Section A: General requests

A1. **Priority request:** Please provide evidence supporting the validity of the description of the clinical pathway and a justification for the assumption of the proportion of patients whose disease fails each treatment and continue with another line of therapy. The ERG has received advice from clinical experts that the current treatment pathway illustrated in Figure 2 (page 20 of the manufacturer's submission) does not accurately reflect clinical practice.

The clinical pathway depicted in the STA submission was devised using information from the NICE clinical guideline on prostate cancer (CG58), the European Association of Urology (EAU) guidelines on prostate cancer and the NICE Technology Appraisal for abiraterone (TA259). In addition, as detailed within the STA submission on page 137 and the data on file reference number 7, Ferring consulted with four clinical experts via an advisory board and follow-up questionnaires to validate the clinical pathway presented. Finally, this clinical pathway has been corroborated by the HTA body in Wales.

NICE has requested further information on the following:

(a) What treatments people get depending on patient characteristics (e.g. age, stage)

In response to this clarification request, Ferring has consulted for further information from external clinical experts. The responses gained indicated that each patient factor, e.g age or stage, cannot be taken into consideration in isolation. Therefore, treatment decisions are based on multiple factors, including patient age, patient preference, stage of disease at presentation, as well as variation in local practice.

(b) The proportion of people that get these treatments through the pathway and **(c)** Whether people continue on those treatments through the pathway.

It is recognised that whilst in practice it is possible that not all patients will receive all treatments within the treatment sequence, there is paucity in data in which to base any alternate assumptions and therefore a simplifying assumption was made to assume all patients follow the entire sequence.

In response to the clarification requests A1(b) and A1(c), Ferring has consulted for further information from external clinical experts to determine whether people continue on treatments through the pathway. This expert opinion indicates:

1. Step 1 in treatment sequence:
   Given that a patient fails (defined as ‘experiences PSA progression’) on treatment with LHRH agonists/antagonists the chance of them receiving anti-androgen addition for androgen deprivation (also known as complete androgen blockade) is >95%.

2. Step 2 in treatment sequence:
   Given that a patient fails (defined as ‘experiences PSA progression’) on androgen deprivation, the chance of them moving to anti-androgen withdrawal is high (85%-100%), with most, if not all patients going through anti-androgen withdrawal.

3. Step 3 in treatment sequence:
   Given that a patient fails (defined as ‘experiences PSA progression’) after anti-androgen withdrawal, the chance of them moving onto chemotherapy treatment with docetaxel or abiraterone is 50-70%, since many patients receive abiraterone via the Cancer Drugs Fund - however, docetaxel was placed before abiraterone in the clinical pathway presented in line with the reference case.

4. Step 4 in treatment sequence:
   Of those patients that have been treated docetaxel and failed, 70% will go on to receive abiraterone.

These percentages described above are largely in line with the assumptions made in the NICE STA model submitted and the response provided to D4, which provides sensitivity analysis results using these assumptions within the economic model.

A paucity in nationwide data defining the exact percentage breakdown for the above three requests from NICE has prevented Ferring including such data within this STA submission.

A2. Please clarify further Section 2.6 (page 21) by describing any variations or uncertainty relating to current clinical practice.

Local and regional guidance indicate that there is an inequality in patient access to degarelix across the UK. Gained through Ferring's communications with the NHS at primary and secondary level, the following examples highlight how both guidance and access varies:

1. The North of England Cancer Drugs Approval Group (NECDAG):

In November 2011, NECDAG approved degarelix for first-line treatment of advanced hormone-dependent prostate cancer with a prostate-specific antigen (PSA) level >20 ng/l at presentation. There are little or no issues with initiating and maintaining degarelix in the North East.

2. York and surrounding areas:

The circumstances in York demonstrate inequality in patient access that can occur within a single Clinical Commissioning Group's (CCG's) catchment area; some patients in the north of the Vale of York CCG are initiated on degarelix at the Friarage Hospital and are subsequently maintained on it in the community. Conversely, patients registered at the York Hospital are unable to receive both the initiation and maintenance doses for degarelix; the York and Scarborough Formulary supports the initiation of degarelix, but only on the basis that patients are subsequently switched to a luteinising hormone-releasing hormone (LHRH) agonist in primary care.

3. Greater Manchester Medicines Management Group (GMMMG):

Due to the GMMMG 'red' RAG [red, amber, green] status of degarelix, patients within the Greater Manchester catchment area can currently only receive degarelix if it is both initiated and maintained in secondary care. In addition, the recommendation from the Interface Prescribing and New Therapies Subgroup (IPNTS) states that prescribing is to remain with specialists and is recommended only for patients who are particularly vulnerable to the clinical effects of a testosterone flare. As a result, hospital clinicians are unwilling to initiate treatment in the knowledge that hospitals are unable to fund degarelix for the intention-to-treat (ITT) prostate cancer population. In addition, patients initiated on degarelix will not be maintained in the community, and there is a concern that patients will be switched to an LHRH agonist in primary care, as opposed to receiving maintenance treatment with degarelix in secondary care.

4. Surrey and surrounding areas:

CCGs including Surrey Heath, Guildford and Waverly, Surrey Downs and North West Surrey all fund the initiation and maintenance dose of degarelix, allowing patients to be maintained on this in primary care. However, the M25 acts as a boundary for prescribing, with neighbouring CCGs such as Kingston typically not offering patients the option to be maintained on degarelix in primary care.

Section B: Clarification on literature searching

B1. **Priority request**: Please provide the search strategies for Medline, Medline in-Process, Embase and Web of Science which are absent in Appendix 2 (page 231).

Please see Appendix 1 for the full search strategies employed to search the MEDLINE, MEDLINE-In-Process and Embase databases. Please see Appendix 2 for the full search strategy employed to search the Web of Science.

B2. **Priority question**: The Cochrane Library search strategy supplied for Section 6.1 “Identification of studies” (page 232) does not contain any subject-headings. Please confirm if MeSH subject headings and Emtree thesauri terms were included in Medline and Embase search strategies, respectively.

The terms used for the search of the Cochrane Library are shown in Appendix 3.

The Ovid search terms described in Appendix 1 allowed both the MEDLINE and Embase databases to be searched simultaneously, using a single search strategy. MeSH subject headings and Emtree thesauri terms were, therefore, not respectively specified. With the mapping of the key topic terms (including “degarelix”, “prostate”, and “cancer”), the search of MEDLINE and Embase was sensitive so that any relevant studies were unlikely to be missed.

B3. **Priority request:** Please provide the inclusion/exclusion criteria for the identification of the studies for the mixed treatment comparison (MTC; Section 6.7.1, page 81) and the resulting flow diagram for the MTC.

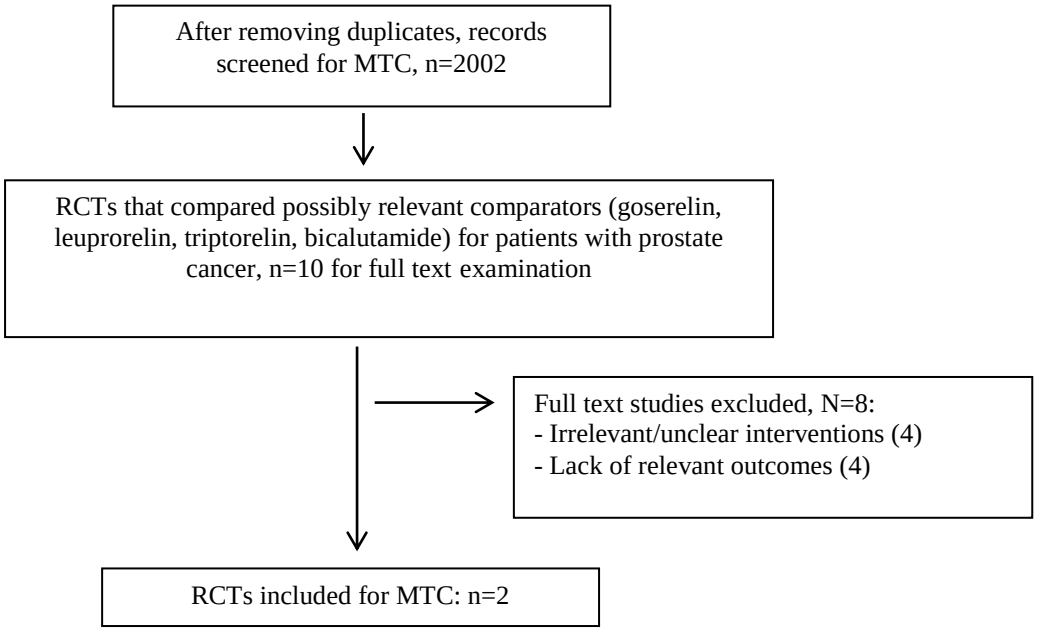
The inclusion and exclusion criteria used for study selection in the mixed treatment comparison (MTC) and the resulting flow diagram are presented in the table and figure below.

Study inclusion and exclusion criteria for the MTC

Population	Adult male patients with advanced hormone-dependent prostate cancer*
Interventions and comparators	Degarelix LHRH agonists: goserelin, leuprorelin, triptorelin Bicalutamide monotherapy
Outcomes	Outcome measures to be considered: • Overall survival • Progression-free survival • Response rate • Testosterone response • PSA response (PSA percentage change from baseline and PSA progression [recurrence or failure]) • PSA progression-free survival • Time to PSA progression • Adverse effects of treatment • Health-related quality of life
Study design	Randomised controlled trials
Language restrictions	No language restrictions

* Available clinical trials of degarelix usually included patients with prostate cancer of all stages, so studies of patients with all stages of prostate cancer suitable for treatment with hormonal therapy were included.

MTC study selection flow diagram



B4. In the flow diagram (page 38 of the manufacturer's submission), please clarify whether the Cochrane Central Register of Controlled Trials records were included in the 2237 (1862 + 375) records from the database searches before duplicates were removed.

Records identified from the Cochrane Central Register of Controlled Trials (CCRCT) were not included in the flow diagram (Figure 3 on page 38 of submission). The majority of the references identified by searching the Cochrane library were duplicates from the MEDLINE, Embase, and Web of Science searches. The CCRCT search results were, therefore, not combined with the MEDLINE, Embase and Web of Science results to populate the flow diagram. As a response to this ERG request, the academic systematic review team at the University of East Anglia confirmed the search of the CCRCT (using the search strategy detailed in Appendix 3) identified 737 references in total, with 502 of the 737 records being duplicates of the MEDLINE, Embase or Web of Science searches. None of the 235 remaining studies was eligible for inclusion.

B5. Please clarify reasons for omission of the following studies from the manufacturer's submission. If any of the trials were identified and subsequently excluded from the searches in the submission please state the explicit reasons for exclusion:

The systematic review team were aware of these studies. Please see the inserted column titled 'Reasons for omission' in the table below for clarification.

