1.1 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

1.1.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

As expected and as shown in Table 1, the results in the model are similar to those of the clinical trials.

Table 1. Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
Degarelix: Percentage alive after 1 year	97.4% (CS21) 98.3%(pooled trials)	93.7%
LHRH agonist: Percentage alive after 1 year	95.1% (CS21) 96.7%(pooled trials)	93.5%
Degarelix: Percentage who have not had PSA progression after 1 year	91.1% (CS21)	91.0%
LHRH agonist: Percentage who have not had PSA progression after 1 year	85.9% (CS21)	85.2%
Degarelix: Percentage who have had a fracture after 1 year	0.9% (pooled trials)	0.9%
Leuprorelin: Percentage who have had a fracture after 1 year	2.1% (pooled trials)	1.8%
Degarelix: Percentage who have had a joint-related sign and symptom after 1 year	5.2% (pooled trials)	4.7%
Leuprorelin: Percentage who have had a joint-related sign and symptom after 1 year	8.3% (pooled trials)	7.7%
Degarelix: Percentage of those with cardiovascular risk at baseline who have a serious cardiovascular event after 1 year	5.4% (pooled trials)	6.2%
Leuprorelin: Percentage of those with cardiovascular risk at baseline who have had a serious cardiovascular event after 1 year	12.9% (pooled trials)	13.9%

Key: LHRH = luteinising hormone-releasing hormone; PSA = prostate-specific antigen

1.1.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Figure 1 and Figure 2 illustrate how patients move through the model states over time when treated with degarelix and goserelin, respectively. The diagrams illustrate that over the first few years, a large proportion of patients remains on first-line treatment but that after five years of treatment, the patients who remain alive are predominantly on supportive and palliative care. Comparing the diagrams, it is clear that the model estimates that patients remain on first-line treatment for longer when treated with degarelix. This is consistent with the trial data from CS21, which was used to estimate the time to PSA progression.

Figure 1. Markov trace diagram for patients treated with degarelix

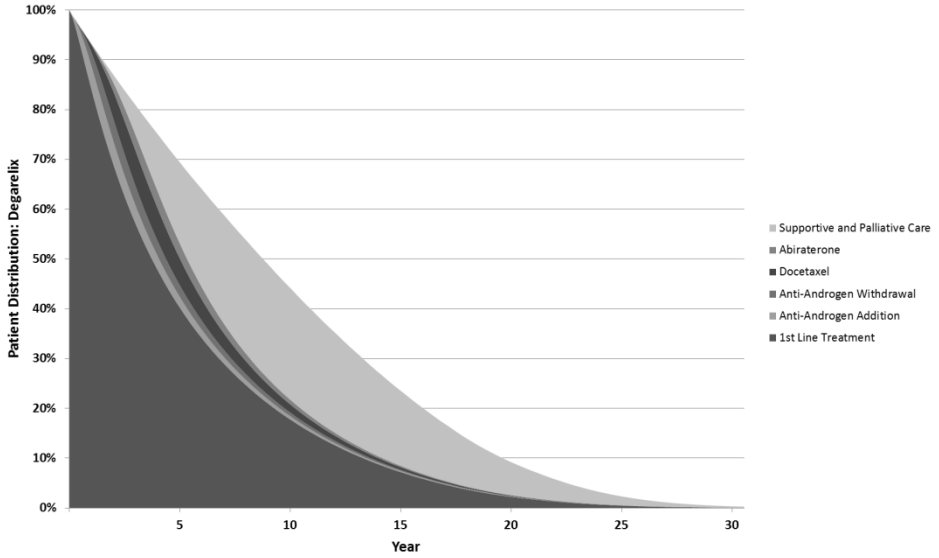
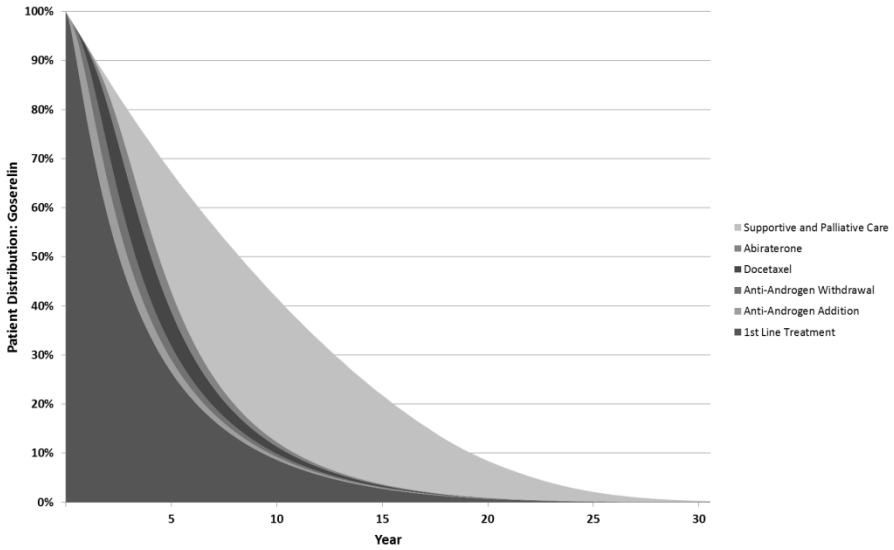


