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Confidential/strictly confidential

Reference number: AstraZeneca Response to ERG Clarification Questions **[Redacted]**

31 May 2011

Dear Kate,

Please find below AstraZeneca's Response to ERG Clarification Questions on Fulvestrant 500mg.

Yours sincerely,

[redacted]

[redacted]
T: [redacted] | F: [redacted]
E: [redacted]

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SECTION A - Clarifications of the CONFIRM data:

A1. Please provide a version of the Clinical Study Report (CSR), including working links and appendices, and a copy of the protocol and statistical analysis plan for the CONFIRM trial.

Response to A1: commercial in confidence

[redacted]

A2. Neither the average length of follow-up nor the duration of treatment appears to be reported in the manufacturer's submission (MS), it is simply stated that patients were treated until progression. Please provide the information on the length of follow-up and duration of treatment for each study arm and the overall trial population (mean, median, minimum and maximum).

Response to A2: The mean duration of treatment for each study arm was reported in Table B43 in Section 6.2.4. of the manufacturer's submission.

The attached tables A2.1 and A2.2 provide the requested summaries of follow-up for time to progression in months and days for each study arm and the overall population in the full analysis set. The Full Analysis Set (FAS) population includes all randomised patients and compares the treatment groups on the basis of randomised treatment, regardless of treatment actually received (Number of patients, n : Fulvestrant 500mg n=362, Fulvestrant 250mg n=374).

Table A2.3 provides the requested duration of treatment summary for each study arm in the safety set. The total Fulvestrant exposure is defined as [earlier of (date of death, (last dose date + 28)) - first dose date+1]. The safety set population includes all randomised patients who received at least one dose of the study treatment and compares the treatment groups on the basis of treatment actually received. (Number of patients, n: Fulvestrant 500mg n = 361, Fulvestrant 250mg n=374).

Section A Question 2.PDF

A3. If available for each study arm and the overall trial population, for previous adjuvant therapy and previous advanced disease therapy, please provide the proportion of patients who received previous endocrine therapy with an anti-oestrogen (AO) only, aromatase inhibitor (AI) only and both an AO and AI (as in the 'Adjuvant therapy' and 'Advanced disease therapy' rows in table B6 on p47 of the submission).

Response to A3: AstraZeneca received clarification on the ERG requirements for this question on Friday 27/05/2011. It has been agreed that a response will be provided to this question by the new deadline of 03/06/2011.

A4. If available, for each study arm and the overall trial population, for previous adjuvant therapy and previous advanced disease therapy, please provide the baseline characteristics (as in Table B6 of the MS) and the findings for overall survival (OS), time to progression (TTP) and overall response rate (ORR) for patients who received previous endocrine therapy with an AO only, AI only and both an AO and AI.

Response to A4: AstraZeneca received clarification on the ERG requirements for this question on Friday 27/05/2011. It has been agreed that a response will be provided to this question by the new deadline of 03/06/2011.

A5. It is noted from section 1.6 of the MS that more mature survival data are expected. Please provide these data if they are now available.

Response to A5: For the CONFIRM study, an additional survival analysis will be performed after approximately 75% of patients (n = 554) have died. The death event rate is being regularly monitored and from modeling of the deaths recorded on the database as at April 2011, the latest estimated timing for 554 death events is in the first quarter of 2012, with full analysis results to be reported approximately two months later.

A6. No data regarding post-progression treatments given to patients in the CONFIRM trial appear to have been provided. Please provide information on the post-progression treatments given to patients in both arms of the trial and the number of patients who received each treatment.

Response to A6: First subsequent systemic breast cancer therapy received following discontinuation of randomised treatment and details of response to treatment is the only treatment specific data that was collected from patients post-progression. The limited data that we have can be found in Table 11.2.7.1 of the CSR for the CONFIRM study: Summary of best overall tumour response to first subsequent therapy. It is important to note that this data is immature, as is the data available at the time of the initial cut-off for progression free survival, hence there would be insufficient time for follow-up of all patients on first subsequent therapies.