Clinical trial no.	Trial title	Status	Enrolment	Sponsor/ collaborators	Reasons for omission
NCT00 117949	Study Investigating the Pharmacokinetics, Pharmacodynamics and Safety of FE200486	Completed 2004; Has results	82	Ferring CS06	Pharmacokinetics and pharmacodynamics design. Single dosing regimen (40-160 mg) of degarelix was not relevant.
NCT00 117312	Extension Study Investigating the Long-Term Safety and Tolerability of Repeat Doses of FE200486 in Prostate Cancer Patients	Terminated 2005; Has results	37	Ferring CS06A	Early safety and tolerability investigation. Only 37 of the 82 patients in CS06 were included
NCT00 818623	Investigation of a New Trial Drug (FE200486) in Prostate Cancer Patients	Completed 2004; Has results	172	Ferring CS07	A single dose study investigating the pharmacokinetics, pharmacodynamics and safety of degarelix
NCT00 245466	Study Investigating the Long-Term Safety and Tolerability of Repeated Doses of Degarelix in Prostate Cancer Patients	Terminated 2006; Has results	88	Ferring CS02A	In CS02, the loading dose regimen was no longer relevant. Only 88 of the 129 patients in CS02 were included in CS02A
NCT00 215657	Extension Study Investigating the Long-Term Safety and Tolerability of Repeat Doses of FE200486 in Prostate Cancer Patients	Terminated 2006 Has Results	131	Ferring CS07A	CS07 was a trial for ascending single doses. Only 131 of the 172 patients were recruited in CS07A
NCT00 117286	Extension Study Investigating the Long-Term Safety of Degarelix One-Month Depots in Patients With Prostate Cancer	Completed 2009; Has results	57	Ferring CS14A	All patients receive 160mg maintenance dose, which is not relevant in terms of licensed dose regimen (240/80 mg)
NCT01 071915	Efficacy and Safety of Degarelix One Month Dosing Regimen in Korean Patients With Prostate Cancer	Completed 2011; Has results	157	Ferring CS42	The results for CS42 were reported in CS42A, which was referred to within the submission.
NCT01 220869	A Study of Degarelix in Taiwanese Patients With Prostate Cancer	Completed 2012; No results available	110	Ferring CS43	No results available yet.
NCT00 738673	Degarelix as Second-Line Hormonal Treatment After Prostate-specific Antigen (PSA)-Failure in GnRH Agonist Treated Patients With Prostate Cancer	Completed 2011; Has results	37	Ferring CS27	An exploratory study of second-line degarelix treatment after PSA-failure in GnRH agonist treated patients

Clinical trial no.	Trial title	Status	Enrolment	Sponsor/ collaborators	Reasons for omission
NCT00 801242	Intermittent Treatment With Degarelix of Patients Suffering From Prostate Cancer	Completed 2013; No results available	220	Ferring CS29	No results available yet.
NCT01 491971	Intramuscular Injections of Degarelix Administered in 1-Month Dosing Regimens in Patients With Prostate Cancer	Completed 2012; No results available	76	Ferring	No results available yet.
NCT01 344564	Initiation of Androgen Deprivation Therapy for Prostate Cancer Using Degarelix Followed by Leuprolide	Completed 2012; No results available	50	Urology of Virginia/ Ferring	No results available yet.

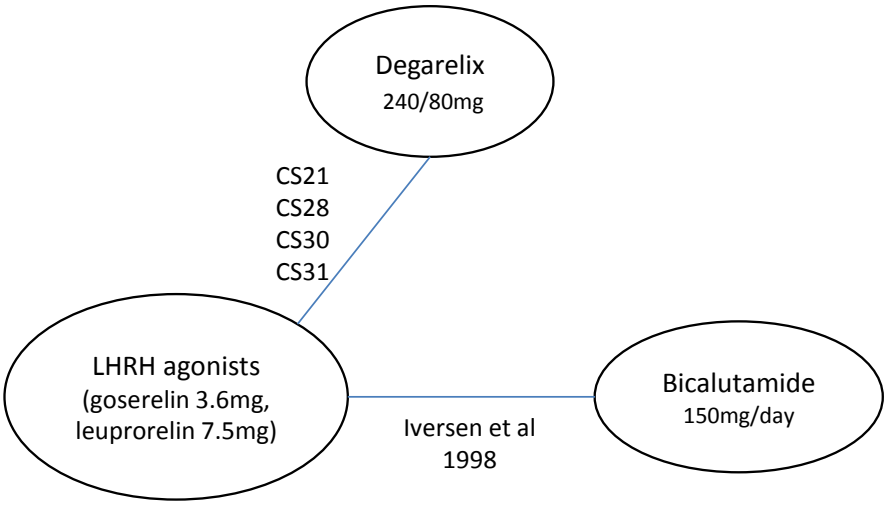
Section C: Clarification on effectiveness data

C1. **Priority request**: Please provide results of the MTC including bicalutamide as a comparator. If it is not possible to undertake a naïve indirect comparison for bicalutamide (with appropriate subgrouping from CS21) please justify why this is the case.

Bicalutamide monotherapy was included as a comparator in the MTC, as described on pages 81–88 in the submission. A naive indirect comparison for bicalutamide was not completed as it may provide misleading or biased estimates of treatment effects.[1]

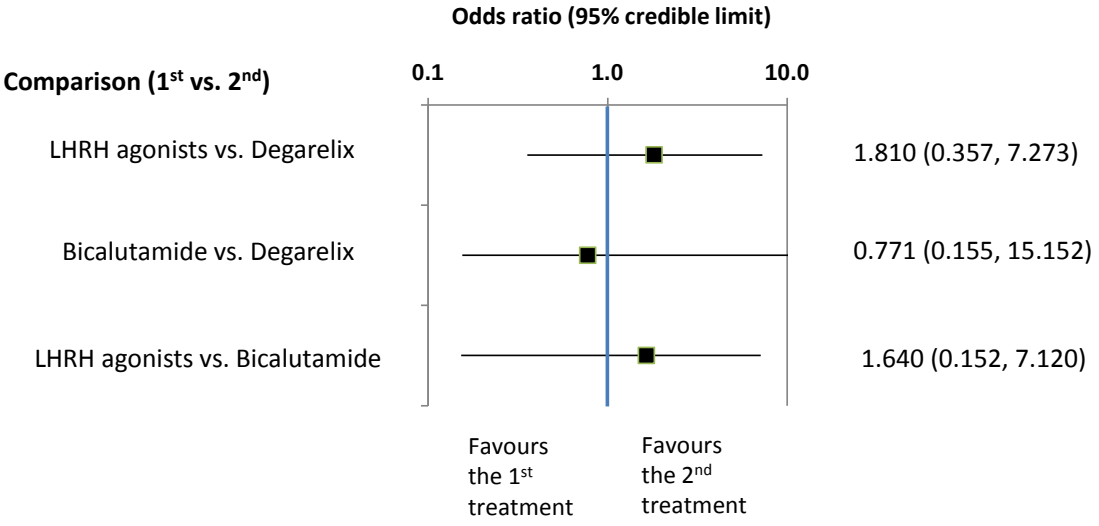
C2. **Priority request**: Please provide the results of the MTC with all the luteinising hormone-releasing hormone (LHRH) agonists so that there are 3 groups within the MTC network: degarelix; LHRH agonists (including goserelin, leuprorelin and triptorelin); as well as bicalutamide monotherapy.

For this request, the three LHRH agonists (goserelin, leuprorelin and triptorelin) were considered as the same treatment. The study by Heyns *et al* (2003)[2] could not be included in this MTC, as it compared different LHRH agonists (leuprorelin and triptorelin). The modified network of trials, in which three interventions were compared (degarelix, LHRH agonists and bicalutamide monotherapy), is shown below.



The results of the MTC are shown in the figure below. The differences between degarelix and LHRH agonists or bicalutamide monotherapy were not statistically significant (odds ratio [OR]=1.81; 95% credible limit [CL] 0.36 to 7.27 for comparing with LHRH agonists; and OR=0.77; 95% CL 0.16 to 15.15 for comparing with bicalutamide). The difference between LHRH agonists and bicalutamide was, similarly, non-significant.

MTC between degarelix, LHRH agonists and bicalutamide – overall survival outcome (odds ratio)



C3. **Priority request**: Please provide the results of the MTC for all outcomes including adverse events in the MTC. If this is not possible, please justify.

Overall survival was a common outcome from studies included within the MTC. MTC was impossible for other efficacy and safety outcomes, as they were measured and reported very differently across trials. An exception was the rate of hot flushes, which can be used for MTC. The results of this MTC indicated that there were no statistically significant differences in the hot flush rate between degarelix and comparators (see table below).

	Odds ratio	95% credible limits	
Leuprorelin vs. Degarelix	0.224	0.072	1.570
Goserelin vs. Degarelix	1.149	0.457	3.731
Triptorelin vs. Degarelix	0.229	0.057	3.861
Biaclutamide vs. Degarelix	0.145	0.038	1.603

Note: OR <1 indicates the first treatment was associated with fewer hot flushes compared with the second treatment

C4. Please provide full details of methods, data description and results for pooled analyses including:

- Prostate-specific antigen (PSA; page 70)
- Level of alkaline phosphatase in serum (s-ALP) (page 72)
- testosterone ≤.5mg/ml (page 74)
- summary of model results provided in Table 52 (page 190).

Prostate-specific antigen (PSA; page 70)

A full description of patient baselines statistics and results from the pooled data from CS21 and CS35 can be found in Appendix 4, and raw pooled data found in Appendix 5. As described in the STA submission, Kaplan-Meier method and log-rank test, and adjusted HRs were calculated using Cox regression.

Level of alkaline phosphatase in serum (s-ALP) (page 72)

A full description of pooled raw data and Kaplan-Meier analyses completed to assess s-ALP can be found in Appendix 6 – please consult 'Table 1.7: Adjusted mean change from baseline in S-ALP - Metastastic Patients'.

Testosterone ≤0.5mg/ml (page 74):

Data from four trials (CS21, CS28, CS30, and CS31) were combined to form a dataset – the data used from individual trails can be found in:

- CS21: CSR Table 9-10[4]
- CS28: CSR Table 9-7[5]
- CS30: EOT Table 6.2.2.7[6]
- CS31: EOT Table 76.[7]

Using data presented in these tables, a single dataset was constructed equivalent to individual patient data from a single trial. Subsequently, the Kaplan–Meier method was used to estimate the pooled cumulative probability of testosterone ≤0.5 ng/ml. The pooled data set can be in Appendix 7.

Summary of model results provided in Table 52 (page 190):

The 'data on file' reference on individual patient-level data supplied to NICE (number 110 in the submission)[3] provides a description of the data and methods used for the pooled analysis performed to populate the model and used to validate model results in Table 52 of the submission. Description of the methods and data can be found on pages 106–117 of the submission; Kaplan–Meier data for musculoskeletal events can be found on pages 118–166; Kaplan–Meier data for cardiovascular events can be found in the Appendix 8, provided alongside this clarification. Results were taken from the relevant Kaplan–Meier data for the period 0 – ≤365.

Please note that there has been a slight error relating to cardiovascular events detailed in Table 52 on page 190 of the submission. This should read as follows:

Outcome	**Clinical trial result**	**Model result**
Degarelix: percentage of those with cardiovascular risk at baseline who have a serious cardiovascular event after 1 year	5.3% (pooled trials)	6.2%
Leuprorelin: percentage of those with cardiovascular risk at baseline who have had a serious cardiovascular event after 1 year	13.2% (pooled trials)	13.9%

C5. Please clarify how the non-significant difference in overall survival (page 86) between LHRH agonists in the MTC demonstrates equivalence in clinical efficacy and effectiveness.

