazard ratios based on a regression model without this term is used for the final economic model.

The cost-effectiveness model for degarelix has also been updated to address the views of the ERG and AC. The changes made to the model in response to the ACD are summarised as follows:

- Incorporation of sensitivity analysis by one-step fixed effects meta-regression model for safety and efficacy data
- Provision of additional scenario analyses around the data used to fit the curves for PSA progression for degarelix (detailed in section 3.2)
- Development of the treatment sequence following anti-androgen withdrawal to account for the more clinically relevant treatment patterns described at the AC (use of abiraterone before docetaxel and use of enzalutamide)
- Change in comparator drug cost to a weighted average of three-monthly LHRH agonists used in the UK, based on sales figures.
- Continuation of first-line hormonal therapy until death (in line with the ERG base case presented)
- Quality of life (utility) estimates derived from the algorithm published by McKenzie and van der Pol,[23] as recommended by the ERG.

In their 'most plausible scenario', the ERG assumed that the hazards of PSA PFS progression were equal between degarelix and LHRH agonists after one year. As this is likely to produce a very conservative estimate of the cost-effectiveness of degarelix, two base cases are presented here. The first is an updated base case, based on the initial analyses submitted, with changes based on comments from the AC and ERG, which assumes the comparative efficacy is sustained over the duration of the model. The second adopts the conservative efficacy assumption of the ERG base case and does not include any benefit from reduced risk of fractures (as this was non-significant), but is otherwise identical to the updated base case. It is anticipated that the true incremental cost-effectiveness ratio (ICER) will be within the range indicated by these two scenarios.

The updated base case ICERs generated (shown in **Table A6**) from these changes are £2,733, £4,509 and £6,539 for the overall, PSA > 20 ng/ml, and locally advanced and metastatic populations respectively.

In the conservative base case, with the additional efficacy assumption (equal efficacy after one year), these ICERs are £19,510, £17,516 and £20,847 for the overall, PSA >20 ng/ml and locally advanced and metastatic populations, respectively.

Table A6. Updated base case ICERs

Population	Base cases	
	Updated base case	**Conservative base case**
Overall (FAS)	£2,733	£19,510
PSA >20 ng/ml (FAS)	£4,509	£17,516
Locally advanced and metastatic (FAS)	£6,539	£20,847

Abbreviation: FAS: full analysis set

The overall ICER for the conservative base case remains similar to the ERG's original 'most plausible scenario' ICER (£14,798) despite the removal of benefits from a reduction in fractures from this analysis. The majority of scenario analyses, both within the updated base case and conservative base case produce ICERs well below the standard cost-effectiveness threshold of £20,000–30,000 per quality-adjusted life-year (QALY) and the probabilistic ICERs are similar too (lower than) the deterministic ICERs.

3.2. Updated parametric curve fits for PSA progression and scenario analysis surrounding data used to model PSA progression

To address concerns regarding the use of different lengths of data to fit curves for degarelix compared with LHRH agonists, curve fitting has been carried out using both one-year and five-year data from the degarelix trials.

Figure A3 below shows four curve fits to PSA PFS data for patients in the FAS population treated with degarelix, using a log-normal parametric fit (the best fitting based on AIC and BIC). Two curves are fitted to data from the CS21 trial, and two curves are fitted to the combined data from the CS21 and CS35 trials. For each of these datasets, one curve has been fitted to five years of long-term data, and one curve to the first year of data only (the duration of the comparative trial period). The goodness of fit statistics for these curves, along with the other curve fits considered, are shown in **Table A7.**

Figure A3. Comparison of CS21 and meta-regression curves, showing fits to 1 year and 5 years of data – FAS population

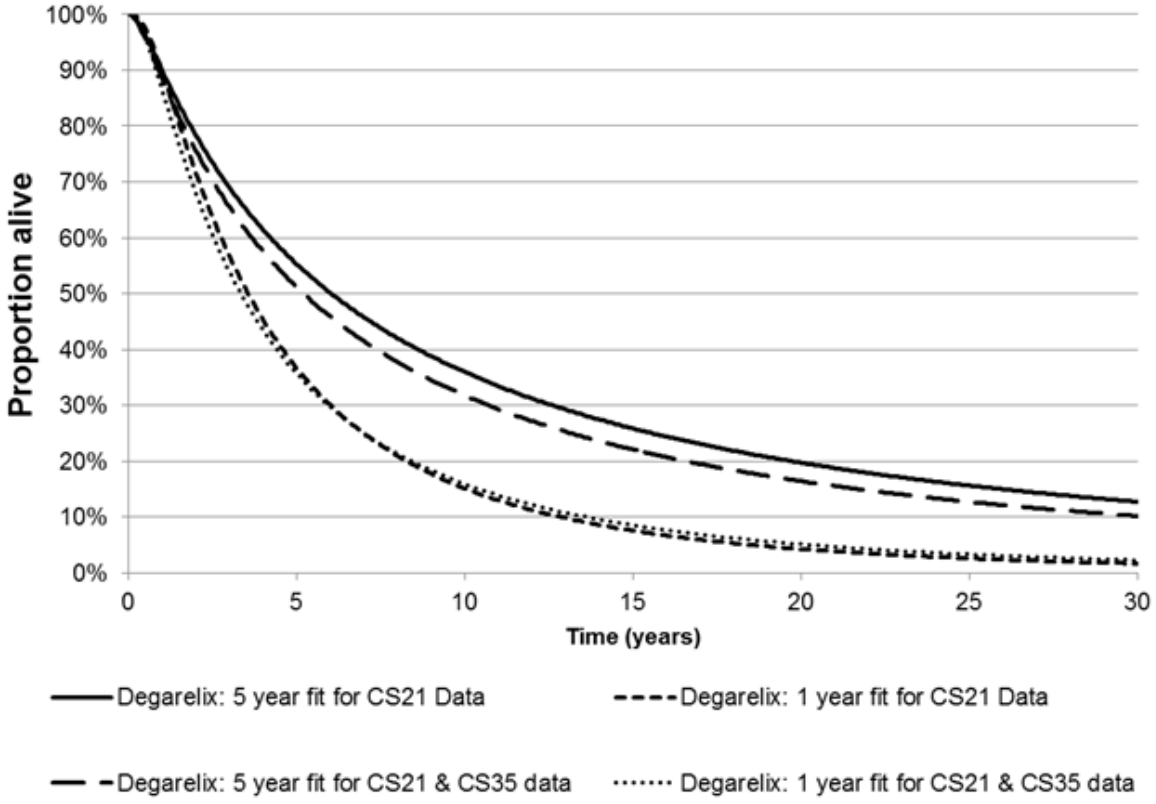


Table A7. Goodness of fit statistics of the 5-year curves for each population

CS21 & CS35	Overall population (FAS)		PSA >20 ng/ml population (FAS)		Locally advanced and metastatic population (FAS)	
5-year curves	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Log-normal	1,234	1,244	837	846	864	873
Log-logistic	1,251	1,261	849	857	878	886
Exponential	1,267	1,272	870	874	894	898
Weibull	1,264	1,273	865	874	893	901
1-year curves	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Log-normal	802	812	575	584	601	609
Log-logistic	803	813	578	586	603	612
Exponential	845	849	617	621	643	647
Weibull	804	814	580	588	605	613
CS21						
5-year curves	**AIC**	**BIC**	**AIC**	**BIC**		
Log-normal	1030	-	795	-		
Log-logistic	1033	-	798	-		
Exponential	1035	-	800	-		
Weibull	1036	-	802	-		
Gompertz	1099	-	858	-		
1-year curves	**AIC**	**BIC**				
Log-normal	131	137	106	111		
Log-logistic	131	138	106	111		
Exponential	138	142	113	116		
Weibull	131	138	106	111		
Gompertz	132	139	107	113		

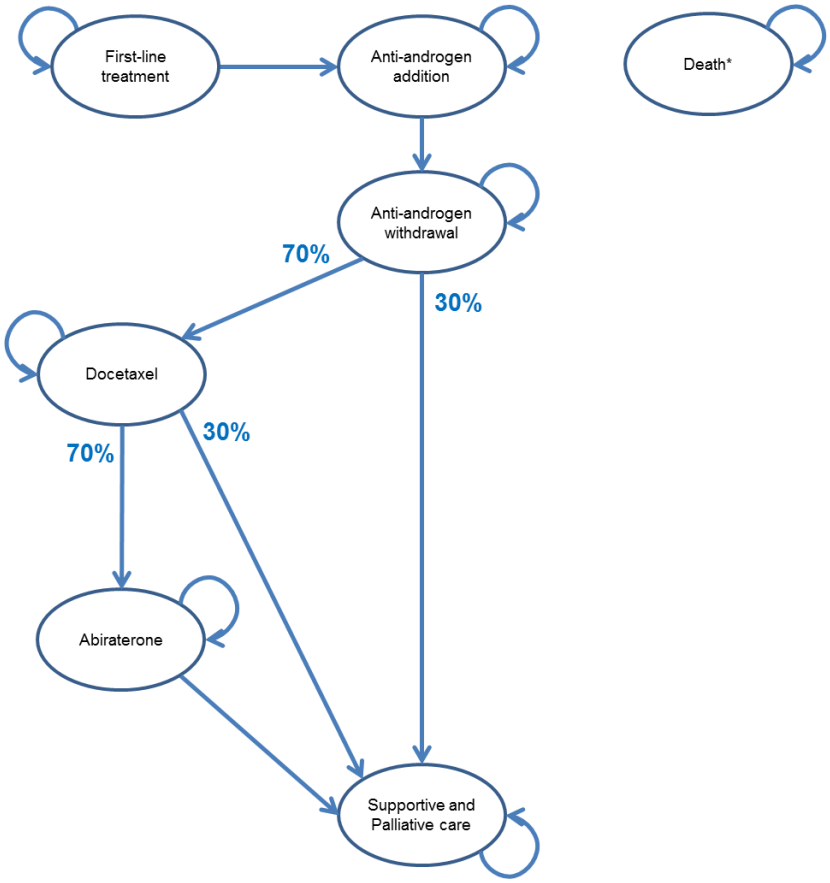
Abbreviations: AIC = Akaike's Information Criterion; BIC = Bayesian Information Criterion; FAS: Full analysis set; PSA = prostate-specific antigen

3.3. Introduction of enzalutamide into treatment algorithm

To address the AC's concerns with respect to the placement of abiraterone in the treatment pathway **[page 26, section 4.2]** and the exclusion of enzalutamide from the treatment algorithm **[page 26, section 4.2]**, scenario analyses to evaluate the positioning of abiraterone prior to docetaxel following disease progression and the introduction of enzalutamide are provided.

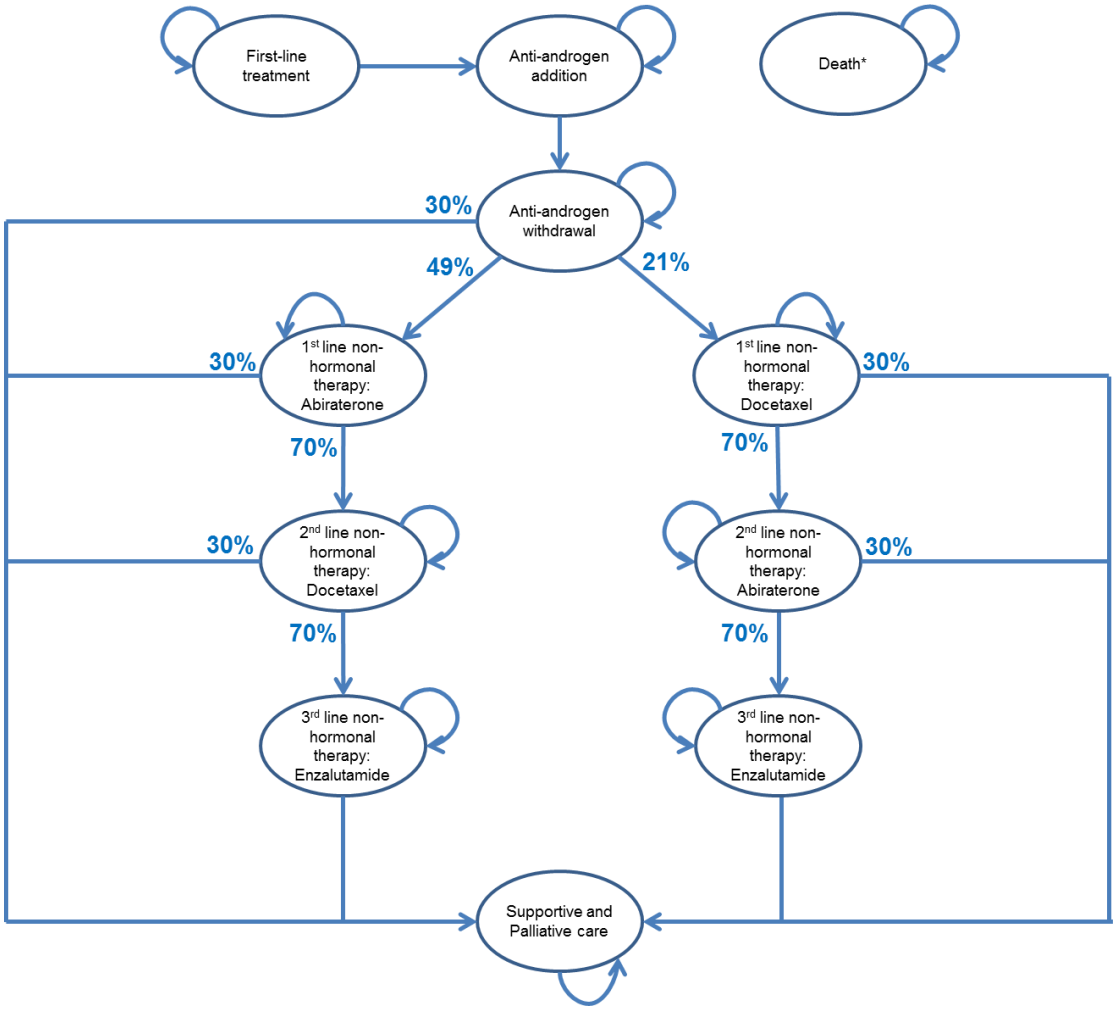
In the original submission of evidence, the treatment sequence followed the general pattern shown in **Figure A4** with the 70/30% transition probabilities introduced in response to ERG questions based upon clinician feedback and inputs from the NICE costing templates for docetaxel and abiraterone.

Figure A4. Treatment pathway represented in ERG base case



To address concerns from clinical experts at the AC meeting that this sequence does not reflect common practice, the pathway was amended to represent the sequence shown in **Figure A5.** The transition probabilities between the treatments are based on the 70/30 splits taken from clinical expert input and calculated based upon the NICE costing templates for docetaxel and abiraterone, but can be freely changed within the model. The main adaptation was the inclusion of enzalutamide, which is restricted to third line non-hormonal therapy in the base case, for patients who have already received both docetaxel and abiraterone.

Figure A5. Treatment sequence represented in updated economic model



3.3.1. Parameterisation of enzalutamide

The following sections introduce the parameterisation of the enzalutamide health states that have been added to the model. This parameterisation was based on the manufacturer's evidence submission to the NICE technology appraisal of enzalutamide for the treatment of metastatic prostate cancer.[24]

3.3.2. Duration of response

Although the mean duration of treatment response is commercial in confidence in the manufacturer's submission, the economic case for enzalutamide is based on a (at least) non-inferior efficacy profile compared to the primary comparator, abiraterone. Based on this, the duration of response to enzalutamide is assumed to be equal to that of abiraterone in the updated base cases.