Figure 2. Markov trace diagram for patients treated with goserelin (10.8 mg)



1.1.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Figure 3 and Figure 4 illustrate how QALYs are accumulated over time when patients are treated with degarelix and goserelin, respectively. As would be expected from Figure 1 and Figure 2, the QALYs are initially primarily accrued in the first-line model state; as time continues, the QALYs are increasingly accrued in the supportive and palliative care model state. When comparing Figure 3 and Figure 4, it is evident that the model predicts a greater number of total QALYS accrued when patients are treated with degarelix compared with

goserelin. It is also evident that when patients are treated with degarelix, a relatively higher proportion of the total QALYs accumulated are in the first-line model state.

Figure 3. QALY accumulation over time – degarelix

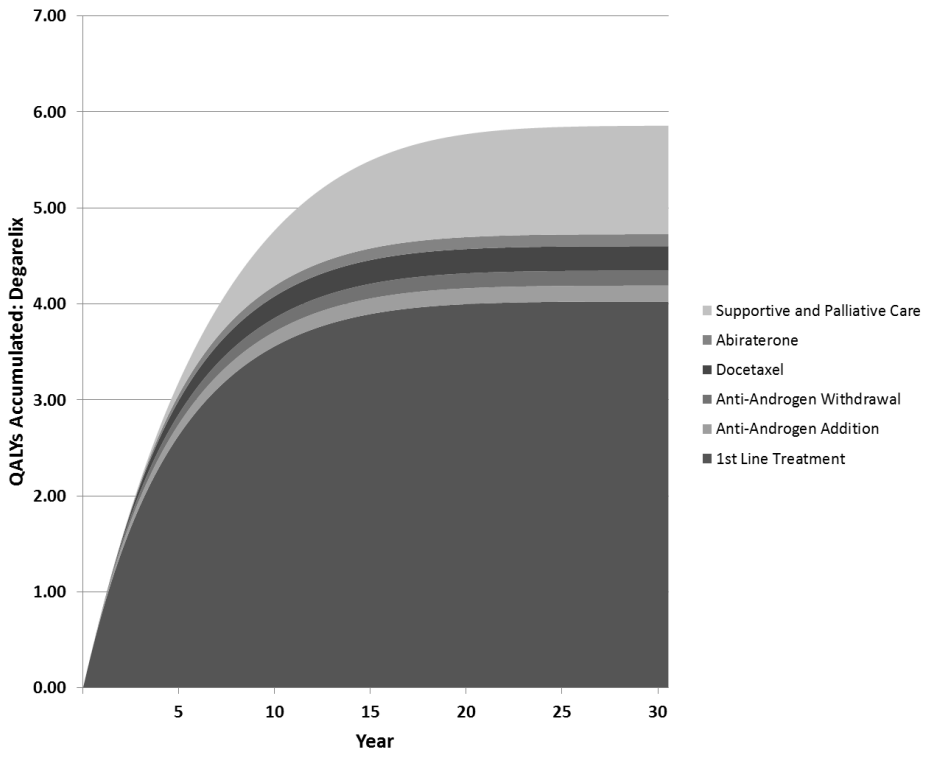
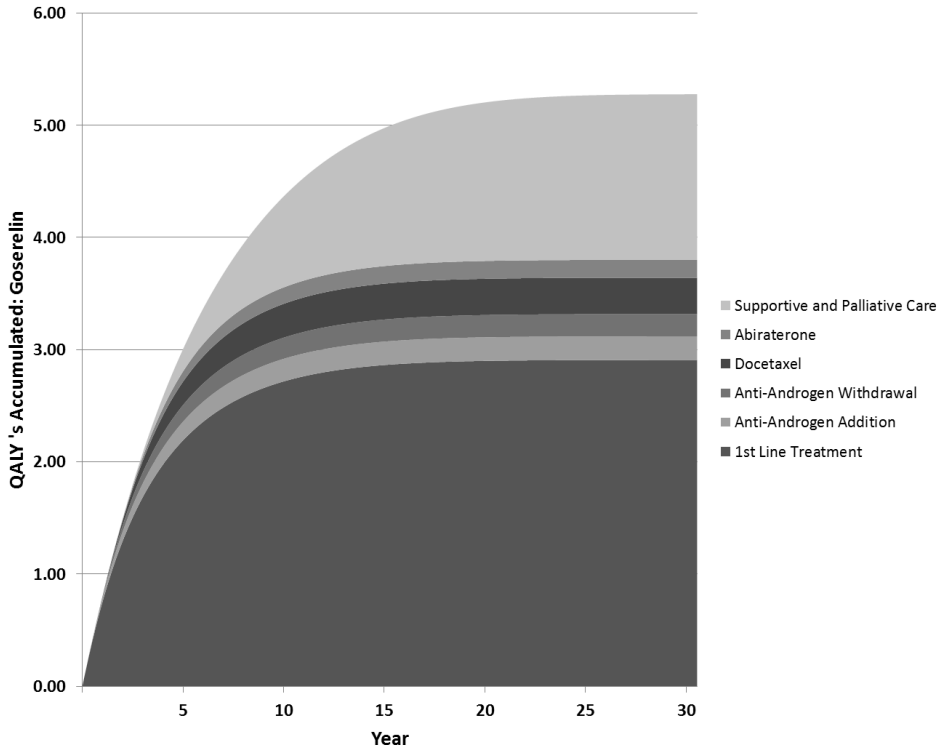