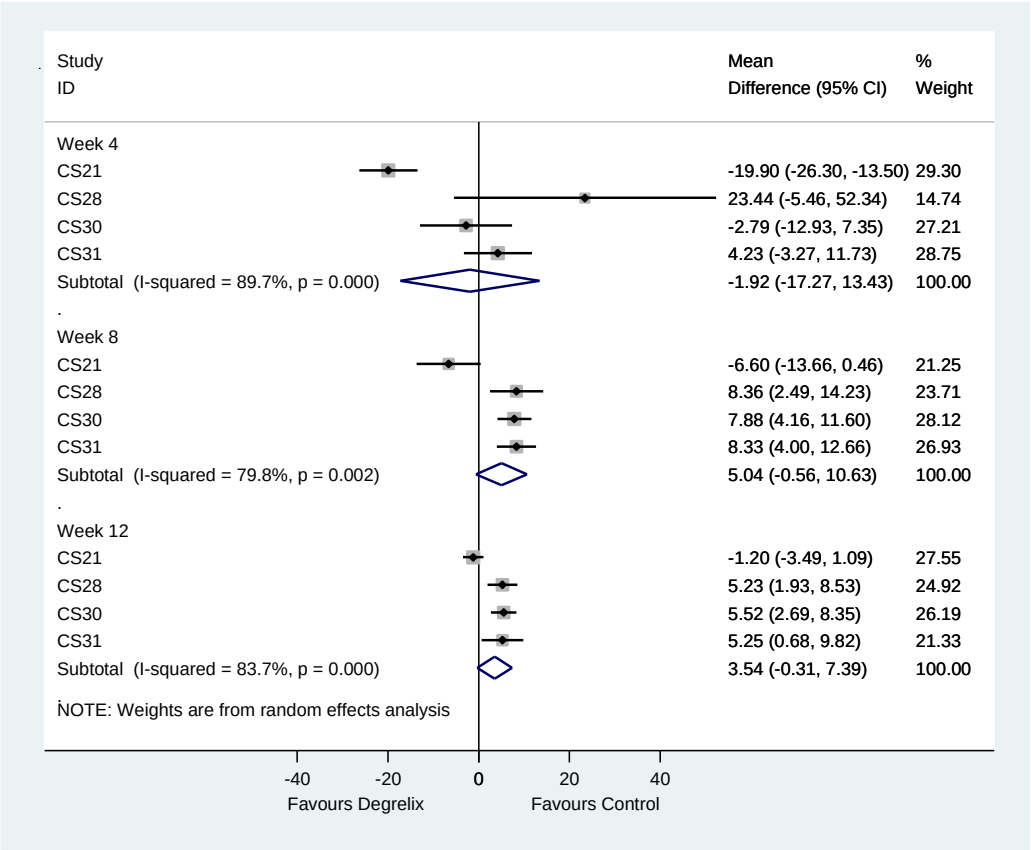
The difference between degarelix and LHRH agonists was statistically non-significant, due to wider 95% CLs. The non-significant difference may be due to insufficient statistical power, as

shown by the response to request C2, in which all relevant LHRH agonists were combined as a single comparator (OR 1.810; 95% CL 0.357 to 7.273). It is recognised that while the MTC provided does not conclusively demonstrate equivalence in clinical efficacy and effectiveness, the results from the MTC support the findings from previous systematic reviews and meta-analyses[8,9] that none of the LHRH agonists exhibit superior clinical efficacy of effectiveness over another.

C6. Please clarify why only 4-week and 12-week data were used to report PSA response results (page 7) and why 8-week data were not reported.

Data on the percentage change in PSA may not be normally distributed, and the exploratory meta-analysis was conducted using the Week 4 (28 days) and Week 12 (84 days) data. The forest plot below shows that the results of the percentage change in PSA at Week 8 were similar to the results at Week 12 (see figure below)

Mean difference between degarelix and control in percentage change in PSA from baseline at Week 4, Week 8 and Week 12



C7. Please clarify which methods were used to handle crossover in CS21A (page 90)? If none, please justify.

It was by study design in CS21A that patients treated with leuprorelin 7.5 mg during CS21 were switched to degarelix treatment (at first 160 mg or 80 mg, then all patients switched to degarelix 80 mg after the subsequent approval of Protocol Amendment 2 [03 September 2009]). Patients in CS21A were followed up for five years, and outcomes were compared between patients who continued degarelix treatment and those who switched from leuprorelin to degarelix.

For the purposes of economic modelling analysis has been conducted for the following patient groups in order to avoid the problem of crossover confounding results:

- Leuprorelin 7.5mg up to 1 year (prior to crossover)
- Degarelix 80mg up to 5 years (patients in this arm did not experience crossover)

C8. Trial CS35 was deemed to be not fully applicable to the decision problem due to the use of an unlicensed dose of degarelix (page 65). However, results from CS35 are included in a pooled analysis for PSA and overall survival (and not highlighted as commercial in confidence). Conversely data from CS37 were excluded from the survival analysis on the basis of an incompatible degarelix maintenance dose (page 78). Please justify the inclusion of CS35 in these analyses.

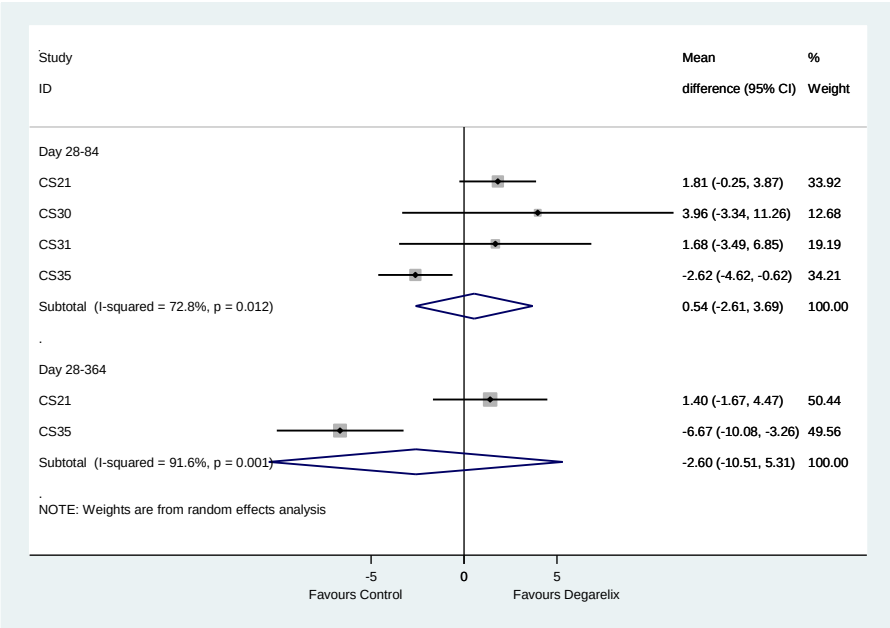
CS35 and CS21 (the pivotal phase III trial) share a similar trial design and patient inclusion criteria, therefore the patient baseline characteristics for these trials are reasonably comparable, warranting data to be pooled. Conversely, the CS37 trial was designed to evaluate intermittent versus continuous therapy, and the patient inclusion criteria were different to the other five RCTs, thus excluded from the meta-analyses. For completion, we have provided all meta-analyses where CS35 could be included below:

Testosterone: CS21, CS28, CS30, CS31, CS35

After including data from CS35, heterogeneity across trials was statistically significant in the meta-analysis of cumulative probability of T≤0.5 ng/mL between degarelix and LHRH agonists from Day 28 to 84 (I^2=73%, P=0.012). There was no statistically significant difference in cumulative probability of T≤0.5 ng/mL between degarelix and LHRH agonists from Day 28 to 84 (MD=0.54, 95% CI: -2.61 to 3.69; P=0.736).

Data on the cumulative probability of T≤0.5 ng/mL between degarelix and LHRH agonists from Day 28 to 364 were also available from trial CS21 and CS35. The results from the two trials were statistically significantly heterogeneous (I^2=92%, P=0.001).

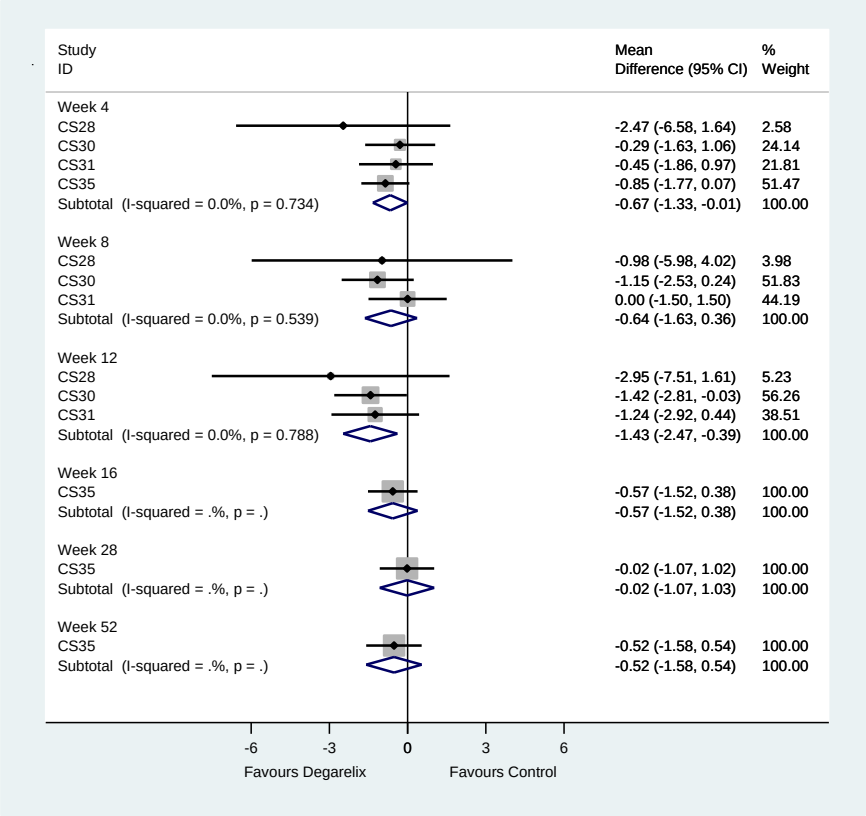
Meta analyses: Difference (%) in cumulative probability of T≤0.5 ng/mL between degarelix and LHRH agonists from Day 28 to 84.



IPSS: CS28, CS30, CS31, CS35

CS35 reported data on changes in IPSS from baseline at week 4, 12, 28 and 52. Pooled analysis was only possible using data at week 4. Results at week 12, 28 and 52 were also shown in the figure below. The results from different studies were not significantly heterogeneous (P=0.734). The differences in changes in IPSS between degarelix and LHRH agonists were statistically significant at week 4 (P=0.047) and week 12 (P=0.007).

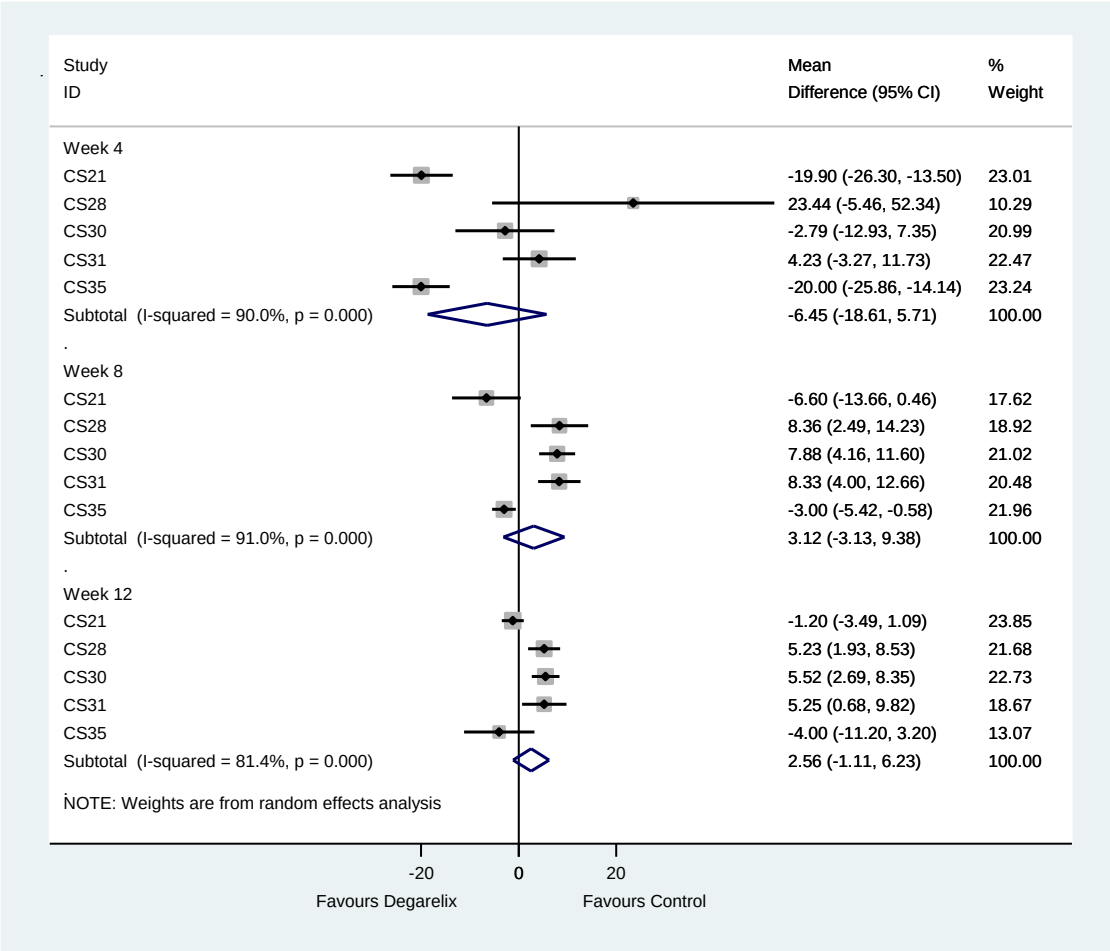
Meta analyses: difference in changes in IPSS from baseline between degarelix and LHRH agonists.