3.3.3. Drug costs

The drug price for enzalutamide was taken as the list price reported in the manufacturer submission; £2734.67 for a pack of 112 40mg tablets, equivalent to 28 days of treatment. In deterministic and probabilistic sensitivity analyses, this drug price is varied between 50% and the full price, to account for uncertainty in the expected patient access scheme (PAS) for enzalutamide which is commercial in confidence.

3.3.4. Administration costs

The resource use requirements of the administration of enzalutamide were obtained from the manufacturer submission to the NICE appraisal, in which increased resource use was assumed to be required for the first three months of enzalutamide treatment. In the updated base cases, the resource use in the first month was increased to account for the additional resource use in the second and third months, and these adjusted resource requirements are shown in **Table A8.** The error introduced by re-distributing resource use in this way is expected to be negligible.

The costs of ECG and ultrasound scans were included as resource costs for enzalutamide, but were not included in the degarelix model previously. **Table A9** shows the NHS reference costs added to the model to be used in the cost calculation for enzalutamide.

Table A8. Resource use associated with the administration of enzalutamide, as reported in manufacturer submission to NICE TA

Parameter	1st cycle	Subsequent cycles	1st cycle	Subsequent cycles
Cost of Staff Time				
Cost of a practice nurse visit	0.0	0.0	£0.00	£0.00
Cost of a GP consultation	0.0	0.0	£0.00	£0.00
Cost of an outpatient urologist consultation	0.0	0.0	£0.00	£0.00
Cost of an outpatient oncologist consultation	2.0	0.50	£226.35	£56.59
Cost of Scans and Tests				
Cost of a bone scan	0.1	0.0	£6.71	£1.68
Cost of a CT scan	0.10	0.03	£10.54	£2.64
Cost of an MRI scan	0.10	0.03	£14.45	£3.61
Cost of a blood test	2.0	0.5	£6.17	£1.54
Cost of other blood tests (5 for each liver test, 10 for each kidney tests, 1 for each PSA test)	32.0	8.0	£39.36	£9.84
Cost of ECG	0.10	0.03	£14.52	£3.63
Cost of ultrasound	0.10	0.03	£5.13	£1.28
Total Administration Cost			£323.23	£80.81

Table A9. Additional NHS reference costs incorporated in the costing of enzalutamide

Resource	Cost	Source
Cost of ECG	£145.15	NHS ref. costs 11-12. OPROC EA47Z
Cost of ultrasound	£51.27	NHS ref. costs 11-12. DIAGIM_OP RA23Z

3.3.5. Quality of life

As quality of life data was marked as commercial in confidence in the enzalutamide manufacturer submission and time constraints did not allow for the systematic identification of utility values, it is assumed that patients receiving enzalutamide have the same quality of life as those receiving abiraterone and docetaxel. This also means that there is consistency for all non-hormonal therapies included in the model. In reality quality of life would be expected to decrease as patients progress through the available treatments, which happens faster on the LHRH agonist arm of the model, therefore the assumption of equal quality of life weights for all non-hormonal treatments provides a conservative estimate of the ICER.

3.3.6. Mortality rates

In line with the efficacy claims of the enzalutamide submission, and the assumption of equal duration of response, it is also assumed that the mortality hazards for patients treated with enzalutamide are comparable to those for abiraterone. Given that the second AC report had not been published at the time of writing, this assumption was considered to be appropriate.

3.4. Use of an alternative utilities algorithm

To address the concerns raised in the ACD with respect to the Kontodimopoulos *et al* (2009) utility mapping algorithm – ie, 'The Committee considered that an alternative algorithm considered by the manufacturer, from McKenzie and van der Pol (2009),[23] was more appropriate….' **[page 36, section 4.16]** – the McKenzie and van der Pol (2009) has been used. Furthermore, within this subsection we provide clarification on the concerns of quality of life (QoL) double counting when using the Kontodimopoulos *et al* (2009)[25] utility mapping algorithm, as expressed by within the ACD: 'The Committee considered that this may have resulted in some double counting of the impact of AEs on quality of life in the model' **[page 36, section 4.16]**.

Double counting is unlikely to have biased the initial analyses provided to the committee due to the method of analysis used to transform the CS21 data into the health states within the model:

- The utility of patients experiencing fractures, JSS or CV events was taken only from patients who had not progressed (and therefore does not double count with progression) – (see Table 38 in the original submission)
- The utility by progression status did include patients experiencing AEs but the difference when these events are excluded is not large (please see below).

To ensure no double counting occurs in the model, utilities by PSA progression status (for patients not experiencing an AE) have been updated to match those presented in **Table A10** for patients not experiencing an AE.

Table A10. Utility by progression status according to whether patients had experienced adverse events or not

Progressed?	AEs	SF-12 v2 mapped to EQ-5D		EORTC QLQ-C30	EORTC-8D	EQ-5D Kontodimopoulos	EQ-5D McKenzie + van der Pol
		n	Utility (sd)	n	Utility (sd)	Utility (sd)	Utility (sd)
Yes	No AEs	63	0.676 (0.154)	63	0.817 (0.125)	0.782 (0.219)	0.713 (0.227)
	All	73	0.673 (0.150)	73	0.806 (0.127)	0.753 (0.238)	0.682 (0.250)
No	No AEs	2522	0.745 (0.132)	2488	0.871 (0.109)	0.891 (0.189)	0.808 (0.189)
	All	2689	0.743 (0.132)	2653	0.868 (0.112)	0.887 (0.195)	0.803 (0.195)

3.5. Update of comparator cost

Based on discussion at the committee meeting, for the purposes of applying the comparator drug costs, the comparator was changed to represent a weighted average of the drug prices of the three-month LHRH agonist regimens, based on their UK sales data.[26] This does not change administration costs or comparator efficacy. Within the ERG base case, the cost of triptorelin was used as this is the cheapest LHRH agonist; however, triptorelin is rarely used within the UK, representing less than 8% of the total market share by pack sales (volume) in 2011–12 and so even less in total value market share.

Updated data for the year up to September 2013 are presented in **Table A11.** The market share of triptorelin by both packs sold and months of treatment remains below 12%, with goserelin (Zoladex) remaining the most prescribed treatment, followed by leuprorelin (Prostap).

Table A11. Pack Sales last 12 months up to September 2013*

Product	Generic	Dose form	Total packs sold	Share by packs sold	Share by months of treatment
DECAPEPTYL SR 11.2MG**	Triptorelin	3-monthly	88258	7.0%	11.3%
DECAPEPTYL SR 22.5MG	Triptorelin	6-monthly	2941	0.2%	0.0%
DECAPEPTYL SR 3MG	Triptorelin	monthly	42997	3.4%	0.5%
GONAPEPTYL DEPOT	Triptorelin	monthly	17305	1.4%	0.4%
PROSTAP 11.25MG**	Leuprorelin	3 monthly	262896	20.9%	33.5%
PROSTAP 3.75MG	Leuprorelin	monthly	128891	10.2%	1.4%
ZOLADEX 10.8MG**	Goserelin	3 monthly	402507	32.0%	51.3%
ZOLADEX 3.6MG	Goserelin	monthly	203516	16.2%	1.5%

*MAT pack sales data sourced from IMS

**In the updated model the comparator is changed to represent a weighted average of the drug prices of the three-month LHRH agonist regimens

3.6. Mortality

There was some uncertainty among committee members surrounding the impact of degarelix on the overall survival of patients. While there is no direct impact of degarelix on overall survival, there is likely to be an indirect improvement in survival resulting from slowed disease progression (as PSA progression is linked to reduced survival in metastatic patients receiving first-line hormonal therapy) and lower risks of fatal CV AEs in patients with pre-existing CVD.

The evidence for differential mortality for these two reasons comes from the following sources:

- Lower risk of death with slower PSA progression in metastatic patients
  - Whilst the comparative evidence available is over too short a time period to be expected to show a difference in overall survival available literature in first-line hormonal therapy indicates a strong link between PSA progression and survival in metastatic patients. This link was supported by the clinicians at the AC and by clinicians consulted at advisory boards prior to submission
  - The paper used to model this link (Hussain et al)[10] provides hazard ratio of 2.39 (95% CI 2.05–2.80, p<0.0001) based upon a sample of 1,029 first-line metastatic

patients with adequate follow-up and covariate information from trial S9346 (435 events).

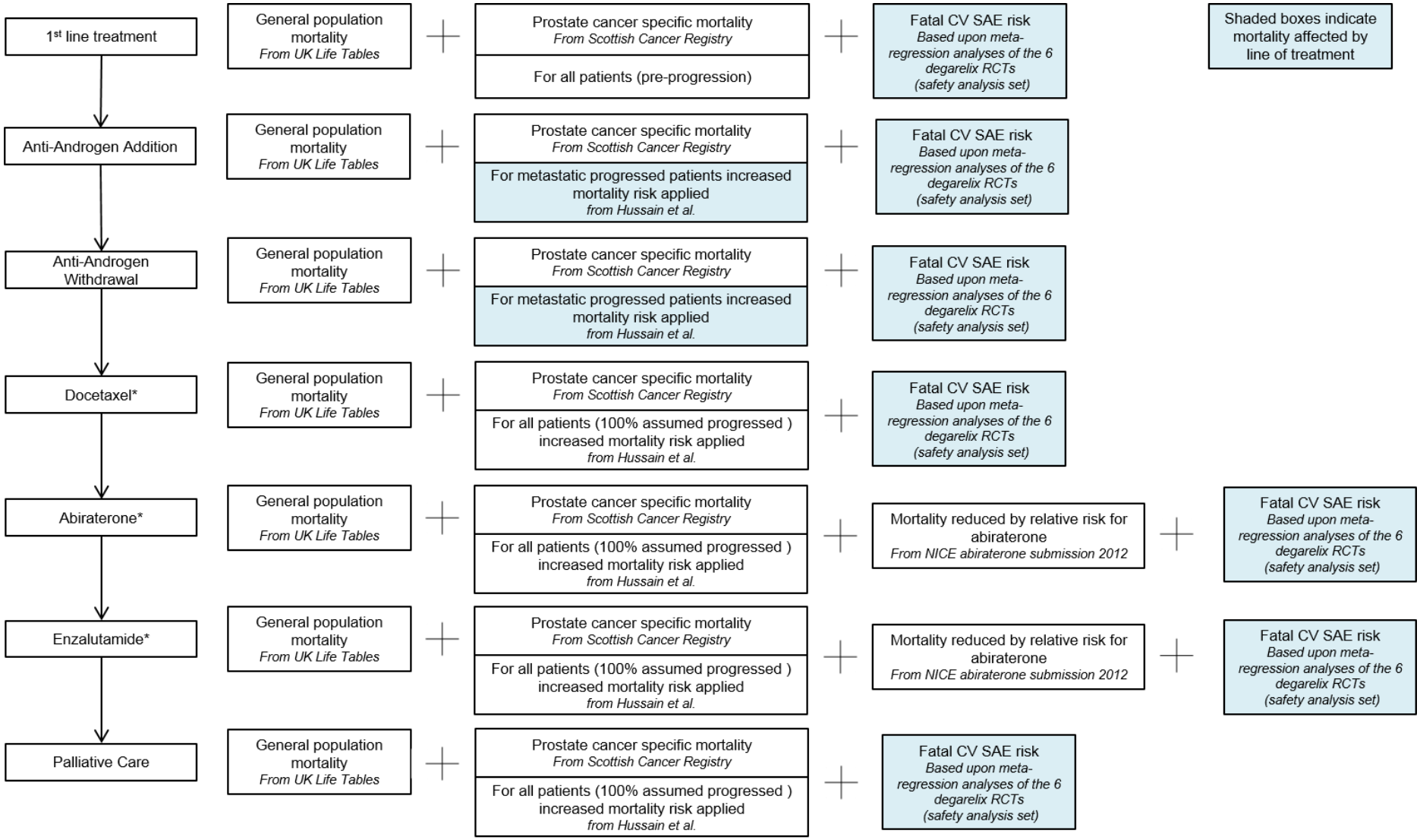
- Lower risks of fatal CV AEs in patients with pre-existing CVD
  - Pooled data from the six degarelix RCTs showed that degarelix significantly reduced the risk of fatal CV AEs in patients with pre-existing CVD
  - The meta regression presented in this analysis which corrects for differences in baseline characteristics and between-study interaction (heterogeneity) also shows that degarelix significantly reduced the risk of CV AEs (including death) in patients with pre-existing CVD with a hazard ratio of [redacted].
  - No between-study or study / treatment interactions were found when statistical tests were carried out.

The evidence submitted included a scenario analysis in which CV death, PSA progression-linked mortality (metastatic patients) and prostate cancer-specific mortality were removed to give an equal number of life-years for each cohort.

Figure A6 below demonstrates how the impact of degarelix on mortality is incorporated into the economic model. The blue shaded boxes indicate where mortality is affected by treatment arm, driven by the increased time before PSA progression and reduced risk of AEs observed with degarelix compared with LHRH agonists.

In the model, the baseline mortality risks are derived from UK life tables, with prostate cancer-specific mortality sources from the Scottish prostate cancer registry. Prostate cancer-specific mortality is applied as the relative mortality experienced by prostate cancer patients, compared with the risks of mortality for the general population.

Figure A6. Illustration of mortality mechanics in the model



* Details of the exact treatment sequence a patient may follow is described in figure 5 above, which shows that they may not be treated with every line of therapy shown.

3.7. Fracture risk

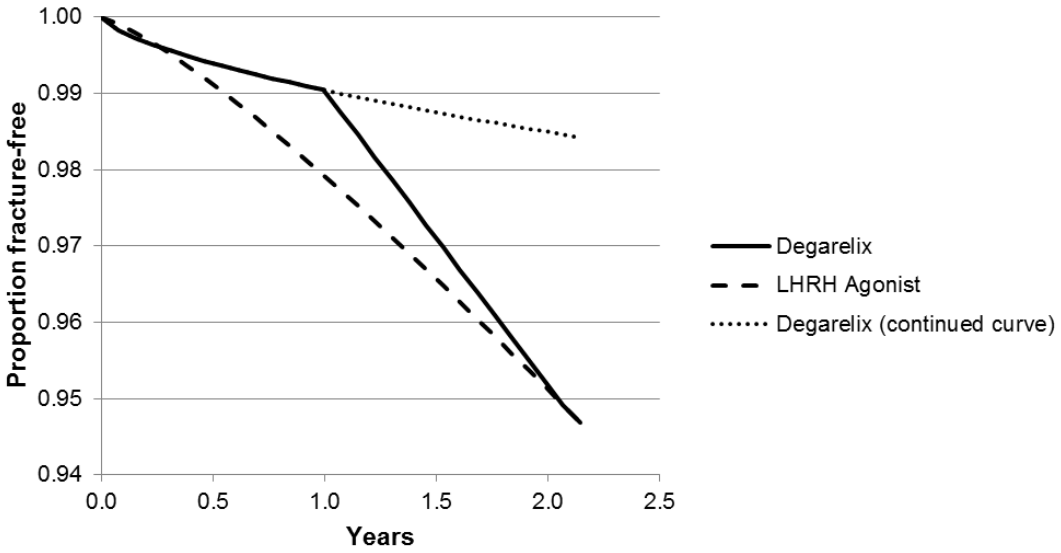
The committee expressed concerns over the long-term modelling of fracture risks and the uncertainty behind this as a potential source of benefit for degarelix-treated patients **[page 31, section 4.9]**.

While there are difficulties recording the nature of fracture (pathological or osteoperotic), which mean that the nature of the fractures recorded in the trials could not accurately be determined, based on the mechanism of action of degarelix compared with LHRH agonists, it would be assumed that the benefits of degarelix come from reducing pathological fractures although as explained by one of the clinicians at the committee standard coding does not allow these type of fractures to be easily identified. Over time, patients receiving either degarelix or LHRH agonists would become increasingly at risk of osteoperotic fractures, which means that in reality the curves for fractures are likely to either stop separating (ie, no incremental benefit is seen) or converge.