Figure 4. QALY accumulation over time – goserelin (10.8 mg)



1.1.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Table 2 and Table 3 below illustrate the life years, QALYs and costs by clinical outcome for patients treated with degarelix and goserelin, respectively. The tables illustrate that compared with patients on goserelin, patients treated with degarelix:

- Spend longer on first-line treatment and accumulate more costs and QALYs in this state,
- Spend less time in all other model states and accumulate lower costs in all except for the anti-androgen addition model state,
- Accumulate less cost as a result of AEs.

The reduced cost as a result of AEs is to be expected, given the results of the pooled clinical trial data reported in Section 6.9.

Table 2. Model outputs by clinical outcomes: degarelix

Outcome	LY	QALY	Cost (£)
First-line treatment	5.39	4.03	£9,720
Anti-androgen addition	0.26	0.17	£627
Anti-androgen withdrawal	0.25	0.16	£574
Chemotherapy	0.45	0.25	£1,464
Abiraterone	0.23	0.12	£7,230
Supportive and palliative care	3.01	1.13	£5,423
Adverse events			£901
Total	9.58	5.86	£25,939

Key: LY = life-years; QALY = quality-adjusted life-year

Table 3. Model outputs by clinical outcomes: goserelin (10.8 mg)

Outcome	LY	QALY	Cost (£)
First-line treatment	3.81	2.91	£4,543
Anti-androgen addition	0.32	0.21	£599
Anti-androgen withdrawal	0.31	0.20	£541
Chemotherapy	0.57	0.32	£1,899
Abiraterone	0.28	0.16	£9,380
Supportive and palliative care	3.92	1.48	£7,115
Adverse events			£3,559
Total	9.21	5.27	£27,636

Key: LY = life-years; QALY = quality-adjusted life-year

1.1.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 4 below shows the QALY gain by health state for degarelix and goserelin. As shown by Figure 3 and Figure 4, patients treated with degarelix accumulate a greater proportion of

their total QALYs while on first-line treatment and accumulate proportionally fewer of their QALYs while treated with supportive and palliative care.