PSA percentage change in PSA from baseline: CS21, CS28, CS30, CS31, CS35

The differences in percentage changes in PSA from baseline between degarelix and LHRH agonists were statistically non-significant (P=0.299 for week 4, P=0.328 for week 8, and P=0.172 for week 12). However, the results of trials were significantly heterogeneous (P<0.001). As mentioned in the main submission, the meta-analysis results for the percentage change in PSA should be interpreted with caution, as the data may not be normally distributed and the existence of significant heterogeneity across trials.

Meta analyses: Differences in percentage changes in PSA from baseline



C9. Please clarify what the timepoint was for the odds ratio in the MTC for death (page 87).

The MTC analysis was based on the limited evidence available. The respective time points were:

- Three months for CS28, CS30 and CS31
- 12 months for CS21
- Nine months for Heynes *et al,* 2003[2]
- Four years for Iversen *et al,* 1998.[10]

C10. For the subgroup analysis of men with pre-existing cardiovascular disease (CVD), please clarify how pre-existing CVD was defined.

Patients with pre-existing cardiovascular disease was defined using the 5 following Standardised MedDRA Queries (SMQs) applied to individual patient medical records:

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

C11. Please provide a rationale behind the assumption that the dose of leuprorelin does not have an effect on the efficacy and safety profile (page 102).

The following papers support the assumption that the dose of leuprorelin does not have an effect on the efficacy and safety profile:

- Reference 136, Akaza 1990: p97[11]
- Reference 137, Akaza 1992: p1[12]
- Reference 138, Bischoff 1990: p3[13]
- Reference 139, Mazzei 1989: p1[14]
- Reference 140, Mazzei 1990: p1[15]
- Reference 142, Rizzo 1990: p1[16]

Further support for the assumption can be found in reference 121, Hemels 2002 and reference 158, Iannazzo 2011.

Section D: Clarification on cost-effectiveness data

D1. **Priority question**: The economic model is based on efficacy data from one trial even though 6 RCTs comparing degarelix to LHRH agonists were identified. Please clarify why these other 5 RCTs have not been used to inform the economic analysis.

For the endpoint of PSA progression (the driver of progression through the lines of treatment in the model), only data from CS21 and CS21A were used. These data are the most relevant because CS21 and CS21A are the only trials reporting this information for the licensed dose of degarelix (240 mg induction, 80 mg maintenance) and include the longest follow-up (5 years).

In addition, as only CS21 and CS21A analysed the time to PSA progression and CS35 and CS37 were the only other studies that included PSA progression (CS37 used a slightly different

definition of PSA progression to CS21 and CS35[a]), a full pooled analysis would not have been possible for this endpoint. Published information is available on pooled data from CS21 and CS35, which showed that the PSA progression-free survival (PFS) failure rate (adjusted for baseline PSA, Prostate cancer stage and Gleason score) was significantly lower with degarelix than with LHRH agonists plus anti-androgen flare protection for all patients (hazard ratio [HR]=0.490; p=0.0028).[17]

For the adverse event endpoints (cardiovascular events, fractures, joint-related signs and symptoms), pooled data from all six randomised controlled trials (RCTs) were used. As these events are relatively rare, pooling of the available data was required to have a large enough sample size. This is standard practice for the reporting of safety data.

Where pooled data have been used, tests were carried out to determine whether the incidence of events was significantly different for the various degarelix dosing regimens. The results of these significance tests are shown in Appendix E, which was submitted alongside the submission. For all outcomes included within the model, the dose of degarelix given did not significantly impact the incidence of events.

D2. **Priority question**: Please provide results of the economic model using the estimates generated from question C1-C3 of the MTC. If this is not possible, please clarify the rationale for this. Please clarify why the MTC was not used to inform the model.

The MTC was not used to directly inform the model for the following reasons:

1. The only outcome relevant to the economic modeling that could be assessed within the MTC was overall survival, as no data were available to assess other outcomes – the outcomes within the model are based on PSA progression (from CS21 and CS21A) and the relative incidence of cardiovascular and musculoskeletal events (from pooled analysis of the six degarelix RCTs).
2. As overall survival data from the six degarelix trials were very immature (<5% of patients had died in each of the trials), the use of direct overall survival data from the trials would not allow accurate analysis of survival over time.

[a] CS21 and CS35: PSA progression [recurrence/failure] defined as PSA increase ≥50% from nadir and ≥5 ng/ml on two consecutive occasions ≥2 weeks apart. CS37: castrate-resistant PSA progression [recurrence/failure] defined as two consecutive increases of PSA at least 2 weeks apart and 50% increases over nadir with testosterone <0.5 ng/ml

3. The results of the MTC contain considerable uncertainty, which is likely due to heterogeneity in the trials contained within the analysis, the immaturity of the data and the small sample sizes of some of the included trials.

D3. **Priority question**: Please provide further justification for the exclusion of key subgroups from the NICE scope (page 32) in the model and clarify what is meant by "a sufficiently large number of patients".

Patients within the following subgroups could not be identified within either the CS21 clinical trial or within the other five degarelix trials in the pooled analysis:

- Patients with spinal metastases with impending or actual spinal cord compression
- Patients with high tumour volume with impending or actual urinary outflow obstruction
- Patients with bone metastases associated with intractable pain
- Patients for whom standard anti-androgen treatment is contraindicated
- Patients at risk of evolving cardiovascular comorbidity

Prostate cancer TNM stage was collected within the clinical trials (and is reported within the submission), however the location of metastases was not collected. This means that patients with either spinal or bone metastases could not be identified.

Patients with high tumour volume with impending or actual urinary outflow obstruction were studied in the CS28 clinical trial (n=42). Data on prostate or tumour volume has not been recorded systematically in any other trials (since TNM staging for the indication was collected). This means that patients with high tumour volume could not be identified outside of CS28.

Data was not collected on whether or not patients were contraindicated to anti-androgen treatment. However, a significant difference in the rates of PSA progression free survival was reported both for CS21,[18] where few patients received anti-androgen treatment, and for a combined analysis of CS21 and CS35[17] with patients who received anti-androgen treatment indicating that degarelix is effective both in patients who received anti-androgens and those who did not.

As it has been assumed in the model that patients who receive flare protection experience the same outcomes as those who do not (page 144), outcomes for patients for whom standard anti-

androgen treatment is contraindicated are assumed to be the same as in the base case analysis. The assumption of equivalence is supported by the following data:

- Clinical rationale that provision of flare cover (<1 month) is not clinically likely to affect long-term PSA progression
- A large observational study of 1,566 patients conducted by Oh *et al*, which concluded that anti-androgen therapy before LHRH agonist treatment in metastatic prostate cancer was not associated with differences in fractures, spinal cord compression, bladder outlet obstruction, or narcotic prescriptions.[19]

Pooled analysis from the CS21 and CS35 trials showed that the PSA PFS failure rate (adjusted for baseline PSA, prostate cancer stage and Gleason score) was significantly lower with degarelix than with LHRH agonists plus anti-androgen flare protection for all patients (HR=0.490; p=0.0028) and that patients receiving LHRH agonists plus anti-androgen flare protection still experienced testosterone surge.[17]

If the risk of PSA progression and musculoskeletal events is assumed to be the same as for the entire population, results can be produced for the final subgroup by setting the proportion of patients with baseline cardiovascular disease to 100%. Results are provided in the table below (updated for the error identified by the ERG in D7).

Treatment arm	**Totals**			**Inc. costs**	**Inc. QALYs gained**	**Inc. life-years gained**	**Cost per QALY**
	Costs	**QALYs gained**	**Life-years gained**				
Goserelin 3-monthly (Zoladex)	£24,492	4.23	7.22				£4,216
Degarelix	£31,348	5.86	9.58	£6,856	1.63	2.36	

Patients at risk of evolving cardiovascular co-morbidity could not be considered as a subgroup since prospective measurements or evaluations were not assessed during the trials. However, 'patients with pre-existing cardiovascular disease' could be assessed as subgroup since retrospective measurements using Standardised MedDRA Queries (SMQs) and individual patient medical records was possible.

D4. **Priority question:** Please specify whether it is assumed in the economic model that all surviving patients receive every line of active treatment in the sequence. If this is the case, please provide evidence supporting this assumption.

It is assumed in the economic model that all patients receive every line of active treatment in the sequence, unless they die on the previous line of treatment before they progress. While, in practice, it is plausible that not all patients will receive all treatments, data on which to base any alternate assumption are sparse and, therefore, a simplifying assumption was made that all patients follow the entire sequence. The simplification should not produce a substantial distortion of the reality being modelled. Clinical experts reviewed both the model structure and the assumptions around the modelled pathway and affirmed that it provided an accurate representation of the treatment experience typically experienced by a patient. The confidence intervals surrounding the mean duration for each of the later lines of treatment were widened above and beyond the information available within the relevant literature in an attempt to account for this uncertainty (see answer to D14).

The proportion of patients expected to receive docetaxel and abiraterone has since been calculated using the information from the relevant NICE costing templates as follows: there are 39,376 new cases of prostate cancer in 2013 (page 212 of submission).

- 22% of all new cases are classed as metastatic
- 22% of cases previously diagnosed as non-metastatic later developing stage IV disease
- Total number of metastatic patients is then 39,376 * 0.22 + 39,376 * (1-0.22) * 0.22 = 15,420
- Of these, 45% (based on expert opinion) are treated with docetaxel; that is 15,420*0.45 = 6,939
- Of these, 70% (based on abiraterone submission) are treated with abiraterone; that is 6,939*0.70 = 4,857.

As the information for docetaxel is presented as a proportion of all metastatic patients (not those who have failed therapy with anti-androgen withdrawal following therapy with anti-androgen addition and first line treatment with LHRH agonists) the proportion of patients who would receive docetaxel after anti-androgen withdrawal has been calculated based upon the costing template and the information on progression through the treatment lines within the economic analysis submitted as follows:

- The proportion of patients who receive docetaxel as a proportion of those who receive LHRH is: 6,939[1] / 15,458[2] = 45%

[1] Calculated based upon the NICE costing template as shown above

- The proportion of patients who receive docetaxel in the economic model is 64% - this represents the proportion of patients who are alive following failure of anti-androgen withdrawal
- The proportion of living patients who fail anti-androgen withdrawal and then receive docetaxel is therefore calculated as: 45%/64% = 70%

The proportion of patients receiving docetaxel or abiraterone following failure of the previous line of therapy estimated from the NICE costing templates are in line with the expert responses provided in the answer to question A1.
Implementing these assumptions into the model:

- 70% of patients receive docetaxel after failure of treatment on anti-androgen withdrawal, the remaining 30% moving to supportive and palliative care
- 70% of patients receive abiraterone following failure of treatment with docetaxel, the remaining 30% moving to supportive and palliative care

produces the following the results (adjusting for the error noted by the ERG in D7). Treatment with degarelix remains dominant.

Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Inc. costs (£)**	**Inc. LYG**	**Inc. QALYs**	**ICER (£)**
Goserelin 3 Monthly (Zoladex)	£22,275	5.23	9.17				
Degarelix	£21,953	5.82	9.55	-£322	0.59	0.38	Dominating

D5. **Priority question**: Please provide additional details in the answer to 7.7.1 "Please explain reasons for any differences between modelled and observed results" on page 189. For example please explain differences between model and trial data for 1-year overall survival.