To address this, an additional scenario analysis has been included in the model in which the risk of fracture for patients treated with degarelix is increased between Years 1 and 2, so that the number of events by two years is equal to that in the LHRH agonist arm. After two years, the risks are equal between the two treatment groups (U-shaped curve).

Figure A7 shows how this change occurs, with the linear convergence of the degarelix curve onto the LHRH agonist curve over one year.

Figure A7. Increased hazards of fracture for degarelix used in scenario analysis



3.8. Additional curve fits for adverse events

In addition to the new curves fitted for PSA PFS, additional curves were fitted to model AEs. Log-logistic and log-normal curves were generated for the CV events (with and without death), JSS and fractures. These curves did not fit better than the Weibull curves for fractures and JSS, based on AIC. As a result, these curve fits were not incorporated into the base case, but are tested in sensitivity analyses. The curve parameters used and the goodness of fits statistics associated with these additional curve fits can be found in **Supplementary Information 4.**

3.9. Updated base case definition

In addition to the changes noted above, the base case has been amended to reflect the clinical expert opinion of the AC that LHRH agonist/degarelix treatment would continue until death **[page 26, section 4.2]** as described in **Table A12** below.

Table A12. Settings used for updated and conservative base cases

Parameter	Updated base case	Conservative base case	Original submission base case	ERG base case
Varying the comparator				
First-line LHRH agonist	Weighted average of 3 monthly LHRH agonists	Weighted average of 3 monthly LHRH agonists	Goserelin 3 monthly	Triptorelin 3 monthly
Varying treatment efficacy assumptions (PSA progression)				
Variation of the parametric curve chosen				
Curve choice for first-line time to PSA progression	CS21+CS35 – Log-normal (using 5 year degarelix data)	CS21+CS35 – Log-normal (using 5 year degarelix data)	CS21 80mg – Log-normal (using 5 year degarelix data)	CS21 80mg – Log-normal (using 5 year degarelix data)
Hazard ratio used				
Source of hazard ratio applied	Meta-regression for CS21+CS35	Meta-regression for CS21+CS35	CS21 data: leuprorelin vs 80mg degarelix	CS21 data: leuprorelin vs 80mg degarelix
Variation in the duration of differential efficacy				
Duration for which hazard ratio applied	Throughout the model	Equal efficacy after 1 year	Throughout the model	Equal efficacy after 1 year
Varying the approach to modelling mortality				
Mortality	i) Increased hazard of mortality post-progression for metastatic patients ii) Prostate cancer specific mortality incorporated	i) Increased hazard of mortality post-progression for metastatic patients ii) Prostate cancer specific mortality incorporated	i) Increased hazard of mortality post-progression for metastatic patients ii) Prostate cancer specific mortality incorporated	i) Increased hazard of mortality post-progression for metastatic patients ii) Prostate cancer specific mortality incorporated
Varying the approach to modelling Musculoskeletal Adverse Events				
Inclusion/ exclusion of MSE's from the model structure				
MSE's incorporated	Fractures, joint-related signs and symptoms and spinal cord compression incorporated in the model	Joint-related signs and symptoms and spinal cord compression incorporated in the model Fractures not	Fractures, joint-related signs and symptoms and spinal cord compression incorporated in the model	Fractures, joint-related signs and symptoms and spinal cord compression incorporated in the model

Parameter	Updated base case	Conservative base case	Original submission base case	ERG base case
		included		
Variation in the parametric curve used to model MSEs over time				
Parametric curve for MSEs	Weibull	Weibull	Weibull	Weibull
Modelling of LHRH agonist event risks				
LHRH AE risks	Fitted curve	Fitted curve	Fitted curve	Fitted curve
Variation of proportion of mild, moderate and severe MSEs across both arms				
Proportion of Mild, Moderate and Severe MSEs	Equal across both arms	Equal across both arms	Equal across both arms	Equal across both arms
Varying the approach to modelling cardiovascular (CV) adverse events				
Inclusion/exclusion of CV events from the model structure	CV events incorporated	CV events incorporated	CV events incorporated	CV events incorporated
Curve choice for CV event	Exponential	Exponential	Exponential	Exponential
Varying the source used for utilities				
Utilities i) First line ii) Post progression iii) Chemo, abiraterone, enzalutamide and palliative care iv) Adverse event	i) McKenzie and van der Pol ii) McKenzie and van der Pol iii) Sourced from systematic search iv) McKenzie and van der Pol	i) McKenzie and van der Pol ii) McKenzie and van der Pol iii) Sourced from systematic search iv) McKenzie and van der Pol	i) Kontodimopolous ii) Kontodimopolous iii) Sourced from systematic search iv) Kontodimopolous	i) Kontodimopolous ii) Kontodimopolous iii) Sourced from systematic search iv) Kontodimopolous
Variation in treatment and administration practice				
Treatment used for flare cover and anti-androgen addition	Bicalutamide	Bicalutamide	Bicalutamide	Bicalutamide
Treatment with LHRH and degarelix takes place in	50% primary care; 50% secondary care	50% primary care; 50% secondary care	50% primary care; 50% secondary care	50% primary care; 50% secondary care
Treatment sequence for non-hormonal therapy	First-line: 49% abiraterone, 21% docetaxel, 30% straight to supportive care Second-line after docetaxel: 70% abiraterone, 30% straight to supportive care Second-line after abiraterone: 70% docetaxel, 30% straight to supportive care Third-line: 70% enzalutamide, 30% straight to	First-line: 49% abiraterone, 21% docetaxel, 30% straight to supportive care Second-line after docetaxel: 70% abiraterone, 30% straight to supportive care Second-line after abiraterone: 70% docetaxel, 30% straight to supportive care Third-line: 70% enzalutamide, 30% straight to	First-line: 100% docetaxel Second-line: 100% abiraterone	First-line: 70% docetaxel, 30% straight to supportive care Second-line: 70% abiraterone, 30% straight to supportive care

Parameter	Updated base case	Conservative base case	Original submission base case	ERG base case
	supportive care	supportive care		
Stopping rule	Don't stop treatment until death	Don't stop treatment until death	Treatment continues until chemotherapy	Don't stop treatment until death
Varying the time horizon				
Time horizon	30 Years	30 Years	30 Years	30 Years

3.10. Updated base case results

The updated results from the base case and conservative base case are show in **Table A13** and **Table A14** below. The mean results from the probabilistic sensitivity analysis for the base case and conservative base case are detailed in **Table A15** and **Table A16** below. Other updated results, including the relevant tornado diagrams, threshold analyses, subgroup analysis, scenario analyses are detailed in **Supplementary Information 5.**

Table A13. Updated base case results

Overall population (FAS)	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**
Weighted average of LHRH agonists	£29,144	9.286	5.044				
Degarelix	£30,049	9.519	5.375	£904	0.23	0.331	£2,733
High risk PSA >20 Population	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**
Weighted average of LHRH agonists	£32,369	8.848	4.595				
Degarelix	£33,765	9.110	4.905	£1,396	0.26	0.310	£4,509
High risk Locally advanced and metastatic population	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**
Weighted average of LHRH agonists	£30,864	9.027	4.789				
Degarelix	£32,560	9.229	5.048	£1,696	0.20	0.259	£6,539

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALYs = quality-adjusted life-years

Table A14. Conservative base case

Overall population (FAS)	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**
Weighted average of LHRH agonists	£26,472	9.401	5.205				
Degarelix	£29,932	9.519	5.382	£3,460	0.12	0.177	£19,510
PSA >20 Population	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**
Weighted average of LHRH agonists	£30,340	8.952	4.723				
Degarelix	£33,651	9.110	4.912	£3,311	0.16	0.189	£17,516
Locally advanced and metastatic population	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**
Weighted average of LHRH agonists	£28,985	9.104	4.889				
Degarelix	£32,445	9.229	5.055	£3,460	0.12	0.166	£20,847

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALYs = quality-adjusted life-years

Table A15. Probabilistic Sensitivity Analysis: Mean results – updated base case

Overall population (FAS)	Mean costs	Mean QALYs	Incremental costs	Incremental QALYs	ICER
Degarelix	£28,720.92	5.38378	£35.28	0.36092	£97.75
Weighted average comparator	£28,685.64	5.02286			
PSA >20 ng/ml population					
Degarelix	£32,011.76	4.91987	£710.12	0.32645	£2,175.27
Weighted average comparator	£31,301.64	4.59342			
Locally advanced and metastatic population					
Degarelix	£31,031.22	5.06238	£950.17	0.28580	£3,324.60
Weighted average comparator	£30,081.04	4.77658			

Table A16. Probabilistic Sensitivity Analysis: Mean results – conservative base case

Overall population (FAS)	Mean costs	Mean QALYs	Incremental costs	Incremental QALYs	ICER
Degarelix	£28,460.50	5.39939	£2,795.16	0.19346	£14,448.27
Weighted average comparator	£25,665.34	5.20593			
PSA >20 ng/ml population					
Degarelix	£31,746.08	4.93229	£2,695.09	0.20859	£12,920.67
Weighted average comparator	£29,050.99	4.72371			
Locally advanced and metastatic population					
Degarelix	£30,741.53	5.07227	£2,779.76	0.18851	£14,746.27
Weighted average comparator	£27,961.77	4.88376			

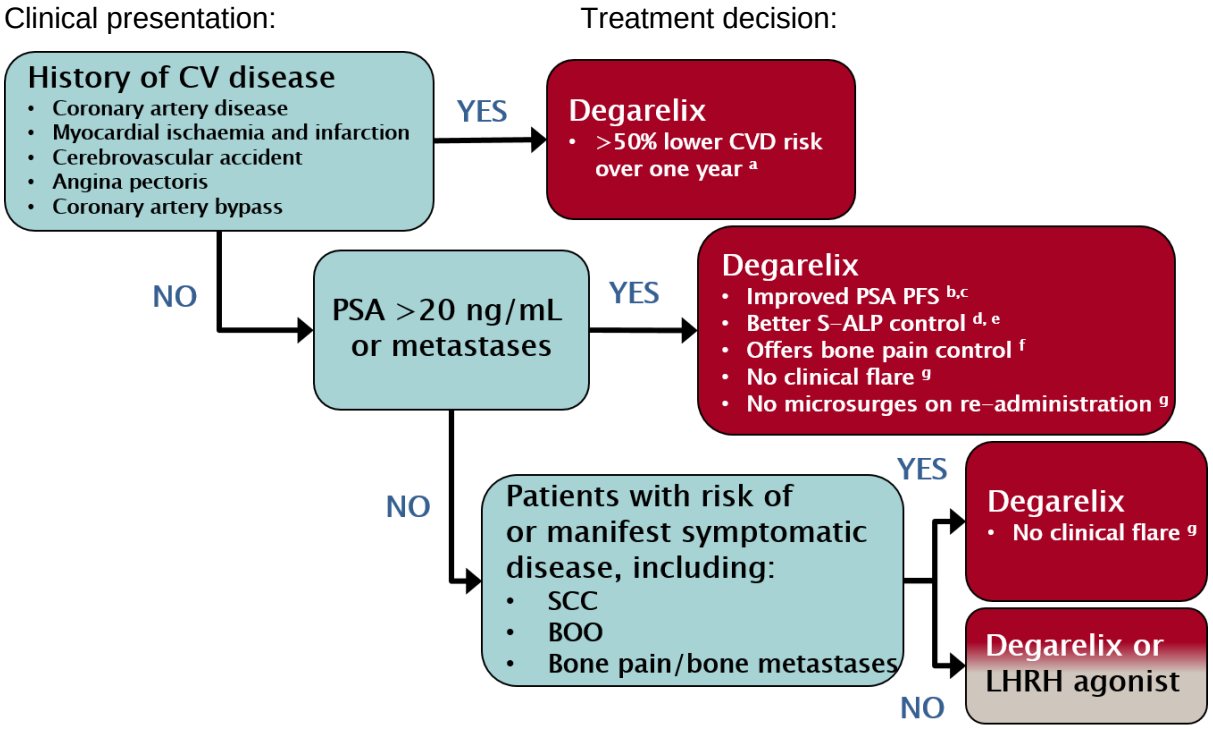
4. Section 4: Conclusion

4.1. Hormonal therapy algorithm

Based on the evidence presented in the initial submission, this ACD response and within the supporting **Appendix A**, Ferring presents a treatment algorithm to summarise the clinical

considerations to be taken into account for the treatment of advanced hormone-dependent prostate cancer based upon patient clinical presentation (see **Figure A8**). It is requested these subgroups, identified as those patients who would particularly benefit from the treatment of degarelix, are considered at the second AC meeting. However, Ferring would also like to note that for patients presenting with none of these characteristics [pre-existing CVD, PSA >20 ng/ml at baseline, or at risk of SCC], degarelix still remains a valid treatment option for the overall population, with Phase III RCT data[2,27-29] and supporting meta-regression analyses (in **Appendix A, Section 2**) together with health economic modelling (in **Appendix A, Section 3**) confirming degarelix is both a clinically effective and cost-effective treatment option compared to LHRH agonists.

Figure A8. A hormonal therapy algorithm based upon the subgroups degarelix offers greatest benefit versus LHRH agonists



Abbreviations: CV: cardiovascular; SCC: spinal cord compression; BOO: bladder outlet obstruction

[a] Albertsen P, et al. 2013 [16]
[b] Tombal et al. 2010[4]
[c] Crawford et al. 2001[8]
[d] Klotz L, et al. 2014[15]
[e] Schroder FH, et al. 2010[30]
[f] Vasdev N, et al. 2013[31]
[g] Klotz L, et al. 2008[2]

4.2. Closing statement

Based upon the additional analyses presented within this response, in conjunction with the original submission, Ferring considers there to be sufficient evidence to support that those patients at high risk of PSA progression and/or with pre-existing cardiovascular disease (CVD) represent additional populations that would particularly benefit from treatment with degarelix. Ferring requests that the AC reconsiders the ACD recommendation and broadens the prostate cancer population for which degarelix is recommended to ensure all relevant patients get access to this valuable medicine in the NHS.