Table 5 illustrates the summary costs by health state and shows that, in total, treatment with degarelix is expected to cost approximately £1,600 less over a patient's lifetime than treatment with goserelin. While the costs accumulated in the first-line disease state are substantially higher when treated with degarelix, the costs incurred due to AEs, first-line chemotherapy, abiraterone, and supportive and palliative care are all substantially lower. This is supported by

Table 6 below which shows predicted resource use by category of cost.

Table 4. Summary of QALY gain by health state

Health state	QALY degarelix	QALY goserelin (10.8 mg)	Increment	Absolute increment	% absolute increment
First-line treatment	4.03	2.91	1.12	1.12	193%
Anti-androgen addition	0.17	0.21	-0.05	0.05	8%
Anti-androgen withdrawal	0.16	0.20	-0.04	0.04	7%
Chemotherapy	0.25	0.32	-0.07	0.07	12%
Abiraterone	0.12	0.16	-0.03	0.03	6%
Supportive and palliative care	1.13	1.48	-0.35	0.35	60%
Total	5.86	5.28	0.58	0.58	100%

Key: QALY = quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee, 2008.

Table 5. Summary of costs by health state

Health state	Cost degarelix	Cost goserelin (10.8 mg)	Increment	Absolute increment	% absolute increment
First-line treatment	£9,720	£4,543	£5,177	£5,177	-305%
Anti-androgen addition*	£627	£599	£28	£28	-2%
Anti-androgen withdrawal	£574	£541	£33	£33	-2%
Chemotherapy	£1,464	£1,899	-£435	£435	-26%
Abiraterone	£7,230	£9,380	-£2,150	£2,150	-127%
Supportive and palliative care	£5,423	£7,115	-£1,692	£1,692	-100%
Adverse Events	£901	£3,559	-£2,658	£2,658	-157%
Total	£25,939	£27,636	-£1,697	£1,697	100%

Key: QALY = quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee, 2008.

* This refers to second-line treatment, whereby an anti-androgen is added as an adjuvant to current LHRH agonist/GnRH antagonist therapy, as opposed to anti-androgen addition for flare protection.

Table 6. Summary of predicted resource use by category of cost

Item	Cost degarelix	Cost goserelin (10.8 mg)	Increment	Absolute increment	% absolute increment
Drug cost: flare cover	£0	£3	-£3	£3	0%
Drug cost: agonist or antagonist	£8,524	£3,978	£4,545	£4,545	-268%
Administration cost during first-line treatment	£1,919	£1,128	£790	£790	-47%
Drug cost: anti-androgens (anti-androgen addition)	£19	£25	-£6	£6	0%
Administration cost during anti-androgen addition	£237	£283	-£47	£47	-3%
Administration cost during anti-androgen withdrawal	£223	£265	-£42	£42	-2%
Drug cost: chemotherapy	£173	£224	-£51	£51	-3%
Administration and side-effect cost during first-line chemo-therapy	£1,291	£1,674	-£383	£383	-23%

Item	Cost degarelix	Cost goserelin (10.8 mg)	Increment	Absolute increment	% absolute increment
Drug cost: abiraterone	£6,475	£8,401	-£1,926	£1,926	-113%
Administration and concomitant medications cost during treatment with abiraterone	£755	£979	-£224	£224	-13%
Cost of follow-on treatment after abiraterone	£617	£801	-£184	£184	-11%
Cost of supportive care	£3,530	£4,673	-£1,143	£1,143	-67%
Cost of palliative care	£1,276	£1,641	-£365	£365	-22%
Cost of SCC	£0	£1,836	-£1,836	£1,836	-108%
Cost of fractures	£120	£993	-£873	£873	-51%
Cost of joint-related signs and symptoms	£124	£179	-£56	£56	-3%
Cost of cardiovascular events	£657	£551	£106	£106	-6%
Total	£25,939	£27,636	-£1,697	-£1,697	100%

Key: SCC = spinal cord compression

Adapted from Pharmaceutical Benefits Advisory Committee Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee, 2008.