SECTION B - Clarifications of the indirect comparisons data:

Please provide sufficient information with regard to the conduct of the network analyses and provide all relevant data so the ERG would have the capability to re-run these analyses. In addition, please provide further clarification on the following:

B1. It appears on first reading of the MS that the extra trials included in the scenario analyses are those that were excluded from the base case due to ER status (p78 of the MS). However, from an examination of the Appendices, it appears only three of these were included in the scenario analyses (Kaufmann 2000, Dombernowsky 1998 and Gershanovich 1998) while a fourth (Rose 2003) was excluded. An additional trial not referred to elsewhere in the MS (EFFECT) is also included in the scenario analyses. Please provide further information with regard to the inclusion and exclusion of trials for the scenario analyses and also why EFFECT was originally excluded.

Response to B1

1. Inclusion/exclusion criteria for base case analysis

Table B22 (p76 in section 5.7.2) in the MS describes the eligibility criteria used in the search strategy for the base case indirect comparison.
The theoretical basis for these criteria was the licensed indication population for fulvestrant 500mg, namely postmenopausal, oestrogen receptor positive (ER+) women who had received prior anti-oestrogen treatment.

Table B22 Eligibility criteria used in search strategy for indirect comparison heading (pasted from p76 of MS)

	Clinical effectiveness
Inclusion criteria	Population – post menopausal women with locally advanced or metastatic breast cancer who had previously received anti-oestrogen treatment (AO) for early or advanced breast cancer, with documented ER+ receptor status of 70% or more Interventions – fulvestrant 250 mg, fulvestrant 500 mg, anastrozole, megestrol acetate, exemestane, letrozole, medroxyprogesterone acetate Outcomes – overall survival, progression free survival, time to progression, tumour response, response rate, adverse events, health related quality of life Study design – Randomised Controlled Trials (RCTS) Language restrictions - none
Exclusion criteria	Population – men, pre-menopausal women, sample populations where all participants had one or more visceral lesions, patients who had not previously received anti-oestrogen therapy Interventions – trials that did not have at least one arm with the comparator of interested as identified at the scoping workshop (fulvestrant 250 mg, fulvestrant 500 mg, anastrozole, megestrol acetate, exemestane, letrozole, medroxyprogesterone acetate) Outcomes – other than those listed above Study design – anything study design other than a phase II or III RCT Language restrictions – none, other than the fact that results had to be presented in a format that was understandable without translating article for example, results presented in an English abstract or tabulated with standard abbreviations e.g. TTP = time to progression

Sections 5.2.1 (p34) highlighted that the primary trial (CONFIRM) supporting the use of fulvestrant 500mg consists of a mixed population that has either received prior anti-oestrogen (AO) treatment or aromatase inhibitor (AI) treatment. Figure 5 (p34) of the MS showed there was no statistical difference between the post AO and post AI subgroup of the CONFIRM trial in hazard ratios for TTP. Also taking into consideration that CONFIRM was the licensing trial and powered for the total population, it was considered most appropriate to include the total population.

Section 5.7.1 (p77-78) explained why the ER + status criterion was relaxed to at least 70%. CONFIRM, FINDER I and FINDER II were the only trials identified with an entire sample documented as ER+. As it was necessary to have a comparator other than Fulvestrant 250mg for the submission, the criteria was relaxed.

Taking the above points into consideration, a total of 8 trials met the inclusion criteria and were selected for the Base case analysis:

1. CONFIRM
2. FINDER I
3. FINDER II
4. Buzdar 1996/1998
5. Howell 2001
6. Osborne 2002
7. Lundgren 1989
8. Buzdar 2001

However as explained in section 5.7.4 (p113), TTP and OS data was not available for some trials; FINDER I and II did not report sufficient OS data, and Lundgren 1989 reported insufficient data for both TTP and OS. Consequently FINDER I and II were excluded from the network meta-analysis for OS and Lundgren was excluded from both OS and TTP network meta-analysis. Please note that EFECT trial population is post-AI and as such does not meet the eligibility criteria based on the licensed population for fulvestrant 500mg.

2. Inclusion/exclusion criteria for Scenario analysis

The scope specified anastrozole, exemestane and letrozole as relevant comparators (in addition to fulvestrant 250mg) for the submission.

Due to the absence of clinical trial data for the licensed dose of exemestane in a post-AO population where 'at least 70% of the sample had a documented ER+ receptor status' (see section 5.7.2.1 for inclusion criteria used for the network meta-analysis for TTP and OS) it was not possible to include this in the base-case network meta-analysis.

In order to inform the decision problem outlined in the scope (see Section 4 p29), a secondary scenario analysis was undertaken to broaden the decision problem in order to evaluate the cost-effectiveness of fulvestrant 500mg versus exemestane (see section 6.7.9 (p223)).