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Supplementary Information

Supplementary Information 1 – SMQ codes used in fractures and joint-related signs and symptoms

SMQ codes and terms for fractures

SMQ code	Term
10017308	Fractured sacrum
10017310	Fractured skull depressed
10018720	Greenstick fracture
10019114	Hand fracture
10020100	Hip fracture
10020462	Humerus fracture
10021343	Ilium fracture
10066386	Impacted fracture
10023149	Jaw fracture
10061599	Lower limb fracture
10049947	Lumbar vertebral fracture
10028200	Multiple fractures
10030527	Open fracture
10031290	Osteoporotic fracture
10034122	Patella fracture
10034156	Pathological fracture
10061161	Pelvic fracture
10069135	Periprosthetic fracture
10048617	Pseudarthrosis
10070286	Pubis fracture
10037802	Radius fracture
10039117	Rib fracture
10039579	Scapula fracture
10070073	Scapulothoracic dissociation
10061365	Skull fracture
10040960	Skull fractured base
10041541	Spinal compression fracture
10041569	Spinal fracture
10042015	Sternal fracture
10042212	Stress fracture
10042856	Synostosis
10049948	Thoracic vertebral fracture
10043827	Tibia fracture
10066094	Torus fracture
10049514	Traumatic fracture
10045375	Ulna fracture
10061394	Upper limb fracture
10048049	Wrist fracture

SMQ codes and terms for joint-related signs and symptoms

SMQ code	Term
10003239	Arthralgia
10065564	Floating patella

10064494	Injection site joint effusion
10053979	Injection site joint movement impairment
10049261	Injection site joint pain
10049263	Injection site joint redness
10049260	Injection site joint swelling
10049262	Injection site joint warmth
10051374	Joint crepitation
10023215	Joint effusion
10048706	Joint range of motion decreased
10023230	Joint stiffness
10023232	Joint swelling
10054106	Joint warmth
10024829	Loose body in joint
10066850	Plica syndrome
10068632	Pogosta disease

Supplementary Information 2 - Meta-regression data, sensitivity analysis and parametric fits

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Supplementary Information 4 - Goodness of fits statistics for additional parametric curve fits

Table 1. Curve parameters used in these additional model fits

CV SAE - Degarelix		**Point estimate**	**Covariance matrix**	
			Intercept	**Scale**
Log logistic	Intercept	2.9461	0.7043	0.1855
	Scale	0.9061	0.1855	0.0538
Log normal	Intercept	3.9489	1.1271	0.5433
	Scale	2.2175	0.5433	0.2793
CV SAE – LHRH agonists				
Log logistic	Intercept	1.8277	0.2188	0.0732
	Scale	0.7951	0.0732	0.0296
Log normal	Intercept	2.3172	0.3191	0.1809
	Scale	1.7394	0.1809	0.1185
CV SAE and death - Degarelix				
Log logistic	Intercept	2.3281	0.3117	0.0901
	Scale	0.8180	0.0901	0.0296
Log normal	Intercept	3.0782	0.4849	0.2490
	Scale	1.9260	0.2490	0.1396
CV SAE and death – LHRH agonists				
Log logistic	Intercept	1.4015	0.0971	0.0358
	Scale	0.7508	0.0358	0.0174
Log normal	Intercept	1.7649	0.1410	0.0848
	Scale	1.5891	0.0848	0.0636
Fractures - Degarelix				
Log logistic	Intercept	7.0163	4.5428	0.8970
	Scale	1.5119	0.8970	0.1857
Log normal	Intercept	10.0313	8.3324	3.2983
	Scale	4.2850	3.2983	1.3404
Fractures – LHRH agonists				
Log logistic	Intercept	3.0676	0.7058	0.1641
	Scale	0.7965	0.1641	0.0411
Log normal	Intercept	4.5305	1.3144	0.5791
	Scale	2.2208	0.5791	0.2675
JSS - Degarelix				
Log logistic	Intercept	3.8071	0.2862	0.0809
	Scale	1.2989	0.0809	0.0256
Log normal	Intercept	5.5337	0.5086	0.2560
	Scale	3.3502	0.2560	0.1399
JSS - Degarelix				
Log logistic	Intercept	3.3155	0.2385	0.0773
	Scale	1.3661	0.0773	0.0296
Log normal	Intercept	4.5694	0.3904	0.2155
	Scale	3.2486	0.2155	0.1352

Table 2. Goodness of fit statistics

CV SAE - Degarelix	AIC	BIC
Exponential	142	146
Weibull	143	152
Log logistic	143	152
Log normal	142	151
CV SAE – LHRH agonists		
Exponential	156	160
Weibull	158	166
Log logistic	158	165
Log normal	157	164
CV SAE and death - Degarelix		
Exponential	187	192
Weibull	189	197
Log logistic	189	197
Log normal	187	196
CV SAE and death – LHRH agonists		
Exponential	210	214
Weibull	210	217
Log logistic	210	217
Log normal	209	216
Fractures - Degarelix		
Exponential	164	169
Weibull	163	174
Log logistic	163	174
Log normal	163	173
Fractures – LHRH agonists		
Exponential	153	158
Weibull	154	164
Log logistic	154	164
Log normal	154	164
JSS - Degarelix		
Exponential	627	632
Weibull	623	634
Log logistic	624	634
Log normal	625	636
JSS - Degarelix		
Exponential	555	559
Weibull	549	558
Log logistic	549	559
Log normal	550	559

Supplementary Information 5 – Updated base case results including cost breakdowns and tornado diagrams

Cost breakdowns:

ITT – updated base case

Item	Cost degarelix	Cost Weighted average comparator	Increment
Drug cost - flare cover	£0	£3	-£3
Drug cost - agonist or antagonist	£12,510	£7,136	£5,374
Administration cost during 1st line treatment	£1,820	£1,198	£622
Drug cost - anti-androgens (anti-androgen addition)	£20	£23	-£3
Administration cost during anti-androgen addition	£253	£269	-£16
Administration cost during anti-androgen withdrawal	£239	£252	-£13
Drug cost - docetaxel	£99	£114	-£15
Administration and side effect cost - docetaxel	£324	£860	-£536
Drug cost - abiraterone	£4,939	£5,675	-£736
Administration and concomitant medications cost - abiraterone	£598	£670	-£72
Cost of follow-on treatment after abiraterone	£141	£162	-£21
Drug cost - Enzalutamide	£2,248	£2,584	-£336
Administration cost - Enzalutamide	£108	£116	-£8
Cost of supportive care	£4,487	£4,917	-£430
Cost of palliative care	£1,367	£1,496	-£129
Cost of SCC	£0	£1,848	-£1,848
Cost of fractures	£120	£1,001	-£882
Cost of joint related signs and symptoms	£123	£180	-£57
Cost of CV events	£654	£641	£13
Total	**£30,049**	**£29,144**	**£904**

PSA >20 – updated base case

Item	Cost degarelix	Cost Weighted average comparator	Increment
Drug cost - flare cover	£0	£3	-£3
Drug cost - agonist or antagonist	£11,927	£6,775	£5,152
Administration cost during 1st line treatment	£1,304	£865	£439
Drug cost - anti-androgens (anti-androgen addition)	£27	£29	-£2
Administration cost during anti-androgen addition	£336	£335	£2
Administration cost during anti-androgen withdrawal	£316	£312	£4
Drug cost - docetaxel	£130	£140	-£10
Administration and side effect cost - docetaxel	£427	£1,059	-£632
Drug cost - abiraterone	£6,512	£6,992	-£481
Administration and concomitant medications cost - abiraterone	£788	£825	-£37
Cost of follow-on treatment after abiraterone	£186	£200	-£14
Drug cost - Enzalutamide	£2,965	£3,182	-£217
Administration cost - Enzalutamide	£142	£143	-£1
Cost of supportive care	£6,053	£6,189	-£136
Cost of palliative care	£1,783	£1,808	-£25
Cost of SCC	£0	£1,773	-£1,773
Cost of fractures	£117	£953	-£836
Cost of joint related signs and symptoms	£120	£175	-£55
Cost of CV events	£633	£612	£20
Total	**£33,765**	**£32,369**	**£1,396**

Locally advanced and metastatic – updated base case

Item	Cost degarelix	Cost Weighted average comparator	Increment
Drug cost - flare cover	£0	£3	-£3
Drug cost - agonist or antagonist	£12,098	£6,925	£5,173
Administration cost during 1st line treatment	£1,466	£1,014	£452
Drug cost - anti-androgens (anti-androgen addition)	£25	£26	-£2
Administration cost during anti-androgen addition	£311	£306	£5
Administration cost during anti-androgen withdrawal	£292	£285	£7
Drug cost - docetaxel	£120	£128	-£8
Administration and side effect cost - docetaxel	£394	£968	-£574
Drug cost - abiraterone	£6,011	£6,389	-£378
Administration and concomitant medications cost - abiraterone	£727	£754	-£27
Cost of follow-on treatment after abiraterone	£172	£183	-£11
Drug cost - Enzalutamide	£2,736	£2,908	-£172
Administration cost - Enzalutamide	£131	£131	£0
Cost of supportive care	£5,548	£5,602	-£54
Cost of palliative care	£1,651	£1,666	-£15
Cost of SCC	£0	£1,804	-£1,804
Cost of fractures	£117	£973	-£855
Cost of joint related signs and symptoms	£121	£177	-£56
Cost of CV events	£639	£624	£15
Total	**£32,560**	**£30,864**	**£1,696**

ITT – conservative base case

Item	Cost degarelix	Cost Weighted average comparator	Increment
Drug cost - flare cover	£0	£3	-£3
Drug cost - agonist or antagonist	£12,510	£7,238	£5,272
Administration cost during 1st line treatment	£1,820	£1,333	£486
Drug cost - anti-androgens (anti-androgen addition)	£20	£21	£0
Administration cost during anti-androgen addition	£253	£239	£14
Administration cost during anti-androgen withdrawal	£239	£224	£15
Drug cost - docetaxel	£99	£101	-£2
Administration and side effect cost - docetaxel	£324	£764	-£440
Drug cost - abiraterone	£4,939	£5,042	-£103
Administration and concomitant medications cost - abiraterone	£598	£595	£3
Cost of follow-on treatment after abiraterone	£141	£144	-£3
Drug cost - Enzalutamide	£2,248	£2,292	-£44
Administration cost - Enzalutamide	£108	£103	£5
Cost of supportive care	£4,487	£4,338	£149
Cost of palliative care	£1,367	£1,334	£32
Cost of SCC	£0	£1,867	-£1,867
Cost of fractures	£0	£0	£0
Cost of joint related signs and symptoms	£126	£186	-£60
Cost of CV events	£654	£648	£6
Total	**£29,932**	**£26,472**	**£3,460**

PSA >20 – conservative base case

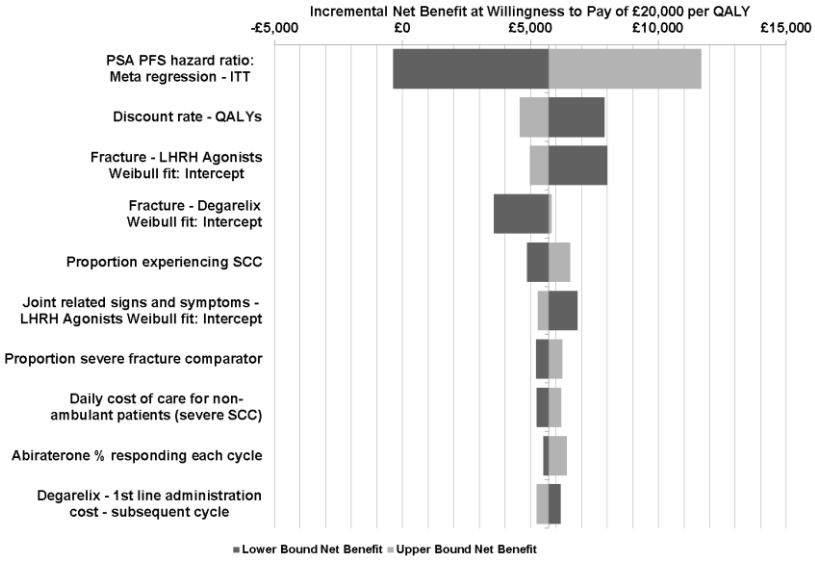
Item	Cost degarelix	Cost Weighted average comparator	Increment
Drug cost - flare cover	£0	£3	-£3
Drug cost - agonist or antagonist	£11,927	£6,862	£5,065
Administration cost during 1st line treatment	£1,304	£963	£341
Drug cost - anti-androgens (anti-androgen addition)	£27	£27	£0
Administration cost during anti-androgen addition	£336	£315	£22
Administration cost during anti-androgen withdrawal	£316	£293	£23
Drug cost - docetaxel	£130	£132	-£1
Administration and side effect cost - docetaxel	£427	£996	-£570
Drug cost - abiraterone	£6,512	£6,577	-£65
Administration and concomitant medications cost - abiraterone	£788	£776	£12
Cost of follow-on treatment after abiraterone	£186	£188	-£2
Drug cost - Enzalutamide	£2,965	£2,991	-£26
Administration cost - Enzalutamide	£142	£135	£8
Cost of supportive care	£6,053	£5,784	£269
Cost of palliative care	£1,783	£1,709	£74
Cost of SCC	£0	£1,790	-£1,790
Cost of fractures	£0	£0	£0
Cost of joint related signs and symptoms	£122	£180	-£57
Cost of CV events	£633	£619	£14
Total	**£33,651**	**£30,340**	**£3,311**

Locally advanced and metastatic – conservative base case

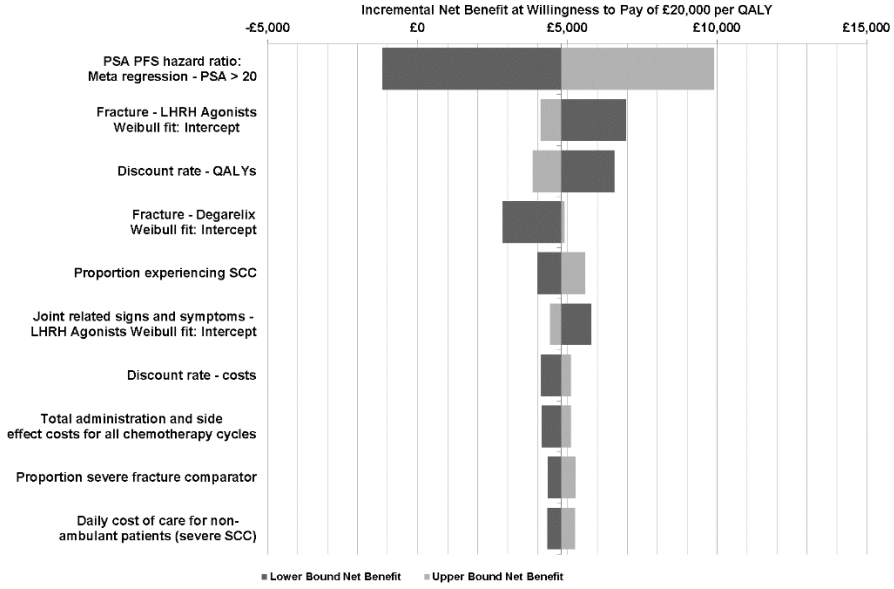
Item	Cost degarelix	Cost Weighted average comparator	Increment
Drug cost - flare cover	£0	£3	-£3
Drug cost - agonist or antagonist	£12,098	£6,990	£5,108
Administration cost during 1st line treatment	£1,466	£1,092	£374
Drug cost - anti-androgens (anti-androgen addition)	£25	£25	£0
Administration cost during anti-androgen addition	£311	£289	£22
Administration cost during anti-androgen withdrawal	£292	£269	£22
Drug cost - docetaxel	£120	£121	-£1
Administration and side effect cost - docetaxel	£394	£915	-£521
Drug cost - abiraterone	£6,011	£6,042	-£31
Administration and concomitant medications cost - abiraterone	£727	£713	£14
Cost of follow-on treatment after abiraterone	£172	£173	-£1
Drug cost - Enzalutamide	£2,736	£2,748	-£12
Administration cost - Enzalutamide	£131	£124	£8
Cost of supportive care	£5,548	£5,273	£275
Cost of palliative care	£1,651	£1,580	£71
Cost of SCC	£0	£1,816	-£1,816
Cost of fractures	£0	£0	£0
Cost of joint related signs and symptoms	£124	£182	-£58
Cost of CV events	£639	£629	£10
Total	**£32,445**	**£28,985**	**£3,460**

Deterministic sensitivity analysis:

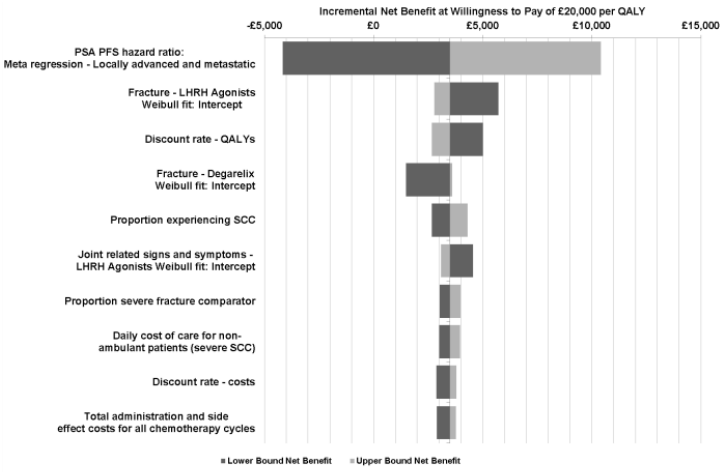
Tornado diagram – ITT – updated base case