Base-case analysis

1.1.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table 7 below illustrates the base case model results. Due to delayed progression to later lines of therapy and reduced AEs, patients treated with degarelix are estimated to live for longer and experience improved HRQL. The improved efficacy and safety profile of degarelix also results in large cost offsets, resulting in degarelix being dominant; that is, both more effective and cost saving compared with goserelin.

Table 7. Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Goserelin (10.8 mg)	£27,636	9.21	5.28				
Degarelix	£25,939	9.58	5.86	-£1,697	0.37	0.58	Dominating

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

Sensitivity analyses

1.1.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Figure 5 below presents a tornado diagram, illustrating the effect on the net benefit of treatment with degarelix of varying the ten most influential parameters between their upper and lower bounds. The assumed willingness to pay for a QALY used in the net benefit calculation is £20,000.

The model is most sensitive to the HR for PSA progression. The lower bound value for the HR of PSA progression is 1.01. This is the lowest value in the 95% CI. Figure 6 illustrates the threshold analysis undertaken to investigate the effect of varying the HR of PSA progression on net benefit.

In all cases, the net benefit at £20,000 remains positive, which means that for all one-way variation in parameters, degarelix remains cost-effective at a threshold of £20,000 per QALY.

For degarelix to no longer be cost-effective at a threshold of £20,000 per QALY, the HR for PSA progression must be less than 1 (approximately 0.96). This is unlikely, as it falls outside of the CIs calculated from the trial.

Figure 5 Tornado diagram containing 10 most influential parameters

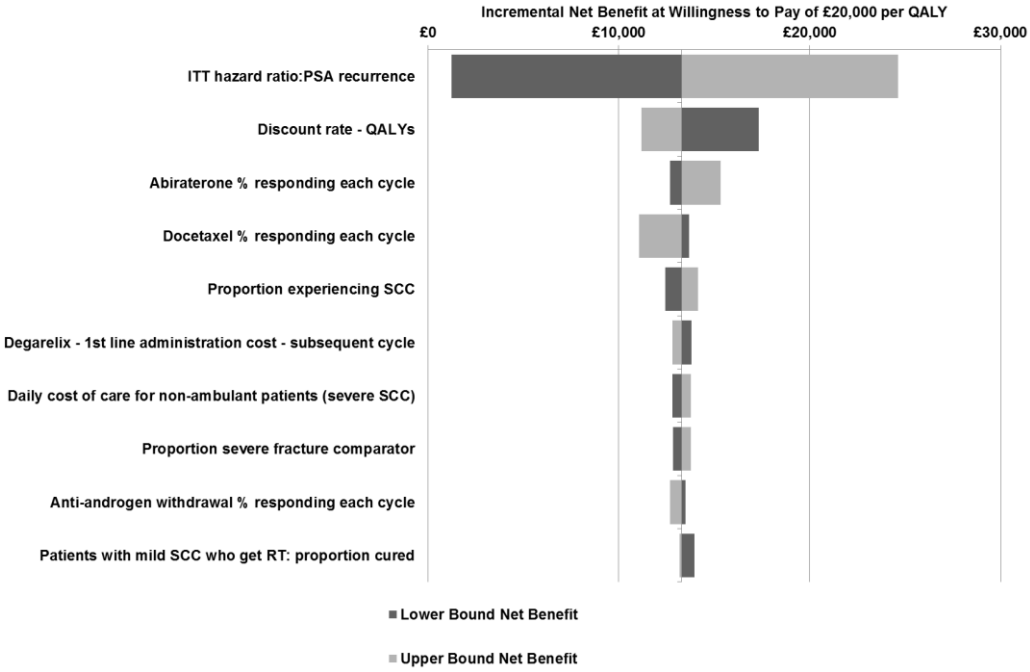
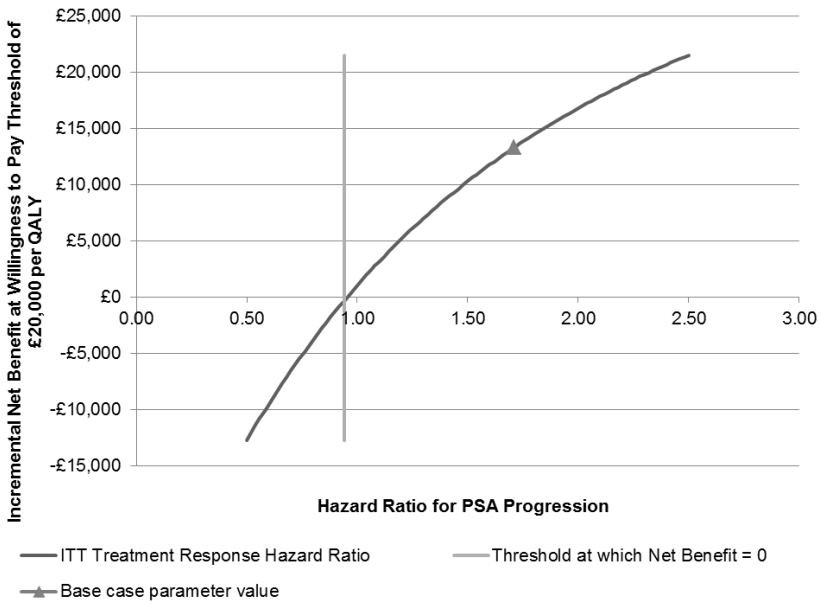