The target population was broadened to postmenopausal women whose disease has progressed post-anti-oestrogen or post-aromatase inhibitor therapy. Inclusion/exclusion criteria for the scenario analyses were the same as for the base case analysis except for the fact that trials including a post-AI population were allowed, and the ER+ criteria was further relaxed to documented general Hormone Receptor (HR) positive status of at least 50% of patients. This was to allow for exemestane data to be eligible as well as to add data to the letrozole part of the network.
Based on these new criteria for the scenario analysis, the EFECT trial was now eligible (it included a post AI population and had 98% HR+ patients), and the trials by Kaufmann 2000, Dombernowsky 1998 and Gershanovish 1998 were now also eligible due to their HR+ proportion being ≥50%.

The Rose 2003 trial mentioned on p78 of the MS did not meet the >70% ER+ criteria for the base case analysis, and in addition did not meet the criteria of at least 50% HR+ for the scenario analysis either. This trial was therefore not included in either the base case or scenario analyses.

Taking the eligibility criteria into consideration, the following trials were selected for the scenario analyses

1. CONFIRM
2. FINDER I
3. FINDER II
4. Buzdar 1996/1998
5. Howell 2001
6. Osborne 2002
7. Lundgren 1989
8. Buzdar 2001
9. EFECT (Chia 2008)
10. Kaufmann 2000
11. Dombernowsky 1998
12. Gershanovich 1998

However, as already mentioned above, OS data was not available for FINDER I and II, and Lundgren 1989 did not report sufficient TTP and OS data. Additionally, EFECT did not report sufficient OS data; therefore EFECT was not included in the network meta-analysis of OS data.

To summarise the eligibility of the different trials for inclusion in the base case and scenario analyses, please find Table 1 below.

Table1 Summary Tables of Trials eligibility for base case and scenario analyses:

Trials		**Base case analysis**				**Scenario analysis**			
	Previous treatment			Included in base case				Included in scenario analysis	
		ER+≥70%	Eligible	TTP data	OS data	HR≥50%	Eligible	TTP data	OS data
CONFIRM	AO/AI	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
FINDER I	AO/AI	Yes	Yes	Yes	No	Yes	Yes	Yes	No
FINDER II	AO/AI	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Buzdar 1996/1998	AO	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Howell 2002	AO	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Osborne 2002	AO	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lundgren 1989	AO	Yes	Yes	No	No	Yes	Yes	No	No
Buzdar 2001	AO	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
EFECT (Chia 2008)	AI	Yes	No			Yes	Yes	Yes	No
Kaufmann 2000	AO	No	No			Yes	Yes	Yes	Yes
Dombernowsky 1998	AO	No	No			Yes	Yes	Yes	Yes
Gershanovich 1998	AO	No	No			Yes	Yes	Yes	Yes

B2. Currently the assessment of proportional hazards for TTP is based only on data from the CONFIRM trial but a parametric model is fitted to all trials. Please provide justification for fitting the same parametric model function to all other trials in the network analysis.

Response to B2: Within clinical trials, time-to-event data like TTP and OS are often reported as hazard ratios, derived from the Cox proportional hazards model. While this is a statistically valid summary statistic, it does not provide a summary of the average survival or progression-free survival for each treatment arm, which is needed for cost-effectiveness analysis. Therefore, it is necessary to use a parametric model to estimate average survival and progression-free survival for ABC patients for the baseline and comparator treatments.

The pivotal CONFIRM trial included the treatment of interest (Fulvestrant 500mg), the common comparator (Fulvestrant 250mg) and represented the largest study (See Table 1) with the longest follow-up period as illustrated in Figure 1. This therefore makes it the most valid source to identify the most appropriate distribution.

Table 1: ITT Sample size per study included in the TTP analysis

	F500	F250	F250 LD	Anas 1	MA	Letro 0.5	Letro 2.5	**N total**
CONFIRM	362	374						**736**
FINDER 1	47	45	51					92
FINDER 2	46	47	51					93
Howell 2002		222		229				451
Osborne 2002		206		194				400
Buzdar 96/98					253		263	516
Buzdar 2001					201		199	400

