**Table 18. *Post hoc* exploratory subgroup analyses of PSA from trial CS21**

| Outcome reported | Degarelix | Comparator | Statistical difference |
|---|---|---|---|
| Proportion of patients with baseline PSA >20 ng/ml who experienced PSA progression | 16.0% (16/100) 240/80 mg | 28.0% (26/93) in the leuprorelin group | p=0.04 |
| Median percentage change in PSA levels from baseline to Day 14 | -63.4% (IR –77.1% to –48.4%) 240/80 mg | –17.9% (IR–35.5% to –5.2%) in the leuprorelin group | p<0.0001 |
| Median percentage change in PSA levels at Day 28 | –84.9% (interquartile range –91.6% to –73.2%) 240/80 mg | –66.7% (interquartile range –81.3% to –47.7%) in the leuprorelin group | p<0.0001 |

The MS states on page 63 that flare in those patients that did receive flare protection was lower (72.7%) compared with those who did not use anti-androgen therapy (80.9%).

However the CSR for trial CS21 states that *"in the leuprolide 7.5 mg group, a greater median percentage change in PSA levels from baseline was observed for patients who received anti-androgen therapy compared with those who did not. For patients who started anti-androgen therapy on or before Day 7, median PSA levels were reduced by 61.7% on Day 14 and 89.1% on Day 28. In contrast, median PSA levels were only reduced by 15.3% on Day 14 and 61.7% on Day 28 for patients not on anti-androgens. The median percentage change in PSA levels from baseline for patients in the leuprolide 7.5 mg group who received anti-androgen therapy was similar to that observed for patients treated with degarelix."*(Page 96 of the CSR for CS21). These results are not discussed in the MS.

***Post hoc* PSA subgroup results taking into account anti-androgen flare protection from: Results of the pooled analyses from the trials CS21 and CS35**

The PSA PFS failure rate for degarelix (n=974) versus comparator comparators (n=69) was reported. A hazard ratio of 0.500 was reported to be statistically significant p=0.0073.

It is not clear why data were pooled from trials CS21 and CS35 for this comparison considering that trial CS35 uses an unlicensed (240mg/ 3-monthly 480mg) dose and the comparators were different (leuprorelin and goserelin respectively). Page 70 of the MS states *"in patients with metastatic disease, mean percentage PSA reduction was greater in those receiving degarelix than those receiving an LHRH agonist plus anti-androgen during the first seven months."* However, the data for this metastatic subgroup are not provided.

survival in men with castrate-resistant metastatic disease.[29] A recent review of prostate cancer biomarkers does not recommend the use of PSA progression as a surrogate endpoint.[29] For PSA progression to be appropriate as a surrogate, its association with survival time should be examined using a statistical measure that allows for censoring in both time to death and biomarker progression, such as the Kendall rank correlation coefficient.[29,30] If a strong association is found, it is recommended that this should be tested in clinical trials.

In the meta-analysis of PSA response, sufficient justification has not been given for assuming leuprorelin and goserelin have equivalent efficacy. Statistically significant heterogeneity has been reported for this analysis and the baseline PSA level was suggested by the manufacturer to cause this significant heterogeneity. However, no formal meta-regression was performed to justify this.