Figure 6. Threshold Analysis investigating the effect of varying the hazard ratio for time to PSA progression



1.1.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Figure 7 below is an ICER scatter plot containing the result of 5,000 runs of the probabilistic sensitivity analysis. As can be seen, the majority are substantially below the line representing the £20,000 threshold. Figure 8 below shows the cost-effectiveness acceptability curve (CEAC) for treatment with degarelix; there is a 99.5% chance that

degarelix is cost saving at a willingness-to-pay threshold of £20,000 per QALY, and a 100% chance at a willingness-to-pay threshold of £30,000 per QALY.

Figure 7. PSA scatter plot

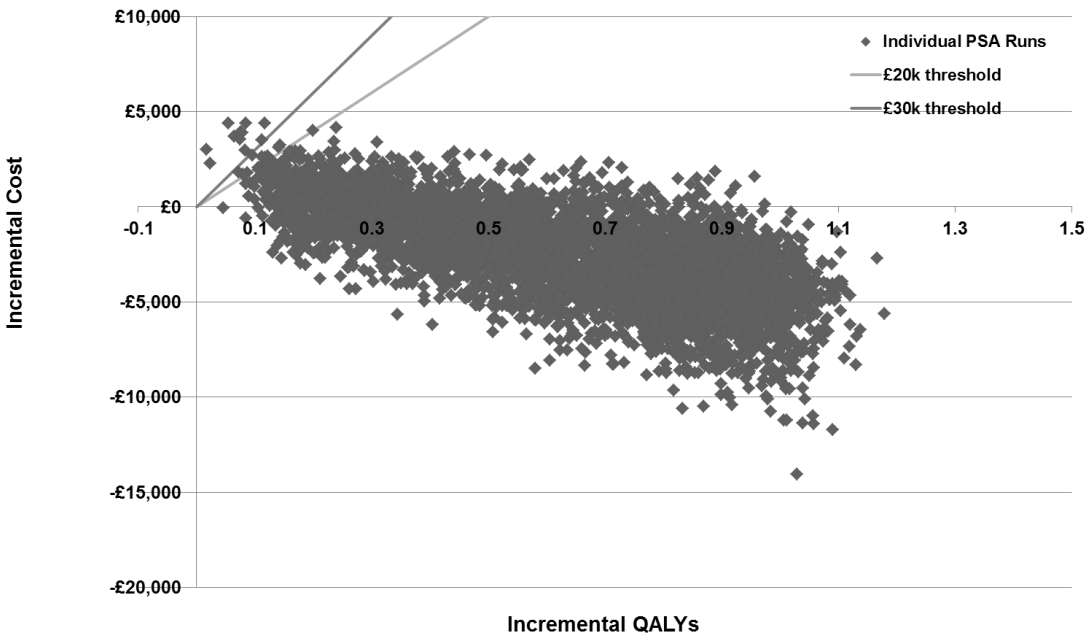
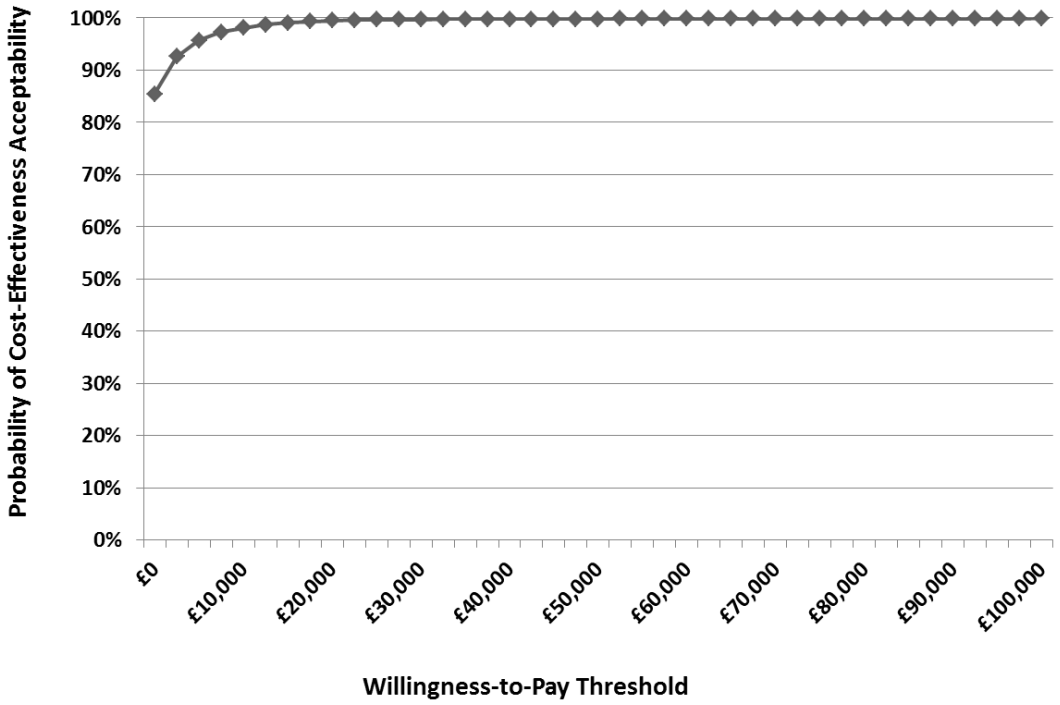