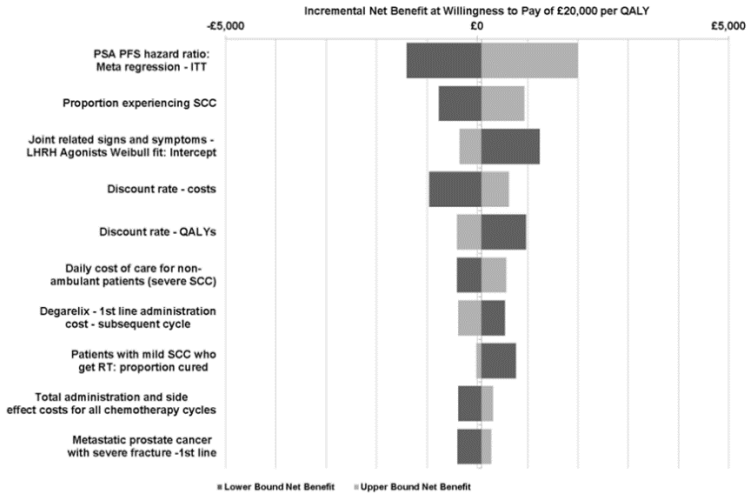
Tornado diagram – PSA > 20 – updated base case



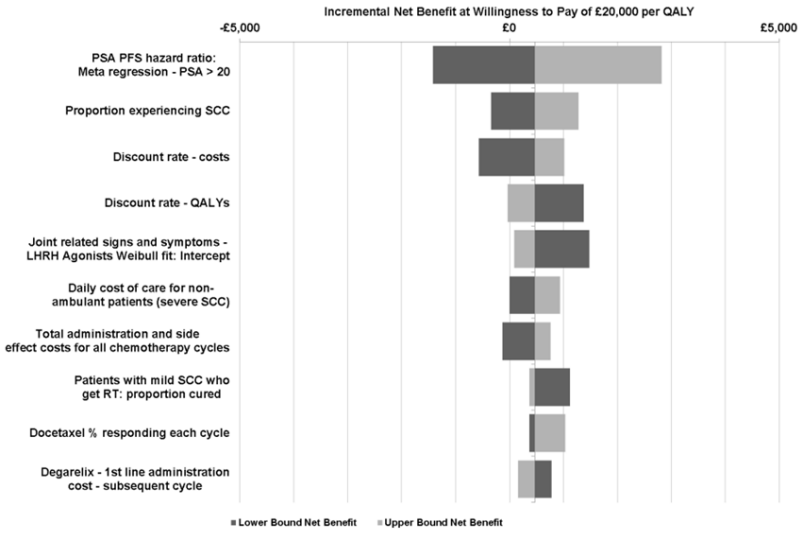
Tornado diagram – locally advanced and metastatic – updated base case



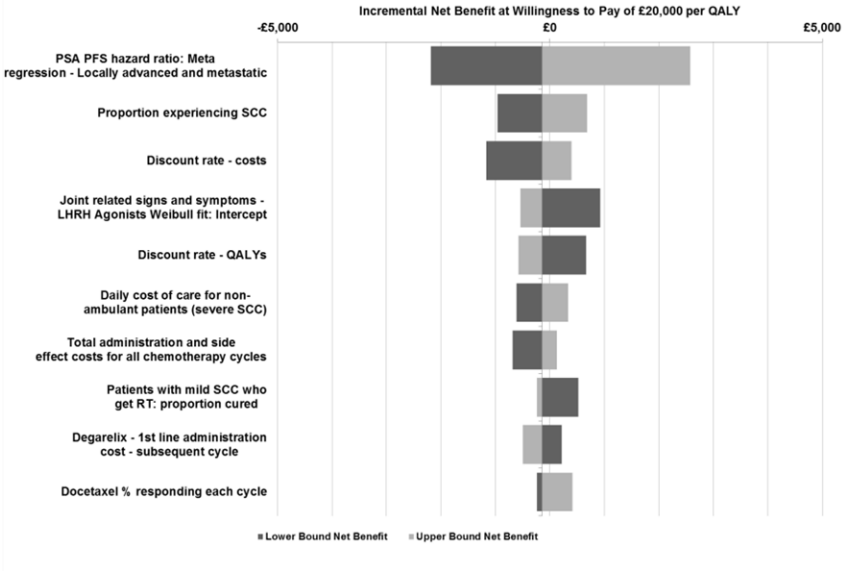
Tornado diagram – ITT – conservative base case



Tornado diagram – PSA > 20 – conservative base case



Tornado diagram – locally advanced and metastatic – conservative base case

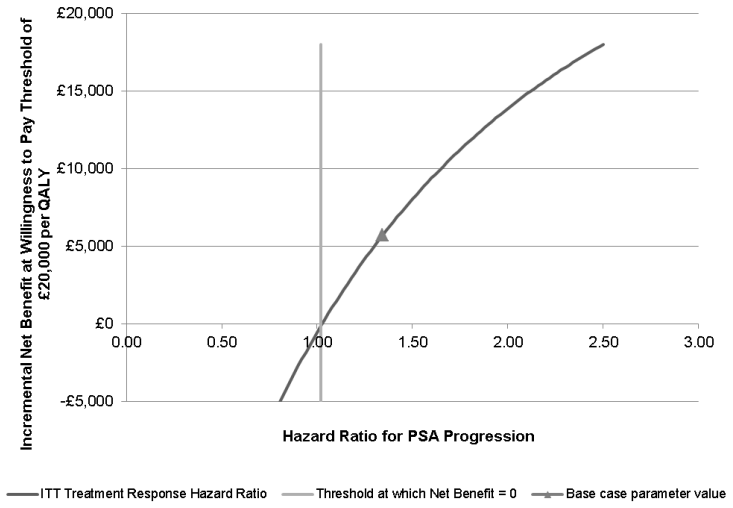


Threshold analysis

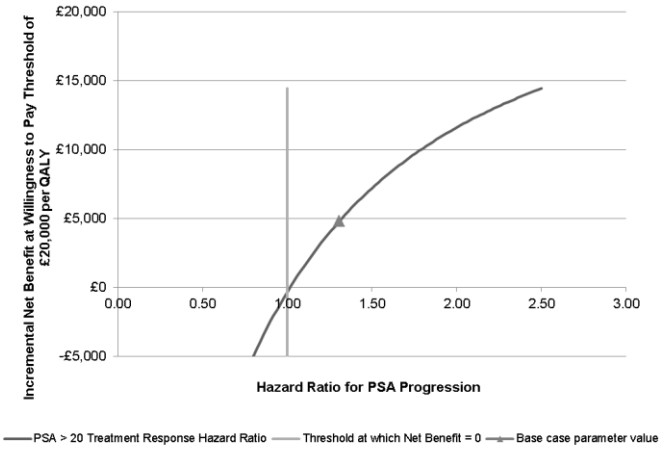
Treatment	HR value at which MNB equals £0
Updated base case, ITT population	1.02
Updated base case, PSA > 20 ng/mL population	1.00
Updated base case, locally advanced and metastatic population	1.00
Conservative base case, ITT population	1.32
Conservative base case, PSA > 20 ng/mL population	1.20
Conservative base case, locally advanced and metastatic population	1.22*

*greater than mean HR estimate

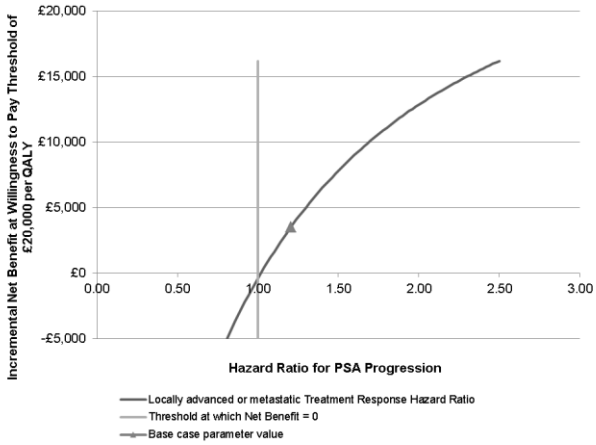
Threshold analysis – ITT – updated base case



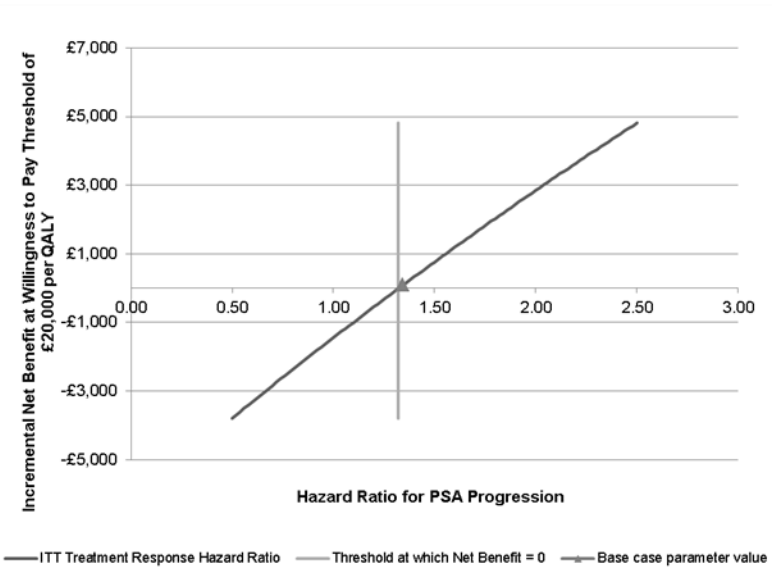
Threshold analysis – PSA > 20 – updated base case



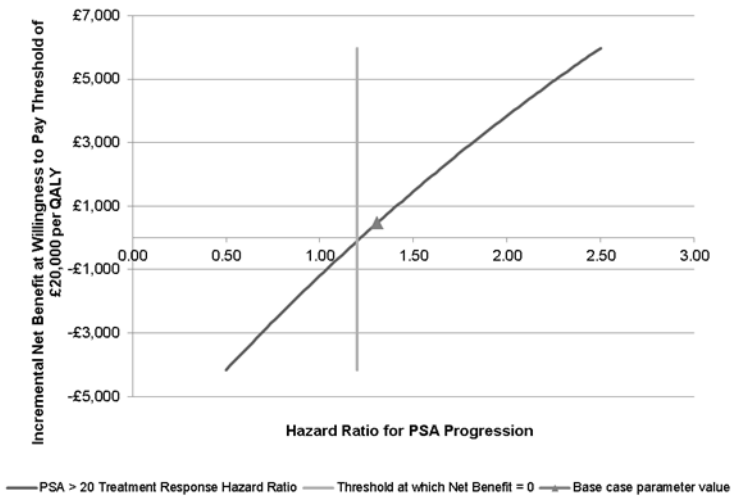
Threshold analysis – locally advanced and metastatic – updated base case



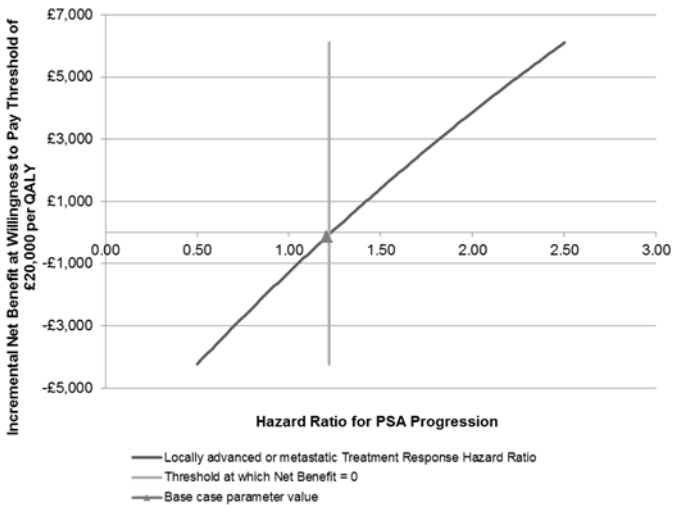
Threshold analysis – ITT – conservative base case



Threshold analysis – PSA > 20 – conservative base case



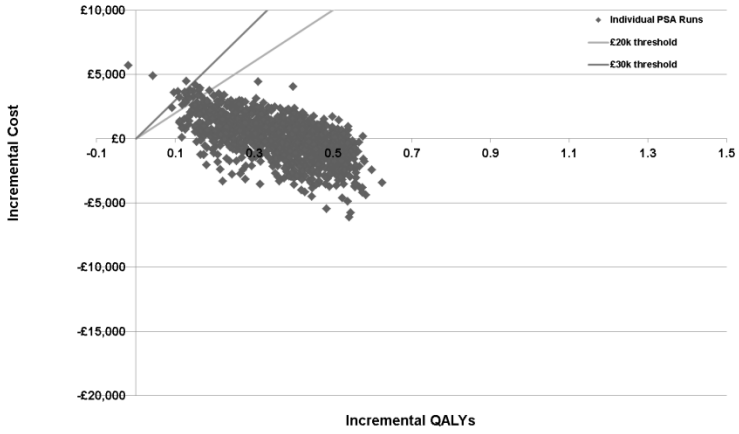
Threshold analysis – locally advanced and metastatic – conservative base case



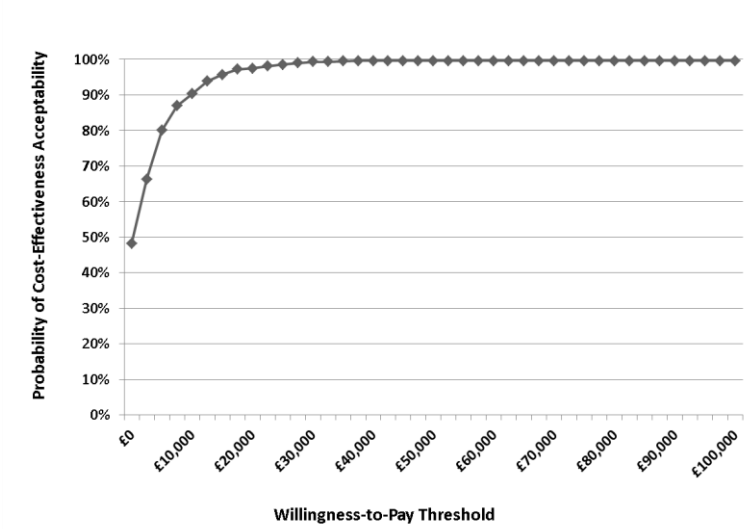
Probabilistic sensitivity analysis:

Updated base case:

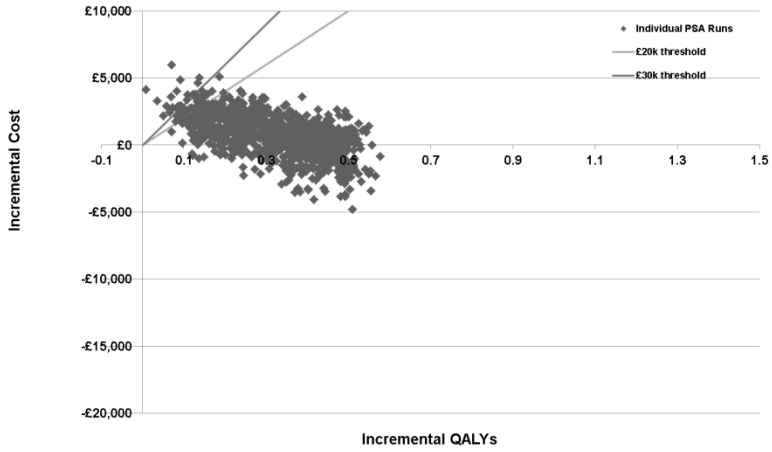
CEP – ITT – updated base case



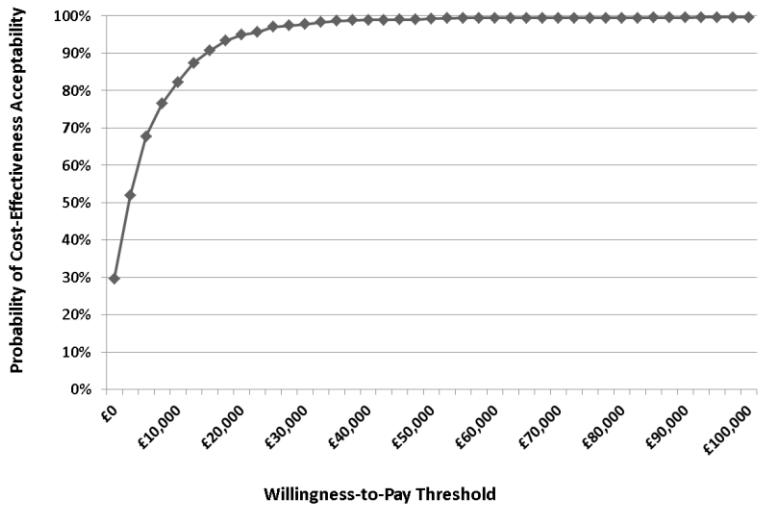
CEAC – ITT – updated base case



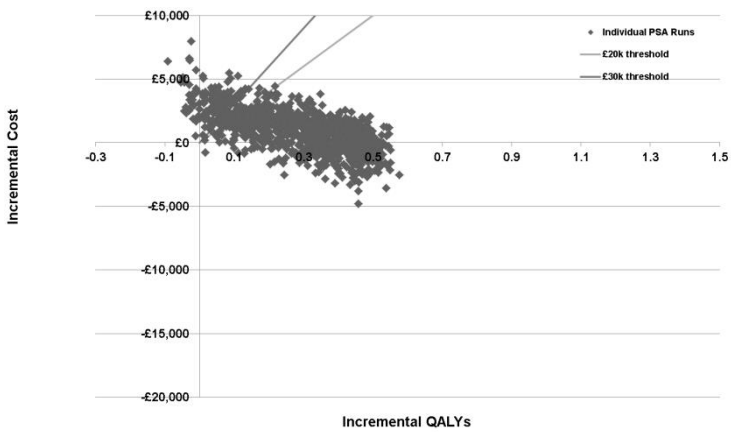
CEP – PSA > 20 – updated base case



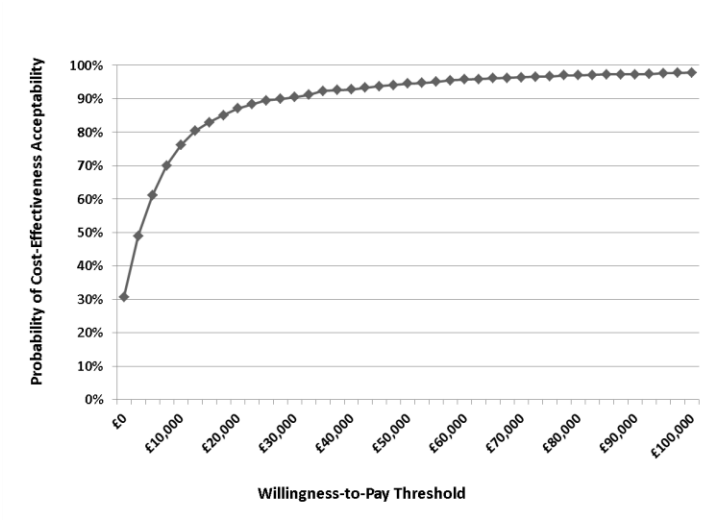
CEAC – PSA > 20 – updated base case



CEP – locally advanced and metastatic – updated base case

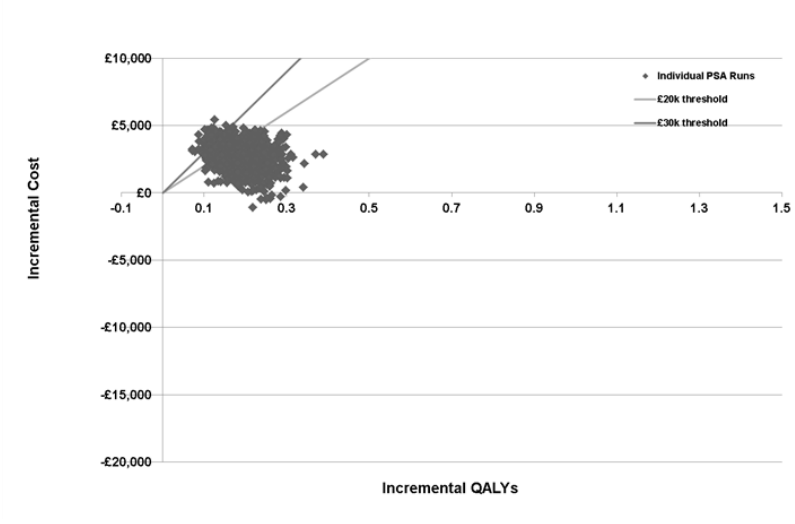


CEAC – locally advanced and metastatic – updated base case

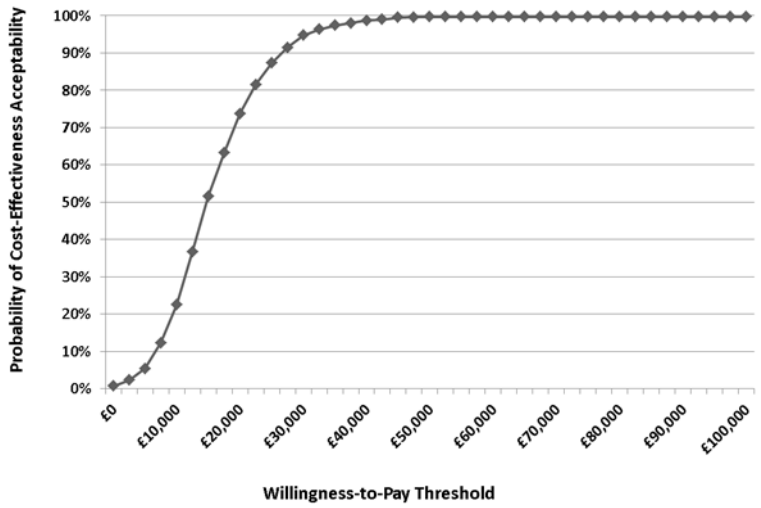


Conservative base case:

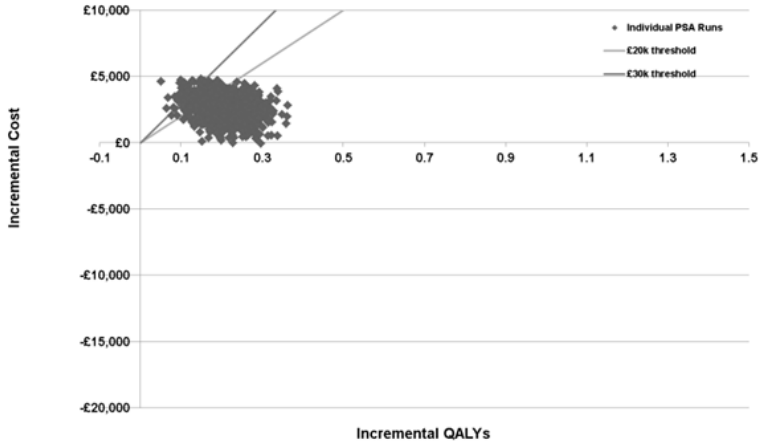
CEP – ITT – conservative base case



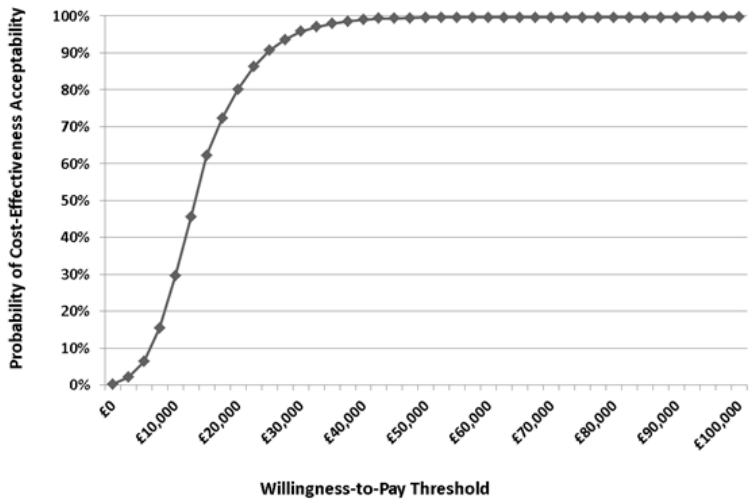
CEAC – ITT – conservative base case



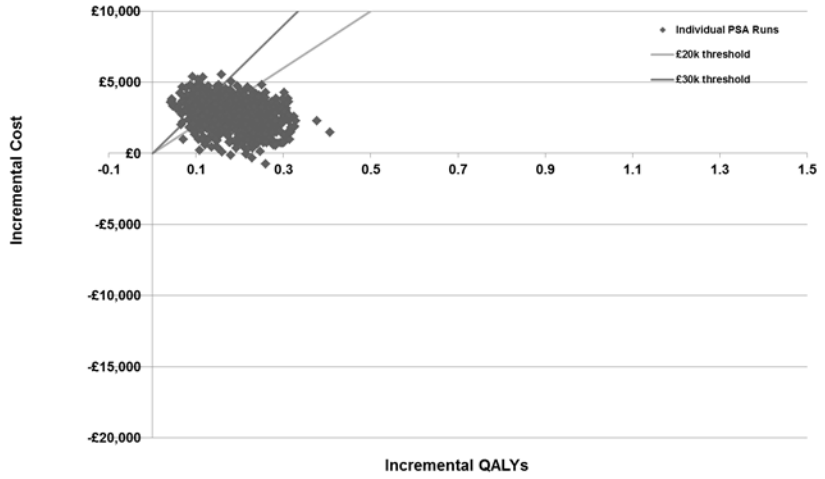
CEP – PSA > 20 – conservative base case



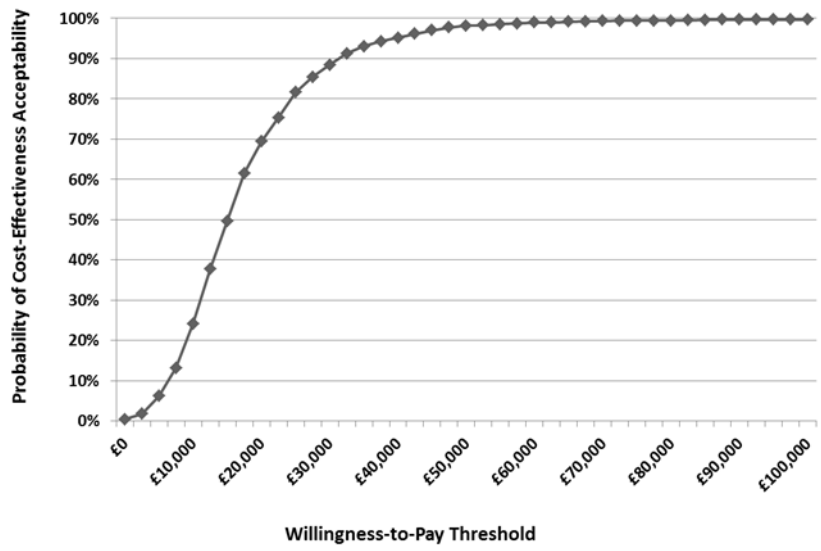
CEAC – PSA > 20 – conservative base case



Threshold analysis – locally advanced and metastatic – conservative base case



Threshold analysis – locally advanced and metastatic – conservative base case



Scenario analyses:

ITT – updated base case

Parameter	Base case	Sensitivity analysis	ICER	Incremental net benefit (threshold £20,000)
Base case	N/A	N/A	£2,733	£5,714
Varying the comparator				
First-line LHRH agonist	Weighted average of 3 monthly LHRH agonists	Triptorelin 3 Monthly (Decapeptyl) *lowest-cost comparator*	£4,864	£5,009
		Triptorelin 3.75 mg (Gonapeptyl) *highest-cost comparator*	£25	£6,610
Varying treatment efficacy assumptions				
Variation of the parametric curve chosen				
Curve choice for first-line time to PSA progression	Pooled Data Log-normal (5 year fit)	Meta regression: Exponential (5 year fit)	£3,265	£5,406
		Meta regression: Weibull (5 year fit)	£3,853	£5,042
		Meta regression: Log-logistic (5 year fit)	£2,897	£5,613
		Meta regression: Exponential (1 year fit)	£3,315	£5,417
		Meta regression: Weibull (1 year fit)	£9,592	£2,387
		Meta regression: Log-logistic (1 year fit)	£5,340	£4,264
		Meta regression: Log-normal (1 year fit)	£3,613	£5,261
		CS21 Exponential (5 year fit)	Dominating	£10,147
		CS21 Weibull (5 year fit)	Dominating	£9,683
		CS21 Log-logistic (5 year fit)	Dominating	£10,481
		CS21 Log-normal (5 year fit)	Dominating	£10,657
		CS21 Gompertz (5 year fit)	Dominating	£10,625
		CS21 Exponential (1 year fit)	Dominating	£10,083
		CS21 Weibull (1 year fit)	£6,750	£3,805
		CS21 Log-logistic (1 year fit)	£2,641	£6,651
		CS21 Log-normal (1 year fit)	£266	£8,983
		CS21 Gompertz (1 year fit)	£11,850	£1,672
Variation in the duration of differential efficacy				
Duration for which hazard ratio applied	Extrapolated curves	Equal efficacy	£24,615	-£553
		Equal efficacy after 1 year	£14,500	£974
Varying the approach to modelling mortality				