As outlined on pages 130–132 and 135–136 of the submission, the duration of overall survival in the model, and therefore the percentage alive after one year, is not derived from the clinical trials. The general rate of mortality is instead calculated using data for the UK general population and the Scottish prostate cancer population. The risk of mortality, death from a fatal cardiovascular event, is subtracted from the degarelix arm, as there is a differential risk between those treated with degarelix and those treated with leuprorelin (current practice), as well as due to supportive evidence from leading clinicians, who indicated that cardiovascular complications were a serious co-morbidity associated with the population and the related treatments.

[2] The number of patients expected to start LHRH therapy in 2013 - page 212 of submission

The model submitted looks to predict survival (and other outcomes) for the expected real life patient cohort. The model, therefore, uses real-life estimations of likely mortality, based on our knowledge of mortality and risk in the different treatment groups (based on PSA progression and cardiovascular events).

The patients within the clinical trial are likely to represent fitter and, in some cases, earlier-stage patients than would be seen in the general population treated with LHRH agonists. It is, therefore, unsurprising that there is a small reduction in the percentage who are alive after one year in the cost-effectiveness model compared with the percentage who are alive after one year in the clinical trial (93.7% versus 97.4% in CS21). The difference in survival projections is, however, relatively small.

D6. **Priority question**: Section 7.2 (page 112) states that degarelix is compared to each of the commonly used LHRH agonists in the scenario analysis but these results do not appear to be provided. Please provide results for all comparators included within the scope.

As mentioned on page 144 of the submission, the model assumes that the different LHRH agonists have an identical efficacy and safety profile. The only implication of changing the LHRH agonist incorporated in the analysis is that the costs will vary due to differences in the treatment and administration costs. The scenario analysis, therefore, reported the results for degarelix against both the most expensive and the least expensive LHRH agonist. If degarelix is cost-effective against the LHRH agonist with the lowest associated costs, it will be cost-effective compared with all the other LHRH agonists.

The table below (updated for the error identified by the ERG in D7) provides the results for degarelix against each of the LHRH agonists.

Treatment arm	Totals			Inc. costs	Inc. QALYs gained	Inc. life-years gained	Cost per QALY gained
	Costs	QALYs gained	Life-years gained				
Leuprorelin 3-monthly (Prostap)	£27,479	5.28	9.21				Dominating
Degarelix	£25,939	5.86	9.58	-£1,540	0.58	0.37	
Goserelin 3-monthly (Zoladex)	£27,636	5.28	9.21				Dominating
Degarelix	£25,939	5.86	9.58	-£1,697	0.58	0.37	
Triptorelin 3-monthly (Decapeptyl)	£27,162	5.28	9.21				Dominating
Degarelix	£25,939	5.86	9.58	-£1,223	0.58	0.37	
Leuprorelin monthly (Prostap)	£27,872	5.28	9.21				Dominating
Degarelix	£25,939	5.86	9.58	-£1,933	0.58	0.37	
Goserelin monthly (Novgos)	£27,022	5.28	9.21				Dominating
Degarelix	£25,939	5.86	9.58	-£1,083	0.58	0.37	
Goserelin monthly (Zoladex)	£27,352	5.28	9.21				Dominating
Degarelix	£25,939	5.86	9.58	-£1,413	0.58	0.37	
Triptorelin monthly (Gonapeptyl)	£28,199	5.28	9.21				Dominating
Degarelix	£25,939	5.86	9.58	-£2,260	0.58	0.37	
Triptorelin monthly (Decapeptyl)	£27,555	5.28	9.21				Dominating
Degarelix	£25,939	5.86	9.58	-£1,616	0.58	0.37	
Triptorelin 6-monthly (Decapeptyl)	£27,075	5.28	9.21				Dominating
Degarelix	£25,939	5.86	9.58	-£1,136	0.58	0.37	

D7. **Priority question**: When the model is run with no adverse events and equal efficacy assumed for first-line treatments then predicted life years on chemotherapy and palliative care differs between degarelix and goserelin. Please describe how this error should be corrected.

This error was due to the fact that a different formula was applied for the transition probability from the docetaxel health state to the abiraterone health state for those patients initially on degarelix compared with those patients initially on a LHRH agonist.

The cells in column BK on sheet 'p_FlowGroup_Degarelix' initially had the formula of:

=IF(Include_arb="Yes",(1-p_responding_chemo),0)*(1-SUM(BM18:BN18))

Where:

- SUM(BM17:BN17) is the sum of the cyclical probability of dying from general mortality or cardiovascular specific mortality in cycle 0
- p_responding_chemo is the cyclical probability of remaining in response to docetaxel

In contrast, the equivalent transition probability for patients initially treated with a LHRH agonist is reported in cells in column BT of sheet 'p_FlowGroup_Comparator'. This has the formula of:
=IF(Include_arb="Yes",MAX(1-p_responding_chemo-SUM(BV28:BW28),0),0)

Where:

- SUM(BV28:BW28) is the sum of the cyclical probability of dying from general mortality or cardiovascular specific mortality in cycle 0

The correction has now been made so that the cells in column BK on sheet 'p_FlowGroup_Degarelix' have the equivalent formula as on the patient flow sheet for those initially treated with an LHRH agonist.

Cell BK17, therefore, has the formula:
=IF(Include_arb="Yes",MAX(1-p_responding_chemo-SUM(BM17:BN17),0),0)

This formula has been applied down the column so that in each row it looks up the appropriate cells in each cycle.

Correcting the error, while making the results consistent, has a minimal effect on the overall result. In the base case, the net benefit of treatment with degarelix increases following the change from £13,068 to £13,296 at a threshold of £20,000 per quality-adjusted life-year (QALY). The corrected results section can be found in Appendix 9.

Additionally it was identified that a similar error had been made in the transition probability to palliative care from docetaxel on both the degarelix and the comparator patient flow sheet. The Cell BL17 on sheet p_FlowGroup_Degarelix has therefore been changed from:

=IF(Include_arb="Yes",0,(1-p_responding_chemo))*(1-SUM(BM17:BN17))
To
=IF(Include_arb="Yes",0,MAX(1-p_responding_chemo-SUM(BM17:BN17),0))

The formula has been applied down the column and the equivalent formula has been applied to column BU on sheet p_FlowGroup_Comparator

D8. Please explain the reasons for the differences in total costs and QALYs between: (1) the *de novo* model included in this submission, (2) the model submitted to the All Wales Medicines Strategy Group, (3) the model submitted to the Scottish Medicines Council (4) the model in the Lu *et al* (2011) publication.

The table below shows the differences in costs and total QALYs between the four models and the inputs and structure used to determine mortality, utilities and costs. The timing of the various models (in terms of data available and alterations to the treatment pathway with the approval of abiraterone) should be noted when comparing the results:

- SMC model – submitted in 2010
- Lu *et al*[20] – published in 2011, likely created in 2010, given *BNF* costs date supplied
- AWMSG model – submitted in 2012, following approval of abiraterone
- Submitted model – 2013, following publication of cardiovascular data and pooled analysis of degarelix trials.

In terms of the QALY calculations, the main differences between the models are as follows:

Factors predominantly affecting the total QALYs on both arms

- The Lu *et al* model focuses on a metastatic population; thus, a much higher mortality rate is used and the life-years, and therefore QALYs, on both arms are lower.
- The AWMSG model has lower QALYs than the SMC model and the model submitted to NICE, as the relative survival data derived from Scottish mortality statistics were applied differently to the SMC model (parametric curve rather than ordinary least squares [OLS]) and the link between PSA progression and mortality was not included. In the submitted model, the use of PSA progression-specific mortality rates reduces mortality prior to progression compared with the original Scottish data. This reduced rate was calculated using the proportion of patients with metastatic disease in the overall prostate cancer population. Mortality is then increased post progression for metastatic patients.
- In addition, the utility values used vary between the NICE model and the AWMSG and SMC models (and Lu *et al*), as analysis of available trial data and a thorough literature review were undertaken to inform the development of the NICE model. This resulted in higher utilities in later lines of therapy than in the other models but similar utilities for the hormonal therapies.

Factors predominantly affecting the incremental QALYs

- The Lu *et al* model assumes that difference in utility is only derived from the prevention of events and does not contain the latest data showing that treatment with degarelix delays progression; therefore, the incremental QALYs are substantially lower.
- Comparing the AWMSG model with the SMC model, the incremental QALYs are lower, because:
    - The AWMSG model includes a gain in life-years for use of abiraterone (which applies more to the LHRH arm, as patients progress faster)
    - The utility for patients receiving chemotherapy or abiraterone is higher (which applies more to the LHRH arm, as patients progress faster).
- Comparing the NICE model with the AWMSG model, the incremental QALYs are higher, because:
    - The NICE model contains the beneficial effects of degarelix in the reduction of cardiovascular events for patients with prior cardiovascular disease
    - The NICE model links PSA progression to mortality, using available evidence (supported by evidence from pooled analysis demonstrating a significant gain in overall survival with degarelix)

- Both the above factors mean that there is a life-year gain, as well as a gain in quality of life, included in the submitted model, which was not included in any of the three previous models
- In addition, the submitted model contains the impact of adverse events (cardiovascular events and musculoskeletal events) on utility – this was included as a sensitivity analysis only for musculoskeletal events in the AWMSG model and was not included in the SMC model.

In terms of the cost calculations, the main differences between the models are as follows:

Factors predominantly affecting the total costs on both arms:

- The Lu *et al* model contains only the costs of first-line treatment and musculoskeletal events, the costs of which are also applied for a much shorter duration, as only the metastatic population is considered. The total costs in this paper are, therefore, much lower than in any of the other models.
- The model submitted to NICE contains more types of costs for adverse events; however, it assumes a much lower cost for the majority of the duration of the final health state, with high palliative care costs only used for the final three months of life (in line with the abiraterone submission to NICE).
- The total costs derived from the SMC model are higher than for the AWMSG model, as although the types of costs considered (and their values) are very similar, the AWMSG model assumes lower life-years in both arms

Factors predominantly affecting the incremental costs:

- The Lu *et al* model assumes that difference in utility is only derived from the prevention of events and does not contain the latest data, which show that using degarelix delays progression; therefore, the incremental costs are substantially higher, as no benefit is seen from delaying progression.
- The AWMSG and SMC models contain a patient access scheme for degarelix, whereas the results presented below for the NICE and Lu *et al* models do not.

	Model submitted to NICE	AWMSG model	SMC model	Lu *et al*
Total QALYs				
Total QALYs – degarelix	5.98	3.79	5.55	2.45
Total QALYs – LHRH	5.43	3.58	5.08	2.44
Factors included in the QALY calculation				
Population	Advanced prostate cancer	Advanced prostate cancer	Advanced prostate cancer	Metastatic prostate cancer only
Prostate cancer mortality rates	Relative survival of prostate cancer patients, using parametric fit applied to 2012 Office for National Statistics (ONS) data[21,22]	Relative survival of prostate cancer patients using parametric fit applied to 2011 ONS data	Relative survival of prostate cancer patients using OLS applied to 2010 ONS data	Background mortality 2009 ONS data[21,22] Transitions to death from Bayoumi *et al*[23] 0.043 per month, not time-dependent
PSA progression linked to mortality	Yes	No	No	No
Cardiovascular events linked to mortality	Yes	No	No	No
Included abiraterone	Yes	Yes	No	No: 1st-line treatment only
Source of utilities	Trial data used prior to chemotherapy Bahl *et al* [24]for chemotherapy & abiraterone Sandbolm *et al*[25] for supportive care	Bayoumi *et al*[23] and AWMSG assessment report for abiraterone	Bayoumi *et al*[23]	Bayoumi *et al*[23]
Comparability of utilities for patients with no adverse events	1st-line 0.89 Anti-androgen addition 0.75 Anti-androgen withdrawal 0.75 Chemotherapy & abiraterone 0.69 Supportive & palliative care 0.55	1st line 0.9 Anti-androgen addition 0.8 Anti-androgen withdrawal 0.8 Chemotherapy 0.69 Palliative care 0.4	1st line 0.9 Anti-androgen addition 0.8 Anti-androgen withdrawal 0.8 Chemotherapy 0.4 Palliative care 0.4	Response 0.83 Progressive disease 0.42
Included utility decrements for adverse events	Cardiovascular events and musculoskeletal events	Sensitivity analysis only (musculoskeletal events)	No	Musculoskeletal events
Total costs				

	Model submitted to NICE	AWMSG model	SMC model	Lu *et al*
Total costs – degarelix	£20,508 (without patient access scheme)	£19,289	£31,704	£3,883
Total costs – LHRH	£20,683	£22,922	£34,344	£3,125
Factors affecting total costs				
Costs included	Drug costs for all lines of therapy Resource use costs for all lines of therapy Adverse events costs – musculoskeletal events, cardiovascular events, adverse events associated with abiraterone and chemotherapy Palliative care cost applied 3 months prior to death	Drug costs for all lines of therapy Resource use costs for all lines of therapy Musculoskeletal event costs included as sensitivity analysis only Palliative care cost applied for all patients in the final health state	Drug costs for all lines of therapy Resource use costs for all lines of therapy Palliative care cost applied for all patients in the final health state	Drug and administration costs for 1st-line therapy Adverse events costs – musculoskeletal events and bladder outlet obstruction
Included patient access scheme	Submitted with and without	Yes	Yes	No
Included abiraterone	Yes	Yes	No	No: 1st-line treatment only

D9. Please clarify which surrogate-final relationships are used in the model (e.g., change in PSA progression leads to change in survival) and provide evidence to justify these relationships.