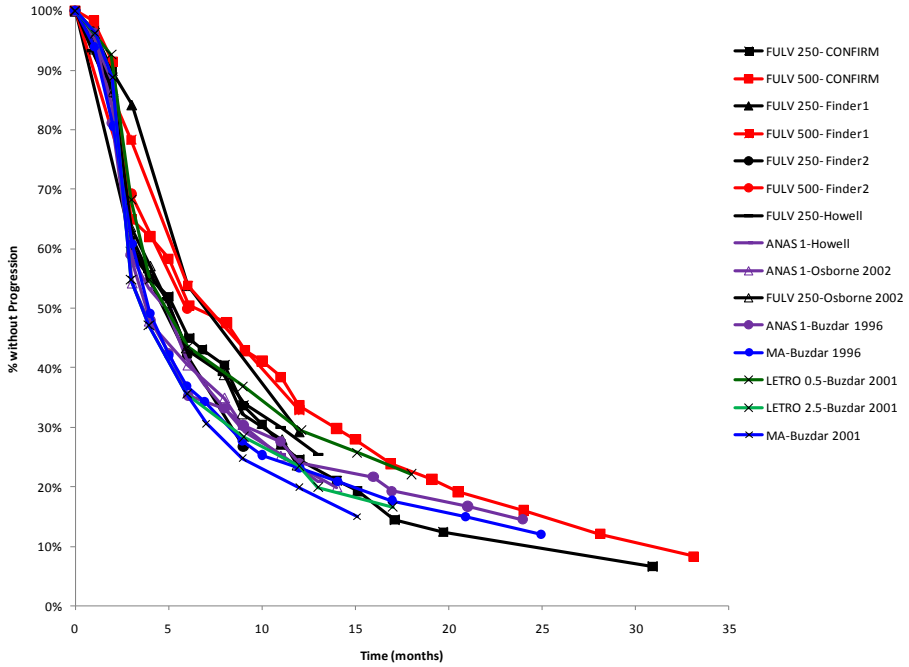
F500=Fulvestrant 500mg; F250=Fulvestrant 250mg; F250LD=Fulvestrant 250mg+ loading dose; Anas 1=Anastrozole 1mg; MA=Megestrol acetate 40mg 4 times daily; Letro 0.5=Letrozole 0.5mg; Letrozole 2.5=Letrozole 2.5mg.

Using patient-level CONFIRM dataset, the three most commonly used parametric distributions in NICE technology appraisals (Guyot and Ouwens, 2009) that include Weibull, log logistic and log normal, were evaluated for fit and the results are presented in p 158-159 and Appendix 14 of the MS.

The best-fitting distribution was selected based on the fit of the curve during the trial period as well as the appropriateness of the extrapolation beyond the trial period. To assess the fit during the trial period, the curves generated were compared to the Kaplan Meier curves from the CONFIRM study.

Despite the application of a lognormal parametric survival distribution (to all interventions, the approach used for the network meta-analysis assessed the difference in the shape and scale parameters of the parametric curves of the different interventions modelled, relative to the common comparator (Fulvestrant 250mg). The approach permits results across studies to be synthesized without breaking randomization whilst allowing for great flexibility of survival distributions across interventions. Most importantly, it does not rely on the proportional hazards assumption. This method is explained in more detail in a recent publication (Ouwens 2011, ref 37 in the MS).

Figure 1: Kaplan Meier curves extracted per study



F500=Fulvestrant 500mg; F250=Fulvestrant 250mg; F250LD=Fulvestrant 250mg+ loading dose; Anas 1=Anastrozole 1mg; MA=Megestrol acetate 40mg 4 times daily; Letro 0.5=Letrozole 0.5mg; Letrozole 2.5=Letrozole 2.5mg.

B3. Currently the findings for TTP are presented in a rather complex manner (Tables B35 and B36 on page 117 of the MS) and have not been interpreted or summarised in the text. Please provide a clinical interpretation for the results of the network analysis of TTP, for example, how the findings for each treatment in Table B36 may relate to fulvestrant 250mg or, ideally, fulvestrant 500mg (see also clarification request B7) in terms of their relative effect on TTP.