Figure 8. Cost-effectiveness acceptability curve



1.1.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Table 8 below reports the results of the scenario analyses. For the scenarios for which treatment with degarelix results in lower costs and higher QALYs, the cells in the right column contain the word 'Dominating'. As can be seen from the results of the scenario analyses, the cost-effectiveness of degarelix is relatively insensitive to changes in the structural assumptions. The least favourable ICER is £11,274 (when no differential efficacy is assumed for PSA progression), which is still substantially below conventional cost-effectiveness thresholds, even in a scenario that goes against the weight of clinical evidence.

Table 8. Results of the scenario analyses

Parameter	Base case	Sensitivity analysis	ICER	Incremental net benefit (threshold £20,000)
Base case	N/A	N/A	Dominating	£13,296
Varying the comparator				
First-line LHRH agonist	Goserelin 10.8mg (Zoladex)	Goserelin 3.6 mg (Novgos)	Dominating	£12,682
		Goserelin 3.6 mg (Zoladex)	Dominating	£13,012
		Leuprorelin 3.75mg (Prostap)	Dominating	£13,532
		Leuprorelin 11.25mg (Prostap)	Dominating	£13,139
		Triptorelin 3.75 mg (Gonapeptyl)	Dominating	£13,860
		Triptorelin 3mg (Decapeptyl)	Dominating	£13,215
		Triptorelin 11.25mg (Decapeptyl)	Dominating	£12,822
		Triptorelin 22.5mg (Decapeptyl)	Dominating	£14,484
Varying treatment efficacy assumptions				
Variation of the parametric curve chosen				
Curve choice for first-line time to PSA progression	Log-normal	Log-logistic	Dominating	£13,140
		Gompertz	Dominating	£13,256
		Exponential	Dominating	£12,798
		Weibull	Dominating	£12,342
Variation in the duration of differential efficacy				
Duration for which hazard ratio applied	For the duration patients remain on first-line therapy	Efficacy of degarelix and LHRH agonists assumed to be equal	£11,274	£1,031
		For one year; the duration for which there is comparative trial data	£3,061	£4,161
Varying the approach to modelling mortality				
Mortality	i) Increased hazard of mortality post-progression for metastatic	No increased hazard of mortality post-progression for metastatic patients	Dominating	£11,683