Mortality	i) Increased hazard of mortality post-progression for metastatic patients ii) Prostate cancer specific mortality incorporated	i) No increased hazard of mortality post-progression for metastatic patients ii) General population mortality incorporated	£2,473	£4,736
		ii) General population mortality incorporated	£3,596	£7,932
Varying the approach to modelling Musculoskeletal Adverse Events				
Inclusion/ exclusion of MSE's from the model structure				
MSE's incorporated	Fractures, joint-related signs and symptoms and spinal cord compression incorporated in the model	Include no MSEs[a]	£15,213	£1,162
		Include all MSEs[a]	£4,960	£5,544
		Only joint related signs and symptoms included	£5,384	£4,846
Variation in the parametric curve used to model MSEs over time				
Parametric curve for JSS and fractures	Weibull	Exponential	£3,860	£5,891
		Log-logistic	£3,336	£5,414
		Log-normal	£4,669	£4,776
Sustained protective effect from fractures	Extrapolated curves	Increased hazards for degarelix to give equal risk at 2 years	£6,227	£3,986
Modelling of LHRH agonist event risks				
LHRH AE risks	Fitted curve	Hazard ratios	£5,115	£5,043
Variation of proportion of mild, moderate and severe MSEs across both arms				
Proportion of Mild, Moderate and Severe MSEs	Equal across both arms	Proportions as seen in trial	£2,537	£5,815
Varying the approach to modelling cardiovascular (CV) adverse events				
Inclusion/exclusion of CV events from the model structure	CV events incorporated	CV events excluded	£1,686	£5,479
Curve choice for CV event	Exponential	Weibull	£2,745	£5,851
		Log-logistic	£2,763	£5,808
		Log-normal	£2,446	£5,781
Varying the source used for utilities				
Utilities i) First line ii) Post progression iii) Chemo, abiraterone, enzalutamide and palliative care iv) Adverse event	i) McKenzie and van der Pol ii) McKenzie and van der Pol iii) Sourced from systematic search iv) McKenzie and van der Pol	i) Kontodimopoulos Algorithm[b] ii) Kontodimopoulos Algorithm[b] iii) Sourced from systematic search iv) Kontodimopoulos Algorithm[b]	£2,373	£6,717
		i) Gray Algorithm[d] ii) Gray Algorithm[4] iii) Sourced from systematic search iv) Gray Algorithm[d]	£3,566	£4,168
		i) Rowen Algorithm[e] ii) Rowen Algorithm[e] iii) Sourced from systematic search iv) Rowen Algorithm[e]	£2,564	£6,150

		i) Bayoumi *et al*. ii) Bayoumi *et al*. iii) Bayoumi *et al*. iv) Predominantly sourced from literature used by Lu *et al*. (MSEs) and NICE clinical guideline (CV events)	£2,092	£7,741
Variation in treatment and administration practice				
Treatment used for flare cover and anti-androgen addition	Bicalutamide	Cyproterone acetate	£2,648	£5,742
Treatment with LHRH and degarelix takes place in	50% primary care; 50% secondary care	All treated in primary care	£3,035	£5,614
		All treated in secondary care	£2,430	£5,814
Incorporation of abiraterone	Incorporated in the treatment pathway	Not incorporated	£7,500	£4,229
Stopping rule	Don't stop treatment until death	Stop treatment on degarelix/ LHRH agonist when castrate/ resistant, in line with the licensed indication	Dominating	£7,348
Varying the time horizon				
Time horizon	30 Years	5 Years	Dominating	£2,495
		10 Years	£662	£4,621
		20 Years	£2,123	£5,791

[a] Including those not incorporated in the base-case as not statistically significant different between treatment arms in the pooled trials or because of evidence of dose-dependency.
[b] EORTC-C30 to EQ-5D using data from gastric cancer patients
[c] EORTC-C30 to EQ-5D using data from inoperable oesophageal cancer patients
[d] SF-36 to EQ-5D using data from the general UK population

PSA > 20 – updated base case

Parameter	Base case	Sensitivity analysis	ICER	Incremental net benefit (threshold £20,000)
Base case	N/A	N/A	£4,509	£4,795
Varying the comparator				
First-line LHRH agonist	Weighted average of 3 monthly LHRH agonists	Triptorelin 3 Monthly (Decapeptyl) *lowest-cost comparator*	£6,672	£4,125
		Triptorelin 3.75 mg (Gonapeptyl) *highest-cost comparator*	£2,086	£5,544
Varying treatment efficacy assumptions				
Variation of the parametric curve chosen				
Curve choice for first-line time to PSA progression	Pooled Data Log-normal (5 year fit)	Meta regression: Exponential (5 year fit)	£5,139	£4,506
		Meta regression: Weibull (5 year fit)	£6,221	£3,898
		Meta regression: Log-logistic (5 year fit)	£4,591	£4,743
		Meta regression: Exponential (1 year fit)	£5,338	£4,411
		Meta regression: Weibull (1 year fit)	£11,597	£1,733
		Meta regression: Log-logistic (1 year fit)	£7,429	£3,274
		Meta regression: Log-normal (1 year fit)	£6,410	£3,777
		CS21 Exponential (5 year fit)	£465	£9,709
		CS21 Weibull (5 year fit)	£710	£9,356
		CS21 Log-logistic (5 year fit)	Dominating	£10,517
		CS21 Log-normal (5 year fit)	Dominating	£10,590
		CS21 Gompertz (5 year fit)	Dominating	£10,952
		CS21 Exponential (1 year fit)	£484	£9,692
		CS21 Weibull (1 year fit)	£8,107	£3,213
		CS21 Log-logistic (1 year fit)	£4,136	£5,722
		CS21 Log-normal (1 year fit)	£2,577	£7,158
		CS21 Gompertz (1 year fit)	£11,529	£1,806
Variation in the duration of differential efficacy				
Duration for which hazard ratio applied	Extrapolated curves	Equal efficacy	£22,866	-£350
		Equal efficacy after 1 year	£13,074	£1,306
Varying the approach to modelling mortality				
Mortality	i) Increased hazard of mortality post-progression for metastatic patients ii) Prostate cancer	i) No increased hazard of mortality post-progression for metastatic patients ii) General population mortality incorporated	£4,835	£3,815

	specific mortality incorporated	ii) General population mortality incorporated	£5,963	£6,217
Varying the approach to modelling Musculoskeletal Adverse Events				
Inclusion/ exclusion of MSE's from the model structure				
MSE's incorporated	Fractures, joint-related signs and symptoms and spinal cord compression incorporated in the model	Include no MSEs[a]	£17,665	£537
		Include all MSEs[a]	£6,609	£4,605
		Only joint related signs and symptoms included	£7,190	£3,974
Variation in the parametric curve used to model MSEs over time				
Parametric curve for JSS and fractures	Weibull	Exponential	£5,534	£4,896
		Log-logistic	£5,134	£4,525
		Log-normal	£6,532	£3,944
Sustained protective effect from fractures	Extrapolated curves	Increased hazards for degarelix to give equal risk at 2 years	£8,234	£3,216
Modelling of LHRH agonist event risks				
LHRH AE risks	Fitted curve	Hazard ratios	£6,660	£4,428
Variation of proportion of mild, moderate and severe MSEs across both arms				
Proportion of Mild, Moderate and Severe MSEs	Equal across both arms	Proportions as seen in trial	£4,298	£4,890
Varying the approach to modelling cardiovascular (CV) adverse events				
Inclusion/exclusion of CV events from the model structure	CV events incorporated	CV events excluded	£3,194	£4,494
Curve choice for CV event	Exponential	Weibull	£4,490	£4,966
		Log-logistic	£4,560	£4,925
		Log-normal	£4,235	£4,873
Varying the source used for utilities				
Utilities i) First line ii) Post progression iii) Chemo, abiraterone, enzalutamide and palliative care iv) Adverse event	i) McKenzie and van der Pol ii) McKenzie and van der Pol iii) Sourced from systematic search iv) McKenzie and van der Pol	i) Kontodimopoulos Algorithm[b] ii) Kontodimopoulos Algorithm[b] iii) Sourced from systematic search iv) Kontodimopoulos Algorithm[b]	£3,995	£5,592
		i) Gray Algorithm[d] ii) Gray Algorithm[4] iii) Sourced from systematic search iv) Gray Algorithm[d]	£5,708	£3,495
		i) Rowen Algorithm[e] ii) Rowen Algorithm[e] iii) Sourced from systematic search iv) Rowen Algorithm[e]	£4,275	£5,133
		i) Bayoumi *et al*. ii) Bayoumi *et al*. iii) Bayoumi *et al*. iv) Predominantly sourced from literature used by Lu *et al*. (MSEs) and NICE clinical guideline (CV events)	£3,662	£6,226
Variation in treatment and administration practice				
Treatment used for flare cover and anti-	Bicalutamide	Cyproterone acetate	£4,425	£4,821

androgen addition				
Treatment with LHRH and degarelix takes place in	50% primary care; 50% secondary care	All treated in primary care	£4,819	£4,699
		All treated in secondary care	£4,199	£4,891
Incorporation of abiraterone	Incorporated in the treatment pathway	Not incorporated	£8,820	£3,506
Stopping rule	Don't stop treatment until death	Stop treatment on degarelix/ LHRH agonist when castrate/ resistant, in line with the licensed indication	Dominating	£7,286
Varying the time horizon				
Time horizon	30 Years	5 Years	Dominating	£3,035
		10 Years	£1,716	£4,442
		20 Years	£3,843	£4,928

[a] Including those not incorporated in the base-case as not statistically significant different between treatment arms in the pooled trials or because of evidence of dose-dependency.
[b] EORTC-C30 to EQ-5D using data from gastric cancer patients
[c] EORTC-C30 to EQ-5D using data from inoperable oesophageal cancer patients
[d] SF-36 to EQ-5D using data from the general UK population

Locally advanced and metastatic – updated base case

Parameter	Base case	Sensitivity analysis	ICER	Incremental net benefit (threshold £20,000)
Base case	N/A	N/A	£6,539	£3,491
Varying the comparator				
First-line LHRH agonist	Weighted average of 3 monthly LHRH agonists	Triptorelin 3 Monthly (Decapeptyl) *lowest-cost comparator*	£9,178	£2,807
		Triptorelin 3.75 mg (Gonapeptyl) *highest-cost comparator*	£3,399	£4,305
Varying treatment efficacy assumptions				
Variation of the parametric curve chosen				
Curve choice for first-line time to PSA progression	Pooled Data Log-normal (5 year fit)	Meta regression: Exponential (5 year fit)	£7,281	£3,202
		Meta regression: Weibull (5 year fit)	£7,994	£2,909
		Meta regression: Log-logistic (5 year fit)	£6,647	£3,445
		Meta regression: Exponential (1 year fit)	£7,561	£3,107
		Meta regression: Weibull (1 year fit)	£13,467	£1,197
		Meta regression: Log-logistic (1 year fit)	£9,513	£2,339
		Meta regression: Log-normal (1 year fit)	£8,445	£2,733
		CS21 Exponential (5 year fit)	-	-
		CS21 Weibull (5 year fit)	-	-
		CS21 Log-logistic (5 year fit)	-	-
		CS21 Log-normal (5 year fit)	-	-
		CS21 Gompertz (5 year fit)	-	-
		CS21 Exponential (1 year fit)	-	-
		CS21 Weibull (1 year fit)	-	-
		CS21 Log-logistic (1 year fit)	-	-
		CS21 Log-normal (1 year fit)	-	-
		CS21 Gompertz (1 year fit)	-	-
Variation in the duration of differential efficacy				
Duration for which hazard ratio applied	Equal after 1 year	*Efficacy of degarelix and LHRH agonists assumed to be equal*	£23,400	-£412
		Clinical trial data	£15,691	£713
Varying the approach to modelling mortality				
Mortality	i) Increased hazard of mortality post-progression for metastatic patients ii) Prostate cancer	i) No increased hazard of mortality post-progression for metastatic patients ii) General population mortality incorporated	£7,345	£2,791

	specific mortality incorporated	ii) General population mortality incorporated	£7,283	£5,204
Varying the approach to modelling Musculoskeletal Adverse Events				
Inclusion/ exclusion of MSE's from the model structure				
MSE's incorporated	Fractures, joint-related signs and symptoms and spinal cord compression incorporated in the model	Include no MSEs[a]	£25,080	-£893
		Include all MSEs[a]	£8,785	£3,309
		Only joint related signs and symptoms included	£9,810	£2,649
Variation in the parametric curve used to model MSEs over time				
Parametric curve for JSS and fractures	Weibull	Exponential	£7,513	£3,628
		Log-logistic	£7,359	£3,209
		Log-normal	£9,222	£2,603
Sustained protective effect from fractures	Extrapolated curves	Increased hazards for degarelix to give equal risk at 2 years	£11,568	£1,869
Modelling of LHRH agonist event risks				
LHRH AE risks	Fitted curve	Hazard ratios	£6,627	£3,657
Variation of proportion of mild, moderate and severe MSEs across both arms				
Proportion of Mild, Moderate and Severe MSEs	Equal across both arms	Proportions as seen in trial	£6,268	£3,588
Varying the approach to modelling cardiovascular (CV) adverse events				
Inclusion/exclusion of CV events from the model structure	CV events incorporated	CV events excluded	£5,545	£3,208
Curve choice for CV event	Exponential	Weibull	£6,417	£3,651
		Log-logistic	£6,506	£3,605
		Log-normal	£6,220	£3,560
Varying the source used for utilities				
Utilities i) First line ii) Post progression iii) Chemo, abiraterone, enzalutamide and palliative care iv) Adverse event	i) McKenzie and van der Pol ii) McKenzie and van der Pol iii) Sourced from systematic search iv) McKenzie and van der Pol	i) Kontodimopoulos Algorithm[b] ii) Kontodimopoulos Algorithm[b] iii) Sourced from systematic search iv) Kontodimopoulos Algorithm[b]	£5,851	£4,101
		i) Gray Algorithm[d] ii) Gray Algorithm[4] iii) Sourced from systematic search iv) Gray Algorithm[d]	£8,489	£2,299
		i) Rowen Algorithm[e] ii) Rowen Algorithm[e] iii) Sourced from systematic search iv) Rowen Algorithm[e]	£6,307	£3,682
		i) Bayoumi *et al*. ii) Bayoumi *et al*. iii) Bayoumi *et al*. iv) Predominantly sourced from literature used by Lu *et al*. (MSEs) and NICE clinical guideline (CV events)	£5,441	£4,537
Variation in treatment and administration practice				
Treatment used for flare cover and anti-	Bicalutamide	Cyproterone acetate	£6,442	£3,516

androgen addition				
Treatment with LHRH and degarelix takes place in	50% primary care; 50% secondary care	All treated in primary care	£6,913	£3,394
		All treated in secondary care	£6,166	£3,588
Incorporation of abiraterone	Incorporated in the treatment pathway	Not incorporated	£10,896	£2,386
Stopping rule	Don't stop treatment until death	Stop treatment on degarelix/ LHRH agonist when castrate/ resistant, in line with the licensed indication	Dominating	£5,819
Varying the time horizon				
Time horizon	30 Years	5 Years	£2,204	£1,981
		10 Years	£4,153	£3,169
		20 Years	£5,793	£3,625

[a] Including those not incorporated in the base-case as not statistically significant different between treatment arms in the pooled trials or because of evidence of dose-dependency.
[b] EORTC-C30 to EQ-5D using data from gastric cancer patients
[c] EORTC-C30 to EQ-5D using data from inoperable oesophageal cancer patients
[d] SF-36 to EQ-5D using data from the general UK population