Response to B3

1. Network meta analysis results for TTP (fulvestrant 250mg comparator)

The difference in scale and shape parameters presented in Tables B35 and B36 describe the TTP curves for each intervention (Figure 24 p118), relative to the scale and shape parameters of the common (baseline) comparator (fulvestrant 250mg). The curve for fulvestrant 500mg is above all the others (signifying improved TTP) relative to the baseline comparator and to the other treatment presented

The sign of the difference in scale shown in Table B36 indicates whether the treatment improves TTP more than the comparator ie if the difference in scale is positive then the treatment is better, if the difference in scale is negative the comparator performs better. If the 2.5th and 97.5th percentiles are of the same sign then the difference is statistically

significant. Results shown in Table B36 suggest that Fulvestrant 500mg (and Letrozole 0.5mg) result in significantly better TTP than fulvestrant 250mg whereas Anastrozole 1mg results in significantly worse TTP than Fulvestrant 250mg. There were no statistically significant differences in TTP between the remaining treatments compared with fulvestrant 250mg.

2. Network meta analysis results for TTP (fulvestrant 500mg comparator) [from answer to B7 query]

The base case analysis was rerun using fulvestrant 500mg as comparator and the results are presented in the answer to B7. The results are interpretable in the same way as described above.

The results show that Fulvestrant 250mg and Anastrozole 1mg (and Megestrol acetate 40mg) result in significantly worse TTP than Fulvestrant 500mg, and that Letrozole 2.5mg (Fulvestrant 250mg LD and Letrozole 0.5mg) do not affect TTP significantly compared with Fulvestrant 500mg.

B4. For all the trials included in the network analyses, please provide the numbers of events and numbers at risk for each time point as extracted from the Kaplan Meier curves, for both OS and TTP, and any directly presented estimates of logHR and SE (logHR) where available from trial reports.

Response to B4

[redacted]

Time to progression

Appendix 7 in the submission presents the dataset extracted from the studies in terms of the times and the proportion of patients with progression for the base case (Pg. 328-329) and alternative scenario (Pg. 335-336). The actual dataset analyzed for TTP and the corresponding calculations are presented in an attached spreadsheet [redacted] The dataset is based on the ln(-ln(%events)) and the associated standard error for time points between which at least 5 patients had an event. The number of events and numbers at risk for each time point are included in the spreadsheet, which were used in the calculation of the standard error for the log normal distribution. The calculation was done by using the formula as presented by Kalbfleish and Prentice 1980 (See reference #72 in the submission) to obtain an upper and lower bound for ln (-ln(S(t))). Further we have transformed these into lognormal equivalents:

$$\ln(-\ln(S(t))) \pm z_{\alpha/2}\sqrt{V}$$

$$V = \frac{1}{(\ln(S(t)))^2}\sum_{t_i \le t}\frac{d_i}{n_i(n_i - d_i)}$$

Table 2 provides more detailed explanations of the calculations presented in the spreadsheet.

Table 2: Spreadsheet definitions

Column	Name	Definition in spreadsheet	Notes
A	Time point	=time from x-axis of Kaplan Meier graph	Extracted using DigitizIt software
B	S	=proportion of patients with no event from Kaplan Meier graph	Extracted using DigitizIt software
C	>5 Events	=yes indicates at least 5 events occurred during interval (t to t+1) and the data point was included =no indicates that less than 5 events occurred during interval (t to t+1) and the data point was excluded	This approach was used to avoid underestimating the uncertainty of the parameters
D	S*N	=S*sample size for treatment arm at start of trial	
E	ln(-ln(S))	= ln(-ln(S))	
F	1/ln(S)^2	=1/ln(S)^2	
G	d	=(1-S)*N at beginning of trial	By using 1-S, an upper bound of d is calculated, implying an upper bound of the variance
H	NR	=reported or calculated	See Appendix 17 for details (P. 325)
I	Sum	=macro called “sum_un” described in visual basic to perform sum in the expression of V based on d and NR	Assumes that there is no censoring (i.e. NR+d at start of interval) implying a larger uncertainty estimate
J	se	=sqrt(V(ln(-ln(S)))) =sqrt(1/ln(S)^2*Sum)	
K	lower bound S	= EXP(-EXP(ln(-ln(S))+1.96*Sum))	Assumes normality for ln (–ln(S))
L	upper bound S	=EXP(-EXP(ln(-ln(S))-1.96*Sum))	Assumes normality for ln (–ln(S))

The hazard ratios for time to progression as reported in the studies (included in the base case or scenario analyses) are presented in Table 3. Please note that an analysis using the reported hazard ratios for TTP was not included in the submission.