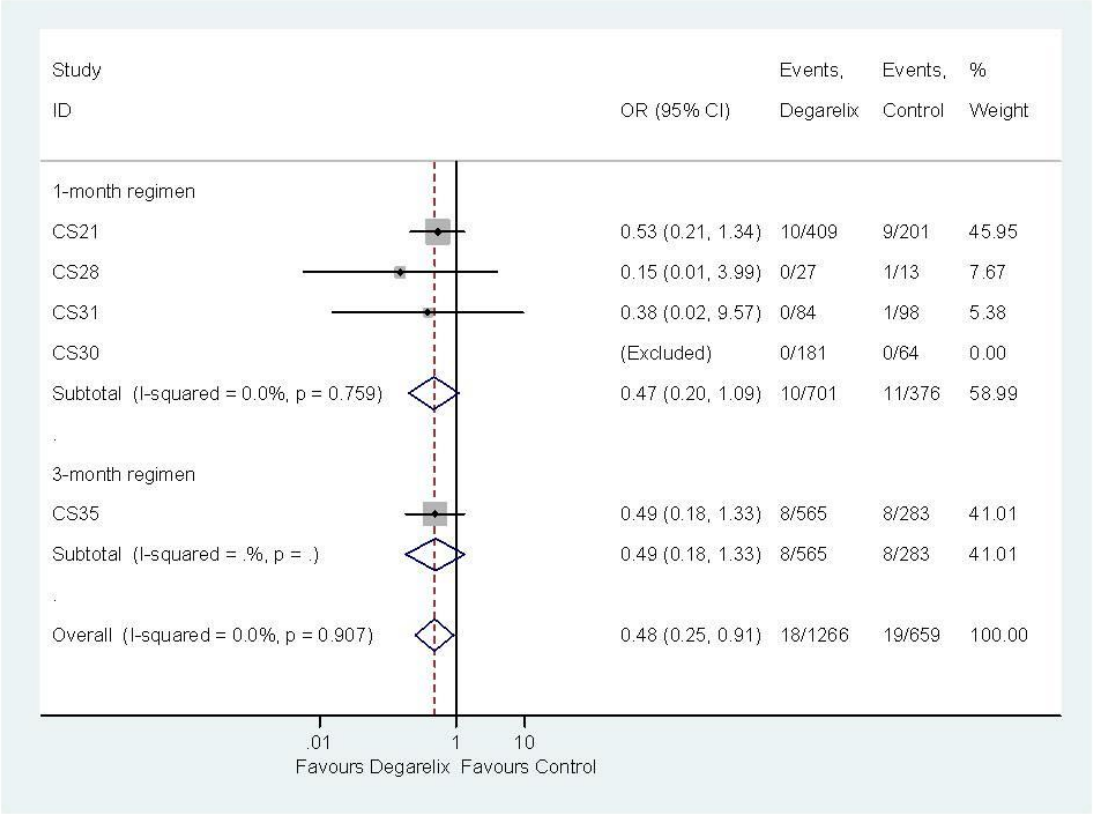
Additionally the manufacturer reports the mean differences between the treatment groups have been used for this meta-analysis rather than the median values "*as the differences between degarelix and the LHRH agonists were symmetrically distributed*" (MS page 76) but the median PSA values were used when reporting the baseline characteristics and analyses for PSA response in the individual trials (MS pages 69/70). The ERG considers that if the data were symmetrically distributed then the median values from the data reported in section 6.5.3 should be similar to the mean values used for the meta-analysis. However, it is not clear that the mean percentage change values are consistently reflective of the median percentage change. For example, the median percentage difference in trials CS30 at day 28 is -0.6 (MS page 69) and the mean percentage difference change used in the meta-analysis at day 28 is -2.79 (MS page 77). These values are not similar and call into question the manufacturer's interchangeable use of median and mean values in the MS.

**Testosterone response**

The ERG requested clarification on the selective exclusion of trial CS35 from certain analyses in the MS. The manufacturer responded that "*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 (I2=92%, P=0.001).*" A forest plot from a meta-analysis that was not presented in the MS was included in the clarification letter and is presented in Figure 6 below.

Furthermore, the use of odds ratio for this analysis has not been sufficiently justified. Using odds ratios does not take into account the different trial durations: 3 months for CS28; CS30; CS31 and 12 months for CS21.

**Figure 7. Meta-analysis of overall survival across trials replicated from page 79 of the MS**




The results from all of the meta-analyses need to be interpreted with caution for the following reasons:

- Sufficient justification has not been given for assuming leuprorelin and goserelin have equivalent efficacy.
- Significant heterogeneity was detected in the meta-analysis of PSA response and formal meta-regression was not performed to justify this.
- Trial CS35 is included in the meta-analysis of overall survival even though it does not use the licensed dose of degarelix (whilst trial CS37 which also used an unlicensed intermittent dosing regimen of degarelix is excluded).
- The use of odds ratio assumes proportional odds over time across trials of varying duration (between 3 months to 12 months).

### 4.5 Conclusions

The ERG is satisfied that all relevant RCTs were included in the clinical effectiveness review for degarelix and the manufacturer was forthcoming in providing clinical study reports and responding to the clarification requests.

As patients with localised and not classifiable prostate cancer were included in the six RCTs of degarelix, the trial population is not entirely reflective of the target population for which degarelix is indicated. For example, 50.3% of the main pivotal trial CS21 population had localised or not classifiable disease. The manufacturer uses of the higher risk (PSA >20 ng/ml) subgroup in the economic analysis, but the baseline characteristics and clinical efficacy results for this subgroup are not provided in the MS.

There is no clear evidence that treatment effect is not dependent on the stage of disease. The manufacturer claims that tests for an interaction between the disease state and treatment effect showed that treatment effect is not dependent on the stage of disease but the ERG could not find evidence substantiating this claim.

Flare protection was not consistently used in the trials for the LHRH comparators. A pooled analysis of degarelix versus LHRH plus anti-androgen flare protection should be interpreted with caution as the manufacturer compares the outcomes of 974 patients who received degarelix with 69 patients who received an LHRH agonist plus bicalutamide.