ITT – conservative base case

Parameter	Base case	Sensitivity analysis	ICER	Incremental net benefit (threshold £20,000)
Base case	N/A	N/A	£19,510	£87
Varying the comparator				
First-line LHRH agonist	Weighted average of 3 monthly LHRH agonists	Triptorelin 3 Monthly (Decapeptyl) *lowest-cost comparator*	£23,543	-£628
		Triptorelin 3.75 mg (Gonapeptyl) *highest-cost comparator*	£14,142	£1,039
Varying treatment efficacy assumptions				
Variation of the parametric curve chosen				
Curve choice for first-line time to PSA progression	Pooled Data Log-normal (5 year fit)	Meta regression: Exponential (5 year fit)	£18,954	£190
		Meta regression: Weibull (5 year fit)	£20,206	-£36
		Meta regression: Log-logistic (5 year fit)	£19,806	£34
		Meta regression: Exponential (1 year fit)	£18,499	£277
		Meta regression: Weibull (1 year fit)	£21,918	-£303
		Meta regression: Log-logistic (1 year fit)	£20,663	-£110
		Meta regression: Log-normal (1 year fit)	£19,525	£83
		CS21 Exponential (5 year fit)	£13,132	£1,624
		CS21 Weibull (5 year fit)	£14,456	£1,228
		CS21 Log-logistic (5 year fit)	£14,066	£1,335
		CS21 Log-normal (5 year fit)	£13,880	£1,385
		CS21 Gompertz (5 year fit)	£12,399	£1,864
		CS21 Exponential (1 year fit)	£13,832	£1,411
		CS21 Weibull (1 year fit)	£19,555	£77
		CS21 Log-logistic (1 year fit)	£17,879	£396
		CS21 Log-normal (1 year fit)	£16,004	£813
		CS21 Gompertz (1 year fit)	£21,707	-£270
Duration for which hazard ratio applied	Equal after 1 year	*Efficacy of degarelix and LHRH agonists assumed to be equal*	£32,065	-£1,448
		Clinical trial data	£5,384	£4,846
Varying the approach to modelling mortality				
Mortality	i) Increased hazard of mortality post-progression for metastatic patients ii) Prostate cancer	i) No increased hazard of mortality post-progression for metastatic patients ii) General population mortality incorporated	£21,971	-£315

	specific mortality incorporated	ii) General population mortality incorporated	£15,393	£1,553
Varying the approach to modelling Musculoskeletal Adverse Events				
Inclusion/ exclusion of MSE's from the model structure				
MSE's incorporated	Only joint related signs and symptoms included	Include no MSEs[a]	£62,707	-£3,668
		Include all MSEs[a]	£16,261	£805
		Fractures, joint-related signs and symptoms and spinal cord compression included	£14,500	£974
Variation in the parametric curve used to model MSEs over time				
Parametric curve for JSS and fractures	Weibull	Exponential	£15,084	£1,102
		Log-logistic	£20,183	-£31
		Log-normal	£21,762	-£282
Sustained protective effect from fractures	Extrapolated curves	Increased hazards for degarelix to give equal risk at 2 years	-	-
Modelling of LHRH agonist event risks				
LHRH AE risks	Fitted curve	Hazard ratios	£18,364	£310
Variation of proportion of mild, moderate and severe MSEs across both arms				
Proportion of Mild, Moderate and Severe MSEs	Equal across both arms	Proportions as seen in trial	£19,161	£150
Varying the approach to modelling cardiovascular (CV) adverse events				
Inclusion/exclusion of CV events from the model structure	CV events incorporated	CV events excluded	£21,061	-£158
Curve choice for CV event	Exponential	Weibull	£18,807	£220
		Log-logistic	£19,064	£171
		Log-normal	£19,166	£147
Varying the source used for utilities				
Utilities i) First line ii) Post progression iii) Chemo, abiraterone, enzalutamide and palliative care iv) Adverse event	i) McKenzie and van der Pol ii) McKenzie and van der Pol iii) Sourced from systematic search iv) McKenzie and van der Pol	i) Kontodimopoulos Algorithm[b] ii) Kontodimopoulos Algorithm[b] iii) Sourced from systematic search iv) Kontodimopoulos Algorithm[b]	£18,280	£326
		i) Gray Algorithm[d] ii) Gray Algorithm[4] iii) Sourced from systematic search iv) Gray Algorithm[d]	£26,956	-£893
		i) Rowen Algorithm[e] ii) Rowen Algorithm[e] iii) Sourced from systematic search iv) Rowen Algorithm[e]	£20,015	-£3
		i) Bayoumi *et al*. ii) Bayoumi *et al*. iii) Bayoumi *et al*. iv) Predominantly sourced from literature used by Lu *et al*. (MSEs) and NICE clinical guideline (CV events)	£18,344	£312
Variation in treatment and administration practice				
Treatment used for flare cover and anti-androgen addition	Bicalutamide	Cyproterone acetate	£19,381	£110

Treatment with LHRH and degarelix takes place in	50% primary care; 50% secondary care	All treated in primary care	£20,071	-£13
		All treated in secondary care	£18,949	£186
Incorporation of abiraterone	Incorporated in the treatment pathway	Not incorporated	£22,990	-£530
Stopping rule	Don't stop treatment until death	Stop treatment on degarelix/ LHRH agonist when castrate/ resistant, in line with the licensed indication	£8,184	£2,095
Varying the time horizon				
Time horizon	30 Years	5 Years	£13,337	£619
		10 Years	£15,993	£587
		20 Years	£18,358	£288

[a] Including those not incorporated in the base-case as not statistically significant different between treatment arms in the pooled trials or because of evidence of dose-dependency.
[b] EORTC-C30 to EQ-5D using data from gastric cancer patients
[c] EORTC-C30 to EQ-5D using data from inoperable oesophageal cancer patients
[d] SF-36 to EQ-5D using data from the general UK population

PSA > 20 – conservative base case

Parameter	Base case	Sensitivity analysis	ICER	Incremental net benefit (threshold £20,000)
Base case	N/A	N/A	£17,516	£470
Varying the comparator				
First-line LHRH agonist	Weighted average of 3 monthly LHRH agonists	Triptorelin 3 Monthly (Decapeptyl) *lowest-cost comparator*	£21,104	-£209
		Triptorelin 3.75 mg (Gonapeptyl) *highest-cost comparator*	£13,329	£1,261
Varying treatment efficacy assumptions				
Variation of the parametric curve chosen				
Curve choice for first-line time to PSA progression	Pooled Data Log-normal (5 year fit)	Meta regression: Exponential (5 year fit)	£16,845	£619
		Meta regression: Weibull (5 year fit)	£18,381	£296
		Meta regression: Log-logistic (5 year fit)	£17,718	£428
		Meta regression: Exponential (1 year fit)	£16,628	£667
		Meta regression: Weibull (1 year fit)	£20,738	-£121
		Meta regression: Log-logistic (1 year fit)	£19,008	£175
		Meta regression: Log-normal (1 year fit)	£18,170	£334
		CS21 Exponential (5 year fit)	£10,296	£2,738
		CS21 Weibull (5 year fit)	£10,908	£2,471
		CS21 Log-logistic (5 year fit)	£10,300	£2,695
		CS21 Log-normal (5 year fit)	£10,203	£2,725
		CS21 Gompertz (5 year fit)	£8,978	£3,355
		CS21 Exponential (1 year fit)	£10,280	£2,746
		CS21 Weibull (1 year fit)	£16,954	£596
		CS21 Log-logistic (1 year fit)	£14,668	£1,163
		CS21 Log-normal (1 year fit)	£13,144	£1,619
		CS21 Gompertz (1 year fit)	£18,985	£180
Variation in the duration of differential efficacy				
Duration for which hazard ratio applied	Extrapolated curves	Equal efficacy	£29,759	-£1,197
		Equal efficacy after 1 year	£7,190	£3,974
Varying the approach to modelling mortality				
Mortality	i) Increased hazard of mortality post-progression for metastatic patients ii) Prostate cancer	i) No increased hazard of mortality post-progression for metastatic patients ii) General population mortality incorporated	£20,382	-£65

	specific mortality incorporated	ii) General population mortality incorporated	£15,631	£1,480
Varying the approach to modelling Musculoskeletal Adverse Events				
Inclusion/ exclusion of MSE's from the model structure				
MSE's incorporated	Only joint related signs and symptoms included	Include no MSEs[a]	£48,459	-£3,030
		Include all MSEs[a]	£14,995	£1,119
		Fractures, joint-related signs and symptoms and spinal cord compression included	£13,074	£1,306
Variation in the parametric curve used to model MSEs over time				
Parametric curve for JSS and fractures	Weibull	Exponential	£14,140	£1,341
		Log-logistic	£18,001	£369
		Log-normal	£19,123	£153
Sustained protective effect from fractures	Extrapolated curves	Increased hazards for degarelix to give equal risk at 2 years	-	-
Modelling of LHRH agonist event risks				
LHRH AE risks	Fitted curve	Hazard ratios	£15,735	£920
Variation of proportion of mild, moderate and severe MSEs across both arms				
Proportion of Mild, Moderate and Severe MSEs	Equal across both arms	Proportions as seen in trial	£17,226	£529
Varying the approach to modelling cardiovascular (CV) adverse events				
Inclusion/exclusion of CV events from the model structure	CV events incorporated	CV events excluded	£18,985	£152
Curve choice for CV event	Exponential	Weibull	£16,774	£641
		Log-logistic	£17,002	£592
		Log-normal	£17,138	£540
Varying the source used for utilities				
Utilities i) First line ii) Post progression iii) Chemo, abiraterone, enzalutamide and palliative care iv) Adverse event	i) McKenzie and van der Pol ii) McKenzie and van der Pol iii) Sourced from systematic search iv) McKenzie and van der Pol	i) Kontodimopoulos Algorithm[b] ii) Kontodimopoulos Algorithm[b] iii) Sourced from systematic search iv) Kontodimopoulos Algorithm[b]	£16,480	£707
		i) Gray Algorithm[d] ii) Gray Algorithm[4] iii) Sourced from systematic search iv) Gray Algorithm[d]	£22,939	-£424
		i) Rowen Algorithm[e] ii) Rowen Algorithm[e] iii) Sourced from systematic search iv) Rowen Algorithm[e]	£17,762	£417
		i) Bayoumi *et al*. ii) Bayoumi *et al*. iii) Bayoumi *et al*. iv) Predominantly sourced from literature used by Lu *et al*. (MSEs) and NICE clinical guideline (CV events)	£16,872	£614
Variation in treatment and administration practice				
Treatment used for flare cover and anti-androgen addition	Bicalutamide	Cyproterone acetate	£17,396	£492

Treatment with LHRH and degarelix takes place in	50% primary care; 50% secondary care	All treated in primary care	£18,021	£374
		All treated in secondary care	£17,011	£565
Incorporation of abiraterone	Incorporated in the treatment pathway	Not incorporated	£21,316	-£247
Stopping rule	Don't stop treatment until death	Stop treatment on degarelix/ LHRH agonist when castrate/ resistant, in line with the licensed indication	£2,958	£3,221
Varying the time horizon				
Time horizon	30 Years	5 Years	£9,746	£1,064
		10 Years	£13,857	£976
		20 Years	£16,455	£663

[a] Including those not incorporated in the base-case as not statistically significant different between treatment arms in the pooled trials or because of evidence of dose-dependency.
[b] EORTC-C30 to EQ-5D using data from gastric cancer patients
[c] EORTC-C30 to EQ-5D using data from inoperable oesophageal cancer patients
[d] SF-36 to EQ-5D using data from the general UK population

Locally advanced and metastatic – conservative base case

Parameter	Base case	Sensitivity analysis	ICER	Incremental net benefit (threshold £20,000)
Base case	N/A	N/A	£20,847	-£141
Varying the comparator				
First-line LHRH agonist	Weighted average of 3 monthly LHRH agonists	Triptorelin 3 Monthly (Decapeptyl) *lowest-cost comparator*	£25,009	-£831
		Triptorelin 3.75 mg (Gonapeptyl) *highest-cost comparator*	£15,743	£707
Varying treatment efficacy assumptions				
Variation of the parametric curve chosen				
Curve choice for first-line time to PSA progression	Pooled Data Log-normal (5 year fit)	Meta regression: Exponential (5 year fit)	£20,548	-£92
		Meta regression: Weibull (5 year fit)	£21,457	-£236
		Meta regression: Log-logistic (5 year fit)	£20,986	-£163
		Meta regression: Exponential (1 year fit)	£19,957	£7
		Meta regression: Weibull (1 year fit)	£22,921	-£438
		Meta regression: Log-logistic (1 year fit)	£21,749	-£275
		Meta regression: Log-normal (1 year fit)	£21,094	-£177
		CS21 Exponential (5 year fit)	-	-
		CS21 Weibull (5 year fit)	-	-
		CS21 Log-logistic (5 year fit)	-	-
		CS21 Log-normal (5 year fit)	-	-
		CS21 Gompertz (5 year fit)	-	-
		CS21 Exponential (1 year fit)	-	-
		CS21 Weibull (1 year fit)	-	-
		CS21 Log-logistic (1 year fit)	-	-
		CS21 Log-normal (1 year fit)	-	-
		CS21 Gompertz (1 year fit)	-	-
Variation in the duration of differential efficacy				
Duration for which hazard ratio applied	Extrapolated curves	Equal efficacy	£30,466	-£1,273
		Equal efficacy after 1 year	£9,810	£2,649
Varying the approach to modelling mortality				
Mortality	i) Increased hazard of mortality post-progression for metastatic patients ii) Prostate cancer	i) No increased hazard of mortality post-progression for metastatic patients ii) General population mortality incorporated	£23,344	-£521

	specific mortality incorporated	ii) General population mortality incorporated	£16,659	£1,086
Varying the approach to modelling Musculoskeletal Adverse Events				
Inclusion/ exclusion of MSE's from the model structure				
MSE's incorporated	Only joint related signs and symptoms included	Include no MSEs[a]	£66,416	-£3,729
		Include all MSEs[a]	£17,357	£533
		Fractures, joint-related signs and symptoms and spinal cord compression included	£15,691	£713
Variation in the parametric curve used to model MSEs over time				
Parametric curve for JSS and fractures	Weibull	Exponential	£16,254	£780
		Log-logistic	£21,535	-£247
		Log-normal	£23,165	-£475
Sustained protective effect from fractures	Extrapolated curves	Increased hazards for degarelix to give equal risk at 2 years	-	-
Modelling of LHRH agonist event risks				
LHRH AE risks	Fitted curve	Hazard ratios	£19,773	£41
Variation of proportion of mild, moderate and severe MSEs across both arms				
Proportion of Mild, Moderate and Severe MSEs	Equal across both arms	Proportions as seen in trial	£20,476	-£80
Varying the approach to modelling cardiovascular (CV) adverse events				
Inclusion/exclusion of CV events from the model structure	CV events incorporated	CV events excluded	£23,342	-£437
Curve choice for CV event	Exponential	Weibull	£19,888	£20
		Log-logistic	£20,186	-£32
		Log-normal	£20,466	-£77
Varying the source used for utilities				
Utilities i) First line ii) Post progression iii) Chemo, abiraterone, enzalutamide and palliative care iv) Adverse event	i) McKenzie and van der Pol ii) McKenzie and van der Pol iii) Sourced from systematic search iv) McKenzie and van der Pol	i) Kontodimopoulos Algorithm[b] ii) Kontodimopoulos Algorithm[b] iii) Sourced from systematic search iv) Kontodimopoulos Algorithm[b]	£19,866	£23
		i) Gray Algorithm[d] ii) Gray Algorithm[4] iii) Sourced from systematic search iv) Gray Algorithm[d]	£28,209	-£1,007
		i) Rowen Algorithm[e] ii) Rowen Algorithm[e] iii) Sourced from systematic search iv) Rowen Algorithm[e]	£21,607	-£257
		i) Bayoumi *et al*. ii) Bayoumi *et al*. iii) Bayoumi *et al*. iv) Predominantly sourced from literature used by Lu *et al*. (MSEs) and NICE clinical guideline (CV events)	£20,760	-£127
Variation in treatment and administration practice				
Treatment used for flare cover and anti-androgen addition	Bicalutamide	Cyproterone acetate	£20,713	-£118

Treatment with LHRH and degarelix takes place in	50% primary care; 50% secondary care	All treated in primary care	£21,429	-£237
		All treated in secondary care	£20,266	-£44
Incorporation of abiraterone	Incorporated in the treatment pathway	Not incorporated	£24,652	-£766
Stopping rule	Don't stop treatment until death	Stop treatment on degarelix/ LHRH agonist when castrate/ resistant, in line with the licensed indication	£5,540	£2,400
Varying the time horizon				
Time horizon	30 Years	5 Years	£13,891	£553
		10 Years	£17,037	£412
		20 Years	£19,644	£58

[a] Including those not incorporated in the base-case as not statistically significant different between treatment arms in the pooled trials or because of evidence of dose-dependency.
[b] EORTC-C30 to EQ-5D using data from gastric cancer patients
[c] EORTC-C30 to EQ-5D using data from inoperable oesophageal cancer patients
[d] SF-36 to EQ-5D using data from the general UK population