Table 3: Time to progression hazard ratios reported per study

Reference	Treatment	Comparator	HR	Lower bound	Upper bound	ln HR	se ln HR
CONFIRM	Fulvestrant 500	Fulvestrant 250	0.80	0.68	0.94	-0.223	0.083
Finder 1	Fulvestrant 250 LD	Fulvestrant 250	NR	NR	NR	NA	NA
Finder 1	Fulvestrant 500	Fulvestrant 250	NR	NR	NR	NA	NA
Finder 2	Fulvestrant 250 LD	Fulvestrant 250	NR	NR	NR	NA	NA
Finder 2	Fulvestrant 500	Fulvestrant 250	NR	NR	NR	NA	NA
Howell 2002	Fulvestrant 250	Anastrazole 1	0.98	0.80	1.21	-0.020	0.106
Osborne 2002	Fulvestrant 250	Anastrazole 1	0.92	0.74	1.14	-0.083	0.110
Buzdar 1996	Anastrazole 1	Megestrol acetate 40mg	0.97	0.75	1.24	-0.030	0.128
Buzdar 2001	Letrozole 0.5	Megestrol acetate 40mg	0.80	0.64	0.99	-0.223	0.111
Buzdar 2001	Letrozole 2.5	Megestrol acetate 40mg	0.99	0.79	1.23	-0.010	0.113
Chia 2008	Fulvestrant 250 LD	Exemestane	0.93	0.82	1.13	-0.073	0.083
Kaufman 2000	Megestrol acetate 40mg	Exemestane	NR	NR	NR	NA	NA
Dombernovsky 1998	Letrozole 0.5	Megestrol acetate 40mg	1.04	0.81	1.32	0.039	0.125
Dombernovsky 1998	Letrozole 2.5	Megestrol acetate 40mg	0.80	0.62	1.02	-0.223	0.127
Gersanovich 1998	Letrozole 2.5	AG	0.72	0.57	0.92	-0.329	0.122

Overall survival

For the overall survival analysis the network meta-analysis was based on hazard ratios, which were applied to a Weibull baseline distribution for Fulvestrant 250mg. With the exception of the study by Kaufman et al. 2000, where the hazard ratio was derived from the Kaplan Meier curves (assuming a constant hazard ratio) (See worksheet entitled: *OS Data* in the file *AZ6234A ERG Response - dataset and calculations v1.0.xls*), the overall survival analysis was based on the reported hazard ratios presented on Pg. 323 of the submission. Additional detail is presented in Table 4 relating to the hazard ratio calculations for trials included in the base case or scenario analyses.

Table 4: Overall survival hazard ratios reported per study

Reference	Treatment	Comparator	HR	Lower bound	Upper bound	ln HR	se ln HR	p-value	z score
CONFIRM	Fulvestrant 500	Fulvestrant 250	0.84	0.69	1.03	-0.174	0.102		
Howell 2005 (Howell/Osborne 2002 pooled analysis)	Fulvestrant 250	Anastrozole 1	0.98	0.84	1.14	-0.020	0.078		
Buzdar 1998	Anastrozole 1	Megestrol acetate 40mg	0.78	0.60	1.00	-0.248	0.127	<.025	-1.960
Buzdar 2001	Letrozole 0.5	Megestrol acetate 40mg	0.79	0.62	1.00	-0.236	0.122		
Buzdar 2001	Letrozole 2.5	Megestrol acetate 40mg	0.92	0.73	1.17	-0.083	0.120		
Kaufman 2000 (derived from Kaplan Meier)	Megestrol acetate 40mg	Exemestane	1.17	0.94	1.45	0.155	0.109		
Dombernovsky 1998	Letrozole 0.5	Megestrol acetate 40mg	1.12	0.87	1.44	0.113	0.129		
Dombernovsky 1998	Letrozole 2.5	Megestrol acetate 40mg	0.82	0.63	1.08	-0.198	0.137		
Gersanovich 1998	Letrozole 2.5	Amino-glutethimide	0.64	0.49	0.85	-0.446	0.141		

B5. In table B38 on page 123 of the MS, the following is listed as a limitation of the CONFIRM trial: “The position of the median quartile for TTP in the CONFIRM trial does not represent the scale of the significant difference seen in AUC on the Kaplan-Meier curves as represented by the 0.8 hazard ratio”. Please clarify what is meant by this.