The only surrogate-outcome relationship used in the model is the relationship between PSA progression and an increased mortality risk for patients with metastatic disease. Pages 131–132 outline how this increased mortality risk is calculated. As mentioned, the evidence which supports this relationship is reported in the study undertaken by Hussain *et al* (2009).[26]

The study uses data from a group of 1,078 patients with hormone-sensitive prostate cancer and metastatic disease. The relationship between PSA progression status and overall survival status was investigated. A number of analyses were undertaken, which investigated the HR for mortality between those who had progressed and those who had not progressed according to the different definitions for PSA progression. The HR applied in the model was derived from a multivariate analysis (adjusting for age, ethnicity, site of patient registration, pre-treatment PSA level, bone pain, Gleason sum and late indication registration), which used the definition of PSA recurrence that was used in the CS21 trial (PSA increase of 50% from nadir AND a PSA reading of 5 ng/ml).

The overall mortality in the model was calibrated such that the weighted mortality rate of patients with prostate cancer in the model for both those who had progressed and not progressed was equal to the mortality rate of the general population when adjusted by the HRs derived from the Scottish Cancer Registry data.

Due to the reliance on one source for this surrogate-outcome relationship, a scenario analysis was undertaken, in which this relationship was assumed to not exist. If the relationship is assumed to not exist, the net benefit of treatment with degarelix, at a threshold of £20,000 per QALY, falls from £13,296 to £11,683 (updated for the error identified by the ERG in D7). The evidence, therefore, indicates that degarelix is a cost-effective use of healthcare resources, even if the surrogate-outcome relationship is assumed to not exist.

D10. Section 6.7.3 of the manufacturer's submission (page 85) states that 'only data from those RCTs that compared one-monthly dosing regimens were used'. Please clarify why 1-monthly dosing regimen was used as a criterion for the economic model.

The one-monthly dosing regimen was used, as this is the only licensed maintenance dose and therefore also the only relevant dose in relation to the decision problem. Please see the answer to D1 for further information.

D11. Please clarify the exact definition of response rate in the submission and the economic model.

Response is defined as the absence of PSA recurrence. In CS21 and CS21A, PSA recurrence is defined as an increase in PSA of ≥50% from nadir and a PSA reading of ≥5 ng/ml.

D12. Please clarify whether duration of response and duration of treatment are assumed to be the same in the economic model.

The duration of response and duration of treatment are assumed to be the same in the economic model. This is based on the advice of leading clinicians who indicated that PSA progression is used to determine when patients are taken off first-line treatment and moved onto a second-line treatment (see page 114 of the submission).

D13. Please clarify why PSA response is used in first-line treatment in the economic model, but response rate is used in subsequent lines of treatment. Please specify how much of the QALY gain is due to first-line treatment.

PSA response (PSA progression) was chosen as the most clinically meaningful measure for response – a range of clinical experts have indicated that PSA progression is a crucial prognostic factor for disease progression and, therefore, treatment escalation (outlined on p120 of submission).

The European Association of Urology (EAU) guidelines provide duration of treatment only in terms of duration of response (page 146 of reference 79 [EAU guidelines] in the submission).[27] Response in relation to the diagram (Figure 1 on page 146 of reference 79) is not defined in the surrounding text; however, the title of the diagram: 'Flowsheet of the potential therapeutic options after PSA progression following initial hormonal therapy' suggests that response in this document is also defined as PSA progression. It has, therefore, been assumed that response duration in the EAU guidelines is equivalent to time

to PSA progression. No alternative published information evaluating PSA progression for all subsequent lines of therapy was available.

In a scenario where no gains are included from either cardiovascular events or musculoskeletal events, the incremental QALY gain from use of degarelix is 0.46 (compared with 0.58 in the base case). This QALY gain represents the additional benefit from remaining on treatment with degarelix longer in first line.

D14. Please clarify why the European Association of Urology guidelines and NICE technology appraisal guidance 259 'Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen' studies were selected to base response on subsequent lines of treatment? Please describe how these studies were identified and selected. Please clarify how the distributions for duration of response were estimated in these studies and used in the economic model.

The NICE technology appraisal guidance for abiraterone was selected as the most relevant UK source for duration of response to abiraterone. The NICE appraisal of docetaxel does not contain the duration of response to docetaxel (as progression was not included within the Phase III trial informing the submission) and the model also does not include an estimation of duration of response. The EAU guidelines were, therefore, selected for all other treatments as no NICE appraisals for LHRH agonists, addition of anti-androgens or withdrawal of anti-androgens are available. The guidelines were selected as the most relevant source, as the same information was not available in either UK guidelines or any other European guidelines.

The distributions for the duration of response for all second-line treatments except abiraterone taken from the diagram on page 146 of reference 79 (converted into probabilities of response and non-response) are shown in the table below, compared with the distributions included in the model.

There was additional uncertainty, in addition to uncertainty around the duration of response, regarding how many patients would progress to later lines of therapy and, therefore, stop receiving previous lines of treatment. This uncertainty was included in the model through the use of wider confidence intervals around the probabilities of response (particularly for the upper end of the range; that is, allowing patients to stay on treatment for substantially longer without progressing to subsequent lines of therapy).

This analysis can be used as a proxy for assuming that only a proportion of patients receive later lines of therapy, such as docetaxel and abiraterone, as:

- In UK practice, prostate cancer patients would not be left without any treatment; that is, LHRH treatment is continued, usually at least until chemotherapy is received
- Docetaxel costs are included in the model as a lump sum based on the average number of UK cycles, meaning that extending the duration of this health state (as a proxy for assuming only a proportion of patients progress to abiraterone) does not incur additional chemotherapy costs.

	Variation in duration of response in EAU guidelines	**Variation in probability of response based upon EAU guidelines**	**Variation included in the model**
Anti androgen addition	4-6 months	0.762-0.834	0.751-0.918
Anti androgen withdrawal	5-6 months	0.805-0.834	0.751-0.918
Docetaxel	10-12 months	0.897-0.913	0.760-0.980

As the cost of abiraterone is high, a scenario assuming no patients achieve this treatment is also provided on page 203 of the submission (updated incremental cost-effectiveness ratio, accounting for error spotted in the model, is £2,072).

D15. Please justify why the algorithm published by Kontodimopoulos *et a*l for mapping the EORTC QLQ-C30 data into preference-based EQ-5D utilities was selected for use in the base case?

As discussed on page 154 of the submission, the algorithm published by Kontodimopoulos *et al*[28] was used in the base case, as it was deemed to provide values that were:

- In greatest accordance with previous studies reported in the literature (this was the substantial advantage compared with the values derived from the mapping algorithm from the SF-36 published by Gray *et al*[29])
- In line with the NICE methods guide (this was the main advantage compared with the values derived from the use of the EORTC-8D published by Rowen *et al,*[30] which were not based on the EQ-5D value set);
- Generated using data from the most comparable population (this was the main advantage compared with the algorithm published by McKenzie and van der Pol,[31] which used data from a population experiencing a particularly severe condition).

Despite the perceived advantages of the values derived using the algorithm published by Kontodimopoulos *et al,* it was acknowledged that there was uncertainty around the health-

related quality of life (HRQL) values used in the model. Scenario analyses were, therefore, undertaken, in which the source was varied. Varying the HRQL source caused the net benefit of treatment with degarelix to range from £9,311 to £15,291 when the threshold was £20,000 per QALY (updated for the error identified by the ERG in D7). In all of the scenarios related to the source of the HRQL values, treatment with degarelix, therefore, remained a cost-effective use of healthcare resources.

D16. Please clarify whether the data used to inform the extrapolation of PSA progression used patient-level time-to-event data or aggregate time-to-event data (page 122)? If the latter, was a simple error-minimising process used or were other more sophisticated approaches (e.g., Guyot *et al*, (2012) BMC Medical Research Methodology, 12:9) used to deal with censoring?

Patient-level time-to-event data were used from the CS21 and CS21A trials to inform the extrapolation of PSA progression. As reported on page 121 of the submission, a number of parametric curves were fitted to the patient-level data and the curve with the lowest Akaike Information Criterion (AIC) score was chosen for the base case.

D17. Please clarify why the cheapest available brand of goserelin (Novgos) was not used in the base case analysis?

Goserelin (Novgos) has only recently been launched and clinicians report that it is currently rarely used. As discussed on pages 112–113 of the submission, goserelin (Zoladex) 10.8 mg was selected as the base case comparator, as it is the most commonly prescribed LHRH agonist. Clinicians indicate that the usage of Novgos is unlikely to rise dramatically. When the treatments are considered clinically equivalent, as is the case of the LHRH agonists, clinicians prefer to prescribe treatments that are administered every three months rather than every month. This is supported by the available market share data, showing <0.1% market share and market share decreasing from January 2012 to December 2012 (see answer to D18).[32]

The results exploring the LHRH agonist with the lowest and highest associated costs were explored in scenario analyses in the submission. The table in the response to question D6 provides the result when goserelin (Novgos) is selected as the comparator. As can be seen, degarelix remains a cost-effective use of healthcare resources, with a net benefit of £12,682 at a threshold of £20,000 per QALY.

D18. Table 6 (page 23) provides details of sales of LHRH agonists in England and Wales. Please provide full information on the source and limitations of this data source. Please explain why the brand of goserelin 'Novgos' and bicalutamide are not included within this table.

The original data detailing LHRH agonist sales in England and Wales was IMS RSA data, to January 2013 (excluding Ferring territories UE1 and UN1). IMS RSA data shows the stock movement from wholesalers to retail pharmacy at a subnational level and may not therefore totally reflective of actual time script requirements (due to stocking, and potentially parallel trade activity). Whilst this is approximately 98% census, the remaining proportion is projected from a panel of pharmacies and is edited to reflect local usage. It does not contain any sales generated and fulfilled within secondary care.

Novgos was not included within the table since the market share for this product is very small, thus not deemed as a relevant comparator to degarelix. In response to this request, Ferring has now provided the market share for Novgos (please see table below) for England and Wales. This market share data is based on value sales, and value market share of this defined marked, based on the value of dispensed products in retail pharmacy for England and Wales.

Product	Calendar Month												
	MTH 01/2012	MTH 02/2012	MTH 03/2012	MTH 04/2012	MTH 05/2012	MTH 06/2012	MTH 07/2012	MTH 08/2012	MTH 09/2012	MTH 10/2012	MTH 11/2012	MTH 12/2012	Grand total
Novgos	0.079%	0.081%	0.065%	0.055%	0.011%	0.007%	0.014%	0.013%	0.007%	0.011%	0.013%	0.011%	0.030%

Source: IMS Xponent BPI Trawling database, August 2013 data[32]

As detailed above, less than 0.1% of patients receiving LHRH agonists received Novgos in 2012. Additional IMS prescription data shows that the number of prescriptions fell throughout the year from 5,790 in January 2012 to 780 in December 2012 indicating that take up of Novgos is neither large nor increasing.