The manufacturer excluded trials CS35 and CS37 for some analyses on the basis of the unlicensed dosing regimen but subsequently included trial CS35 for selected analyses without sufficient justification. Inappropriately pooled analyses, such as trials CS21 and CS35 which use different dosing regimens, for PSA response between degarelix versus LHRH plus flare protection resulted in a far less favourable PSA response rate for the comparator than the subgroup analyses from trial CS21 alone reported in the CSR. Conversely in instances when trial CS35 are less favourable to degarelix such as in testosterone response, this trial is omitted due to heterogeneity or lack of relevance to the decision problem. The ERG considers that trial CS35 should not have been included in any pooled analyses.

The manufacturer conducted simple pooled analyses instead of meta-analyses from the degarelix RCTs for testosterone response; PSA response; PSA PFS; s-ALP; LHRH agonist treatment plus flare protection subgroup and adverse events. Simple pooling ignores the characteristics of individual studies and relies on the assumption that there is no difference between individual studies which may yield counterintuitive or spurious results[21,23]. The

***ERG critique***

*Equivalence of LHRH agonists:*

The ERG believes that the assumption that all LHRH agonists have equivalent efficacy is unjustified. The MS states that this assumption is justified based on evidence from Seidenfeld *et al* (2000)[36] however this study does not include triptorelin. The ERG believes that it would be more appropriate to model the effects of each LHRH agonist individually. The ERG believes that rather than restricting to a single trial, the economic analysis should incorporate all relevant trial evidence.

*Duration of effect on PSA progression:*

The clinical trial data demonstrate a difference in PSA progression rates between degarelix and leuprorelin for a period of 1 year. It is unknown whether a differing PSA progression rate would be likely to continue after one year or if the difference could just be related to the low levels of flare protection administered in the trial. Clinical advice received by the ERG suggests that it is possible that the Kaplan Meier curves for PSA progression could meet again at a time point later than one year. Hence, the ERG believe that the scenario analysis presented in the MS in which the efficacy of degarelix and LHRH agonists were assumed equal after 1 year is most appropriate.

*Relationship between PSA and overall survival:*

Although the MS presents information on overall survival, the short duration of the clinical trials makes them inappropriate for demonstrating a difference in overall survival. Clinical advice received by the ERG suggests that it is not clear that degarelix offers an overall survival benefit compared to LHRH agonists. The ERG believes that the relationship between PSA progression and overall survival assumed within the MS is associated with uncertainty. For example, in contrast to the evidence reported by Hussain *et al*.,[43], clinical advice received by the ERG stated that "*PSA in this setting is flawed as a universal predictor of mortality*". A study by Scher *et al.*, (2013)[29] suggests PSA progression is inappropriate as a surrogate endpoint in castration-resistant cancer patients[29] The ERG recommends an analysis in which degarelix impacts on PSA progression but not on overall survival. Such an analysis is not presented in the MS and was not undertaken by the ERG due to the limitations of the model structure. However, the ERG did undertake an analysis in which the risk of mortality in metastatic patients is not influenced by progression from first-line treatment.

***Treatment continuation:*** *within the base-case analysis, it is assumed that treatment continues until patients progress beyond advanced disease, in line with the license for degarelix. In some UK centers, LHRH or degarelix treatment is actually continued until death. The impact of continuing treatment until death is modeled.*

***Setting of care:*** *the impact of assuming treatment is carried out by practice nurses or wholly in a hospital setting is tested.*

***Modeling of MSEs:*** *there is an option to include MSEs within the model structure or to remove them. Additionally, the curve choice for the time to MSEs is included in a sensitivity analysis as is the type of MSEs included (solely those that were significantly different between the treatments or all events). Within the base case model, the proportion of patients experiencing mild, moderate and severe events is set equal in both arms, sensitivity analysis is conducted using separate trial results for each arm.*

***Modeling of cardiovascular events:*** *within the base case, it is assumed that patients with a history of CVD have a higher risk of fatal and non-fatal cardiovascular events when receiving LHRH agonists than when not receiving LHRH agonists. The impact of assuming the same rate of cardiovascular events for both arms is tested in a sensitivity analysis, as is the curve choice used to model the time to events.*

***Utilities:*** *the model includes the option to use utilities derived primarily from the literature or from alternative utility mappings, using the SF-12 and EORTC QLQ C30 from the CS21 trial.*

***Anti-androgen choice:*** *the model includes the option to analyse the effects of using cypterone acetate rather than bicalutamide for both flare cover and anti-androgen addition.*

***Abiraterone:*** *the impact of inclusion of abiraterone as second-line treatment following docetaxel chemotherapy is tested in sensitivity analysis.'* (MS page 186)

The MS presents the following result of the sensitivity analyses. These results were produced using the corrected model included within the manufacturer's response to clarifications.