	patients			
	ii) Prostate cancer specific mortality incorporated	i) No increased hazard of mortality post-progression for metastatic patients ii) General population mortality incorporated	Dominating	£16,976
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	£2,152	£8,853
		Include all MSEs[a]	Dominating	£13,114
Variation in the parametric curve used to model MSEs over time				
Parametric curve for MSEs	Weibull	Exponential	Dominating	£13,371
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	Dominating	£13,386
Varying the approach to modelling cardiovascular (CV) adverse events				
Inclusion/exclusion of CV events from the model structure	CV events incorporated	CV events not incorporated	Dominating	£13,031
Curve choice for CV event	Exponential	Weibull	Dominating	£13,386
Varying the source used for utilities				
Utility values i) First-line utilities ii) Post-progression utilities iii) Chemotherapy, abiraterone and palliative care utilities iv) Adverse event utilities	i) Kontodimopoulos Algorithm[b] ii) Kontodimopoulos Algorithm[b] iii) Sourced from systematic search iv) Kontodimopoulos Algorithm[b]	i) McKenzie Algorithm[c] ii) McKenzie Algorithm[c] iii) Sourced from systematic search iv) McKenzie Algorithm[c]	Dominating	£11,469
		i) Gray Algorithm[d] ii) Gray Algorithm[4] iii) Sourced from systematic search iv) Gray Algorithm[d]	Dominating	£9,311
		i) Rowen Algorithm[e] ii) Rowen Algorithm[e] iii) Sourced from systematic search	Dominating	£12,458

		iv) Rowen Algorithm[e]		
		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)	Dominating	£15,291
Variation in treatment and administration practice				
Treatment used for flare cover and anti-androgen addition	Bicalutamide	Cyproterone acetate	Dominating	£13,329
Treatment with LHRH and degarelix takes place in	50% primary care; 50% secondary care	All treated in primary care	Dominating	£13,223
		All treated in secondary care	Dominating	£13,368
Incorporation of abiraterone	Incorporated in the treatment pathway	Not incorporated	£2,~~072~~089	£10,~~658~~627
Stopping rule	Stop treatment on degarelix/ LHRH agonist when castrate/ resistant, in line with the licensed indication	Don't stop treatment until death	Dominating	£12,312
Varying the time horizon				
Time horizon	30 Years	5 years	Dominating	£5,068
		10 Years	Dominating	£10,010
		20 Years	Dominating	£13,194

[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
[e] EORTC-C30 to EORTC-8D using data from patients with newly diagnosed with multiple myeloma

1.1.10 What were the main findings of each of the sensitivity analyses?

The main finding of the deterministic sensitivity analysis reported in Section 1.1.7 is that the model is most sensitive to the HR for time to PSA progression. However, the threshold analysis undertaken showed that for all of the values within the 95% CI of the HR, degarelix remains a cost-effective use of healthcare resources, at a threshold of £20,000 per QALY gained.

The probabilistic sensitivity analysis indicated that simultaneous variation in the parameter values did not affect the result that degarelix was cost-effective. This is illustrated by Figure 8, which shows that the model estimates degarelix to have a 100% probability of being cost-

effective at a willingness-to-pay threshold of £30,000 per QALY and 85.4% probability of being cost saving.

The scenario analyses indicated that the cost-effectiveness of degarelix is not sensitive to structural uncertainty. A number of variations were made to the base-case specification; none resulted in an ICER higher than £12,000 per QALY.

1.1.11 What are the key drivers of the cost-effectiveness results?

The key driver of the cost-effectiveness results is the enhanced efficacy and safety profile of degarelix.

The enhanced efficacy profile increases time to PSA progression, which results in: higher patient HRQL, reduced hazard of mortality, and reduced time on abiraterone (with the resulting offsets in medication costs).

The enhanced safety profile results in: higher patient HRQL, reduced mortality from cardiovascular events, and cost-offsets due to the avoidance of costs associated with managing AEs.