Bicalutamide was not included on the basis that the difference between bicalutamide use as a first-line monotherapy, bicalutamide use for initial protection against clinical flare and bicalutamide use as an adjuvant to LHRH agonists in androgen deprivation (also known as complete androgen blockade) could not be distinguished from IMS data. Furthermore, on the basis of the paucity of RCT evidence to robustly compare degarelix with bicalutamide monotherapy, usage data for bicalutamide were not as relevant to the decision problem in comparison with the LHRH agonists.

D19. The ERG believes that it is most appropriate to assume that treatment with degarelix/LHRH agonists will continue until death. Please explain why this assumption has not been used in the base case analysis. Treatment continuation

until death is considered in a sensitivity analysis in page 187, please specify which treatment effect is assumed in this scenario.

As outlined on page 120 of the submission and in line with the instructions in the NICE methods guide and template, the analysis presented in the base case is in line with degarelix's licensed indication and Summary of Product Characteristics:

'Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators.'

'The Appraisal Committee does not normally make recommendations regarding the use of a drug outside the terms of its marketing authorisation, as published in the manufacturer's summary of product characteristics.'

In accordance with this, the base case model assumed that treatment with degarelix and LHRH agonists stopped when a patient's condition would no longer be categorised as hormone-dependent, as at this stage, their condition would have progressed beyond the licensed indication for degarelix and LHRH agonists.

A scenario was reported, in which this assumption was relaxed. When this assumption is relaxed, the only differential treatment effect incorporated is a continuation of the increased risk of a cardiovascular event for patients treated with LHRH agonists. Conservatively, no treatment effect is assumed in relation to the rate of disease progression.

The scenario analyses reported in Appendix 9 and Appendix 10 are repeated with the two assumptions that:

- Treatment with degarelix/LHRH agonists stops once patients can no longer be categorised as hormone-dependent
- Treatment with degarelix/LHRH agonists continues until death.

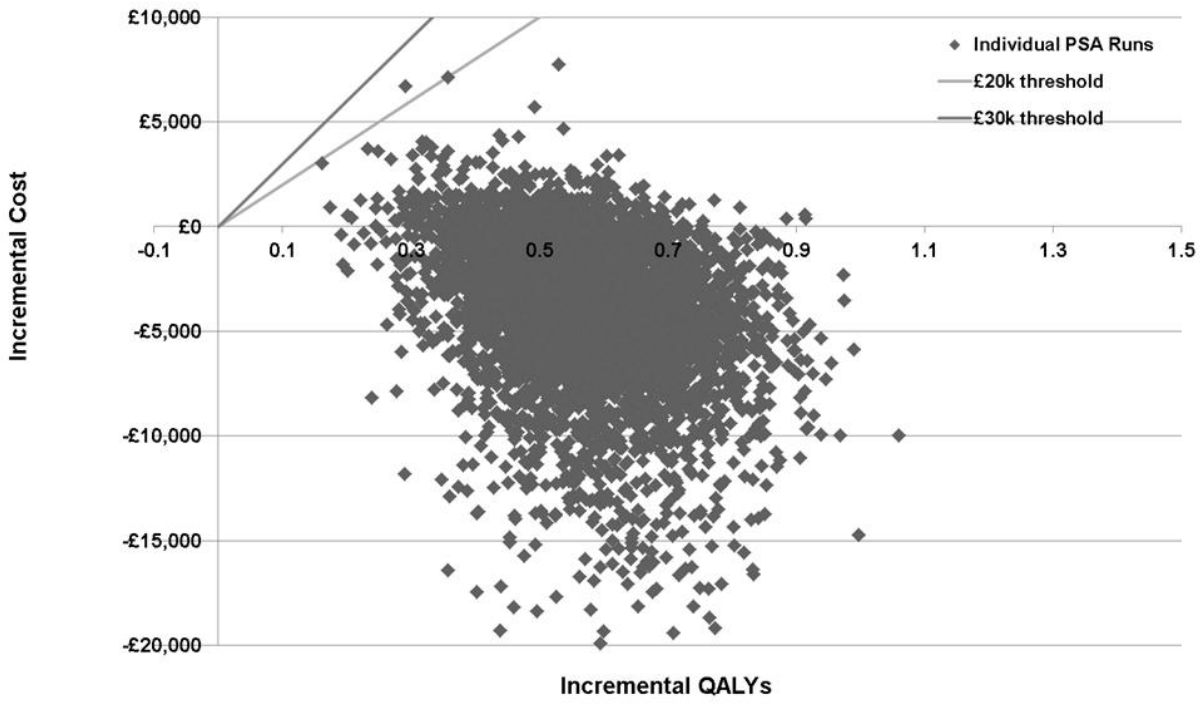
D20. Please explain why the probabilistic sensitivity analysis applies uniform distributions for variables such as hazard ratios and unit costs where lognormal or gamma distributions would normally be used.

To use a log-normal or gamma distribution, we would require information about the shape of the distribution; however, no such data were available and, therefore, a uniform distribution was applied. For the unit cost data, it could be argued from first principles that the data is likely to be skewed and, therefore, a log-normal or gamma distribution might be suitable.

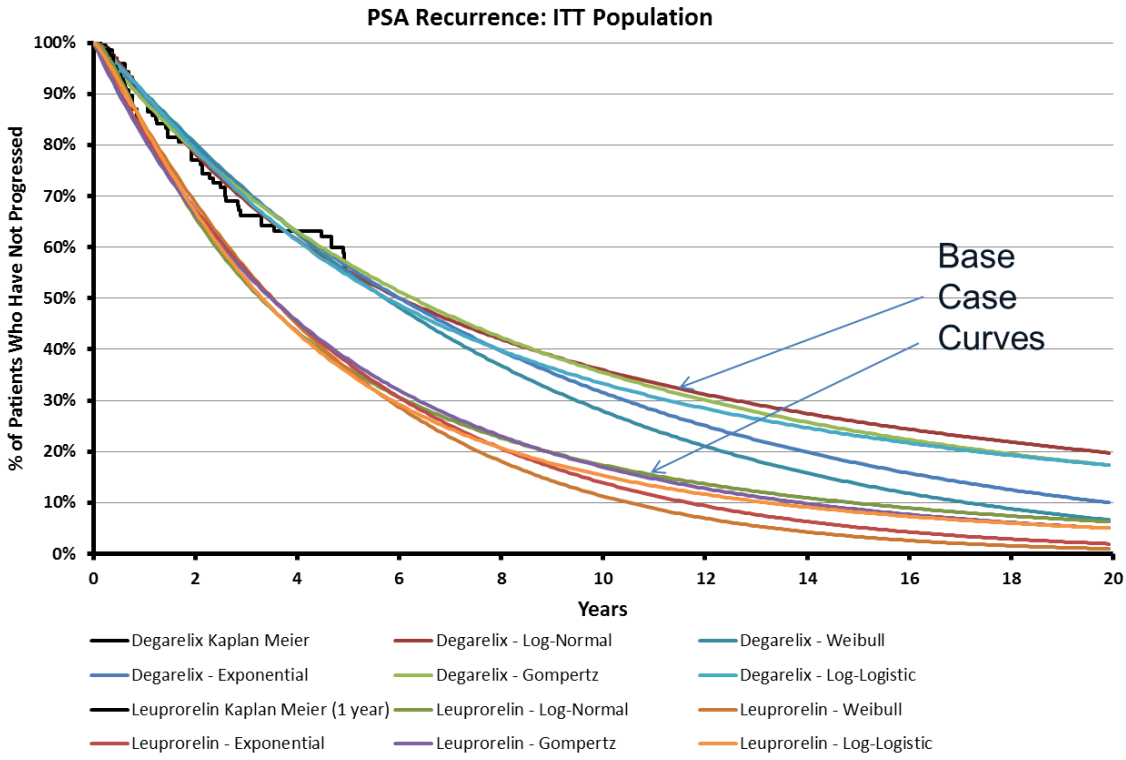
Additional analysis is presented below, using a log-normal distribution for these variables in probabilistic analysis (standard error 10% of the mean for costs and standard error derived from the 95% confidence intervals for the HRs). The model was updated for the error identified by the ERG in D7.

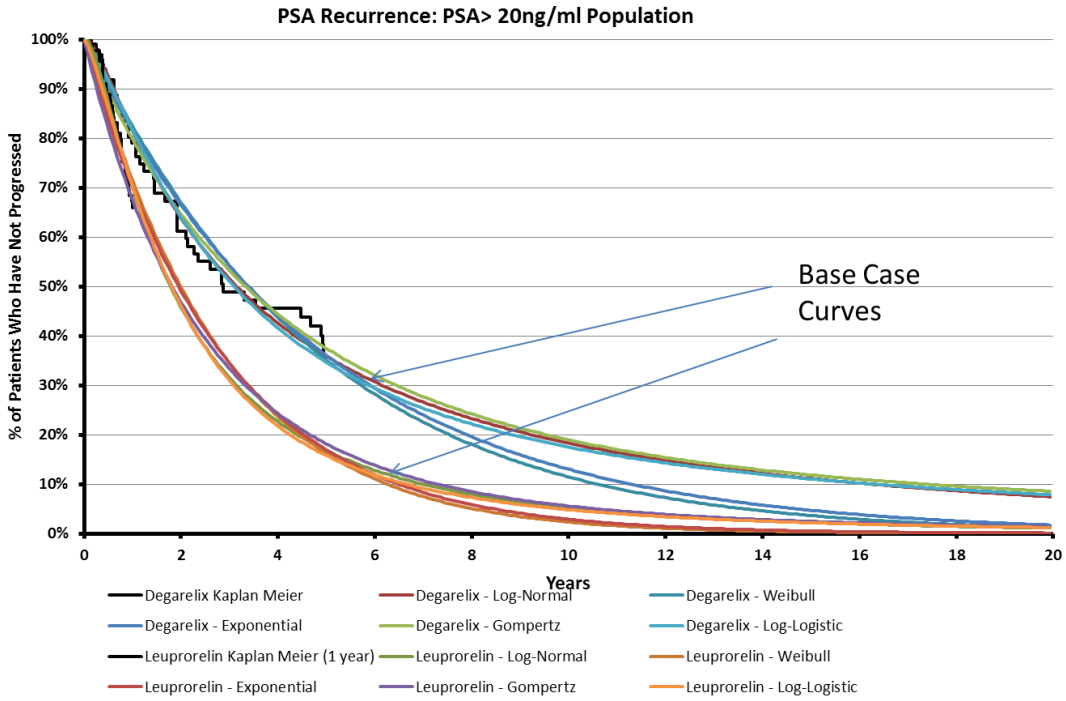
At a willingness-to-pay threshold of £30,000 per QALY, 100% of observations were cost-effective, while 99.9% were cost-effective at a threshold of £20,000 per QALY and 91.5% of observations were cost saving.

Cost-effectiveness plane



D21. Please provide the graphical representation of all curves considered for goodness of fit of the Kaplan Meier data in section 7.





D22. On page 102 it is stated that a pooled analysis concluded that the treatment effect of degarelix is not dependent on disease stage. However, on page 131 it can be read that the efficacy of degarelix is greatest in patients with metastatic disease. Please clarify and justify the rationale for these statements.

To clarify, the pooled analyses detailed in reference 76 shows that endpoints were analysed adjusting for disease stage; the large sample size and similar patient characteristics between the two groups meant significant differences between treatments were found consistently with the Cox (adjusted) and log-rank (unadjusted) methods. Treatment interaction was tested for as part of the analyses for this manuscript (reference 76) and no interaction was found. There is, however, a significant difference in the rate of progression by disease stage independent of treatment effect.[33] This being the case, the benefits of delaying progression are likely to be larger in the metastatic population (who progress faster and are, therefore, more likely to die from prostate cancer).