**Table 41: Deterministic model results for sensitivity analyses on parameter values (replicated from MS Clarification Appendix 9 Table 8)**

| 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 patients | No increased hazard of mortality post-progression for metastatic patients | Dominating | £11,683 |
| | ii) Prostate cancer specific mortality incorporated | i) No increased hazard of mortality post-progression for metastatic patients<br>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 | Include no MSEs | £2,152 | £8,853 |
| | | Include all MSEs[a] | Dominating | £13,114 |

| | | | | |
|---|---|---|---|---|
| | compression incorporated in the model | | | |
| *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<br><br>i) First-line utilities<br><br>ii) Post-progression utilities<br>iii) Chemotherapy, abiraterone and palliative care utilities<br>iv) Adverse event utilities | i) Kontodimopoulos Algorithm[b]<br>ii) Kontodimopoulos Algorithm[b]<br>iii) Sourced from systematic search<br>iv) Kontodimopoulos Algorithm[b] | i) McKenzie Algorithm[c]<br>ii) McKenzie Algorithm[c]<br>iii) Sourced from systematic search<br>iv) McKenzie Algorithm[c] | Dominating | £11,469 |
| | | i) Gray Algorithm[d]<br>ii) Gray Algorithm[4]<br>iii) Sourced from systematic search<br>iv) Gray Algorithm[d] | Dominating | £9,311 |
| | | i) Rowen Algorithm[e]<br>ii) Rowen Algorithm[e]<br>iii) Sourced from systematic search<br>iv) Rowen Algorithm[e] | Dominating | £12,458 |
| | | i) Bayoumi *et al*.<br>ii) Bayoumi *et al*.<br>iii) Bayoumi *et al*.<br>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 | Bicalutamide | Cyproterone acetate | Dominating | £13,329 |

| | | | | |
|---|---|---|---|---|
| addition | | | | |
| 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 | £2,089 | £10,627 |
| 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

Following an ERG request for clarification, the manufacturer provided an additional analysis which explores the assumption that all patients receive each treatment line if they are still alive. The scenario analysis assumes that (1) 70% of patients receive docetaxel after failure of treatment on anti-androgen withdrawal, the remaining 30% moving to supportive and palliative care; and (2) 70% of patients receive abiraterone following failure of treatment with docetaxel, the remaining 30% moving to supportive and palliative care. This analysis (which was run with the corrected model) reduced the total costs considerably in both options (by approximately £4,000) and reduces expected QALYs in both arms by approximately 0.05. The incremental costs change significantly from -£1697 to -£322 but the change to incremental QALYs is negligible.

**Table 42: Scenario analysis with 70% of patients going on to receive each of docetaxel and abiraterone (from MS clarification response D4)**

| **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 |

The MS includes a probabilistic sensitivity analysis which samples from uncertain distributions for the majority of the model parameters. The MS clarification response included

updated PSA result which applied lognormal distributions for some hazard ratio and unit cost parameters for which uncertainty had previously been represented using uniform distributions. The PSA results showed that assuming willingness-to-pay thresholds of £30,000 and £20,000 per QALY gained, the probability of degarelix being cost effective was 100% and 99.9% respectively. The probability that degarelix was cost-saving was 91.5%.

***ERG critique***

The set of sensitivity analyses presented in the MS address many of the key areas of structural uncertainty within the model. The model used to undertake the PSA which used updated distributions following the clarification process was not provided by the manufacturer and so this could not be checked by the ERG.

### *5.2.11 Model validation*

The MS reports that the economic model was validated by leading healthcare professionals and reviewed internally by an economist who had not been involved in the development of the model. One year outcomes were compared to clinical trial data for: overall survival; PSA progression; fractures; joint-related signs and symptoms; and cardiovascular events.

***ERG critique***

The ERG validated the model by reproducing selected sensitivity and scenarios analyses and checking that the results changed in the expected manner. This process identified an erroneous difference in the formulae for the transition probabilities formula used for degarelix and the LHRH agonists. This error was corrected by the manufacturer and a corrected model was provided. No other inconsistencies were found with the results presented by the manufacturer. The ERG noted inconsistencies in the reporting of model parameter values. In particular the SCC treatment costs were confusingly reported with different values reported in different places within the MS and no average cost presented.

The ERG suggests that model validation undertaken by the manufacturer was not comprehensive. Considering the plausibility of the extrapolation of data beyond the trial period is a key part of the validation process. The healthcare professionals consulted by the manufacturer did not review the plausibility of the extrapolation of AE data beyond the clinical trial period. The ERG considers that a robust validation using the comparison of model predictions and trial outcomes at one year (MS Table 52) was not possible as uncertainty surrounding the observed data was not presented.

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