Section E: Textual clarifications and additional points

E1. The Tyrell *et* al (1998) study compares bicalutamide with castration. Page 84 states that the study uses "3.6mg goserelin" as one of the interventions compared. Please clarify where in the Tyrell (1998) paper this information is stated.

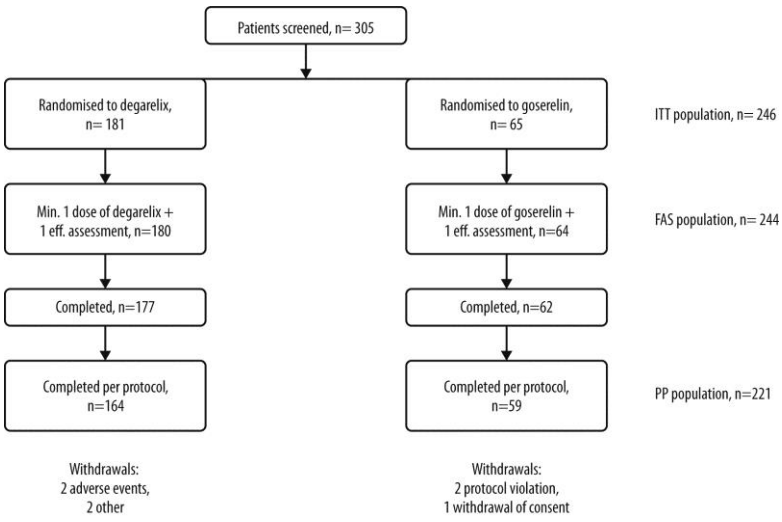
The use of 3.6 mg goserelin by Tyrell *et al* can be confirmed by the associated clinical trial summary report:

'ZENECA PHARMACEUTICALS: Summary: A multicentre randomised trial to compare the effect of two blinded doses of CASODEX (Zeneca 176,334; 100 mg and 150 mg orally daily) and castration in the treatment of advanced carcinoma of the prostate (176,334/0307[34]).'

E2. The CONSORT flow chart for CS30 (page 59) states that only 11 participants completed per protocol in the goserelin group. The ERG believe the correct number for the PP cohort should be 59 – please confirm this is correct.

Yes – the ERG is correct. The PP cohort should be 59. Please see a revised figure below:

CONSORT flow chart for CS30



E3. Please clarify that the data presented in Figure 17 relates to percentage of patients and not events (page 95).

Yes – the data shown in Figure 17 relate to the percentage of patients.

E4. Table 24 (page 125) reports a hazard ratio of 1.71 but does not detail what hazard the values relate to. Table 32 states that 1.71 is the hazard ratio for PSA progression. The economic model ('Efficacy' sheet) states that 1.71 is the hazard ratio for response rate. Please clarify.

It is the HR for PSA recurrence, defined as an increase in PSA of ≥50% from nadir and a PSA reading of ≥ 5ng/ml. As discussed in the response to question D11, PSA recurrence can be considered as a loss of response.

E5. The total QALY gain for goserelin is 5.27 in Table 55 but 5.28 in model. Please clarify.

The value should be 5.28.

E6. In Table 52 on page 190 the comparator is sometimes LHRH agonists and sometimes Leuprorelin. Please clarify.

The comparator in CS21 was leuprorelin; however, in the pooled analysis, data for all LHRH agonists included in the degarelix trials are pooled. For clarity, as there is an assumption of equivalence between LHRH agonists, it would be appropriate to describe outcomes compared with LHRH agonists in all cases.

References

1. Glenny AM, Altman DG, Song F *et al*. Indirect comparisons of competing interventions. *Health Technol Assess* 2005; **9:** 1-134, iii-iv.
2. Heyns CF, Simonin MP, Grosgurin P, Schall R, Porchet HC. Comparative efficacy of triptorelin pamoate and leuprorelin acetate in men with advanced prostate cancer. *BJU Int* 2003; **92:** 226-231.
3. Ferring Pharmaceuticals Ltd. Data on file: Individual Patient Level Data from CS21, CS28, CS30, CS31, CS35 and CS37, 2013.
4. Ferring Pharmaceuticals Ltd. *Data on file: FE200486 CS21: an open-label, multicentre, randomized, parallel group study investigating the efficacy and safety of degarelix one month dosing regimens 160mg (40mg/ml) and 80mg (20mg/ml) ini comparison to Lupron Depot 7.5 mg in patients with prostate cancer requiring androgen ablation therapy*. Langley: Ferring Pharmaceuticals A/S, 2008.
5. Ferring Pharmaceuticals A/S. *Data on file: FE200486 CS28: a randomised, parallel-arm, open-label trial comparing degarelix with goserelin plus anti-androgen flare protection (bicalutamide), in terms of reduction in International Prostate Symptom Score (IPSS), in patients with lower urinary tract symptoms (LUTS) secondary to locally advanced prostate cancer*. Copenhagen: Ferring Pharmaceuticals A/S, 2011.
6. Ferring Pharmaceuticals A/S. *Data on file: End-of-text tables in FE200486 CS30: a randomised, parallel arm, open-label trial comparing degarelix with goserelin plus anti-androgen flare protection (bicalutamide), in terms of prostate size reduction in prostate cancer patients of intermediate-to-high risk, who require neoadjuvant hormone therapy prior to radiotherapy (curative intent)*. Copenhagen: Ferring Pharmaceuticals A/S, 2012.
7. Ferring Pharmaceuticals A/S. *Data on file: End-of-text tables in FE200486 CS31: a randomised, parallel-arm, open-label trial comparing degarelix with goserelin plus anti-androgen flare protection (bicalutamide), in terms of volume reduction of the prostate in patients with prostate cancer being candidates for medical castration*. Copenhagen: Ferring Pharmaceuticals A/S, 2011.
8. Hemels M, Iskedjian M, Iscoe N, Fleshner N, Einarson TR. Meta-analysis of LHRH agonists efficacy in the treatment of metastatic prostate cancer. ISPOR 7th Annual International Meeting. Arlington, Virginia, USA, 2002
9. Seidenfeld J, Samson DJ, Hasselblad V *et al*. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med* 2000; **132:** 566-577.
10. Iversen P, Tyrrell CJ, Kaisary AV *et al*. Casodex (bicalutamide) 150-mg monotherapy compared with castration in patients with previously untreated nonmetastatic prostate cancer: results from two multicenter randomized trials at a median follow-up of 4 years. *Urology* 1998; **51:** 389-396.
11. Akaza H, Aso Y, Koiso K *et al*. Leuprorelin acetate depot: results of a multicentre Japanese trial. TAP-144-SR Study Group. *J Int Med Res* 1990; **18(Suppl 1):** 90-102.
12. Akaza H, Usami M, Koiso K *et al*. Long-term clinical study on luteinising hormone-releasing hormone agonist depot formulation in the treatment of stage D prostatic cancer. The TAP-144-SR Study Group. *Jpn J Clin Oncol* 1992; **22:** 177-184.
13. Bischoff W. 3.75 and 7.5 mg leuprorelin acetate depot in the treatment of advanced prostatic cancer: preliminary report. German Leuprorelin Study Group. *J Int Med Res* 1990; **18(Suppl 1):** 103-113.
14. Mazzei T, Mini E, Eandi M *et al*. Pharmacokinetics, endocrine and antitumour effects of leuprolide depot (TAP-144-SR) in advanced prostatic cancer: a dose-response evaluation. *Drugs Exp Clin Res* 1989; **15:** 373-387.
15. Mazzei T, Mini E, Rizzo M, Periti P. Human pharmacokinetic and pharmacodynamic profiles of leuprorelin acetate depot in prostatic cancer patients. *J Int Med Res* 1990; **18(Suppl 1):** 42-56.
16. Rizzo M, Mazzei T, Mini E, Bartoletti R, Periti P. Leuprorelin acetate depot in advanced prostatic cancer: a phase II multicentre trial. *J Int Med Res* 1990; **18(Suppl 1):** 114-125.

17. Iversen P, Damber JE, Malmberg A, Persson BE, Klotz L. Improved outcomes with degarelix monotherapy compared with luteinizing hormone-releasing hormone (LHRH) agonists plus antiandrogen flare protection in the treatment of men with advanced prostate cancer. 29th Congress of the Scandinavian Association of Urology and Urological Nurses. Vestfold, Norway, 2013
18. Klotz L, Boccon-Gibod L, Shore ND *et al*. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU Int* 2008; **102:** 1531-1538.
19. Oh WK, Landrum MB, Lamont EB, McNeil BJ, Keating NL. Does oral antiandrogen use before leuteinizing hormone-releasing hormone therapy in patients with metastatic prostate cancer prevent clinical consequences of a testosterone flare? *Urology* 2010; **75:** 642-647.
20. Lu L, Peters J, Roome C, Stein K. Cost-effectiveness analysis of degarelix for advanced hormone-dependent prostate cancer. *BJU Int* 2011; **109:** 1183-1192.
21. ISD National Services Scotland. Trends in Cancer Survival in Scotland, 1983-2007. http://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Survival_summary_8307.pdf (last accessed April 2013)
22. Office for National Statistics. Interim Life Tables, England and Wales, 2009-2011. http://www.ons.gov.uk/ons/dcp171778_302422.pdf (last accessed August 2013)
23. Bayoumi AM, Brown AD, Garber AM. Cost-effectiveness of androgen suppression therapies in advanced prostate cancer. *J Natl Cancer Inst* 2000; **92:** 1731-1739.
24. Bahl A, Masson S, Malik Z *et al*. 715 Cabazitaxel for metastatic castration resistant prostate cancer (mCRPC): final quality of life (QoL) results with safety data from the united kingdom (Uk) early access programme (EAP) (NCT01254279) *Journal of Urology* 2013; **189:** e294715.
25. Sandblom G, Carlsson P, Sennfalt K, Varenhorst E. A population-based study of pain and quality of life during the year before death in men with prostate cancer. *Br J Cancer* 2004; **90:** 1163-1168.
26. Hussain M, Goldman B, Tangen C *et al*. Prostate-specific antigen progression predicts overall survival in patients with metastatic prostate cancer: data from Southwest Oncology Group Trials 9346 (Intergroup Study 0162) and 9916. *J Clin Oncol* 2009; **27:** 2450-2456.
27. Heidenreich A, Bastian PJ, Bellmunt J *et al*. *Guidelines on prostate cancer*. Arnhem: European Association of Urology, 2012.
28. Kontodimopoulos N, Aletras VH, Paliouras D, Niakas D. Mapping the cancer-specific EORTC QLQ-C30 to the preference-based EQ-5D, SF-6D, and 15D instruments. *Value Health* 2009; **12:** 1151-1157.
29. Gray A, Clarke P, Rivero O. Estimating the association between SF-36 responses and EQ-5D utility values by direct mapping. 1st Franco-British Meeting in Health Economics. Paris, 2004
30. Rowen D, Brazier J, Young T *et al*. Deriving a preference-based measure for cancer using the EORTC QLQ-C30. *Value Health* 2011; **14:** 721-731.
31. McKenzie L, van der Pol M. Mapping the EORTC QLQ C-30 onto the EQ-5D instrument: the potential to estimate QALYs without generic preference data. *Value Health* 2009; **12:** 167-171.
32. Ferring Pharmaceuticals Ltd. Data on file: IMS Xponent BPI Trawling database, August 2013 data, 2013.
33. Klotz L, Miller K, Crawford DE *et al*. Analysis of disease-control outcomes from five comparative randomised clinical trials of degarelix versus luteinising hormone-releasing hormone agonists. *Eur Urol* 2013**:** [Submitted].
34. Zeneca Pharmaceuticals. *Summary: A multicentre randomised trial to compare the effect of two blinded doses of CASODEX (Zeneca 176,334; 100 mg and 150 mg orally daily) and castration in the treatment of advanced carcinoma of the prostate (176,334/0307)*. www.astrazenecaclinicaltrials.com/_mshost800325/content/clinical-trials/resources/pdf/8609911 (last accessed 2 October 2013)