Response to B5:

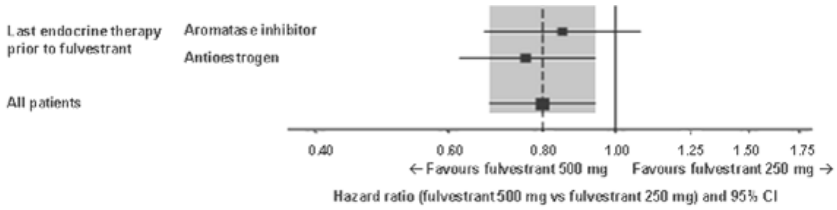
The median quartile for TTP represents the difference in the TTP curves at a single time point, in this case the difference in TTP when 50% of patients have progressed. The Kaplan Meier curves show that the median quartile for TTP in CONFIRM lies at a point where the TTP curves for each of the treatment arms converge, whereas are clearly separated for the majority of the overall follow-up period. Consequently, the median TTP does not reflect the overall difference seen between the two TTP curves. As such, the Hazard ratio of 0.80 which reflects the difference between the two curves over the entire study duration (i.e. the area under the curve (AUC)), may be a more accurate reflection of the scale of the advantage of fulvestrant 500mg over fulvestrant 250mg than the median TTP.

B6. The CONFIRM trial includes patients who have received prior treatment with an AI as well as those that have been pre-treated with an AO, whilst the other trials in the network analysis include only patients that have been pre-treated with an AO. Please provide evidence that these two populations are sufficiently similar so that it can be confidently assumed that the effect estimated in the CONFIRM trial is generalisable to the patients in the other trials.

Response to B6: Further to the justification discussed in Section 5.2.1 of the manufacturer's submission, please see below for the explanations for the generalisability to the populations in the other trials.

- The population recruited to CONFIRM included patients who progression on prior endocrine therapy, including 42.5% progressing on an aromatase inhibitor and 57.5% progressing on an anti-oestrogen.
- There was an overall benefit observed for TTP for 500mg compared to 250mg (HR=0.80; 95% CI = 0.68, 0.94; p=0.006)
- A global interaction test was performed to test whether the treatment effect was consistent across the 6 pre-defined baseline covariate subgroups (Please refer to section 4.1.3 of the CONFIRM study SAP for detail of these pre-defined subgroups). An interaction test was also performed to test whether the treatment effect was consistent across the post-AI/AO subgroups, where post AI/AO is defined as the last treatment received prior to fulvestrant ("post AI : last therapy received, Aromatase Inhibitor (AI)", "post AO L Last therapy received, Anti-Oestrogen Therapy (AO)") The TTP global interaction test p-value = 0.801 [redacted] and the post-AI/AO interaction test p-value = 0.609 indicating that there is insufficient evidence that the treatment effect is different for post-AI and post-AO patients. The numerical differences in the treatment comparison observed are likely to be due to chance.
- The treatment comparison observed for OS was also consistent for post-AI and post-AO patients.
- The TTP Forest plot (Figure 1 – below) of the CONFIRM subgroup analysis (by last endocrine therapy prior to fulvestrant), shows that the subgroups results are consistent with the overall population result.
- It is important to note that the study was powered to show statistical significance for the total population and not within any of the subgroups.

Figure 1: Forest plot of subgroup analysis of TTP by last endocrine therapy prior to fulvestrant (CONFIRM) (see Table **B6** for patient numbers)



B7. Please rerun the network analyses (both OS and TTP) with fulvestrant 500mg as the baseline comparator since they currently compare all treatments to fulvestrant 250mg. Please also provide the probabilities that each treatment is the best.

Response to B7: Time to progression

For time to progression the results of the network meta-analysis are presented in terms of the shape and scale for Fulvestrant 250mg and the difference in the shape and scale relative to Fulvestrant 250mg for the other treatments (see Pg 117 of submission). Since Fulvestrant 250mg provided the link to connect Fulvestrant 500mg into the analysis, these results reflect the basic parameters of the analysis. In response to the ERG question the basic parameters and the variance covariance matrix parameters have been used to derive the parameters versus Fulvestrant 500mg, which are presented in Tables 5 and 6 for the base case analysis (which included the following studies: CONFIRM, FINDER 1, FINDER 2, Howell 2002, Buzdar 1996, Buzdar 2001).

Table 5: Network meta-analysis TTP results: Fulvestrant 500 mg as baseline comparator

Treatment	Scale			Log shape		
	Estimate	2.5th percentile	97.5th percentile	Estimate	2.5th percentile	97.5th percentile
Fulvestrant 500mg	1.90	1.82	1.99	-0.09	-0.24	0.06

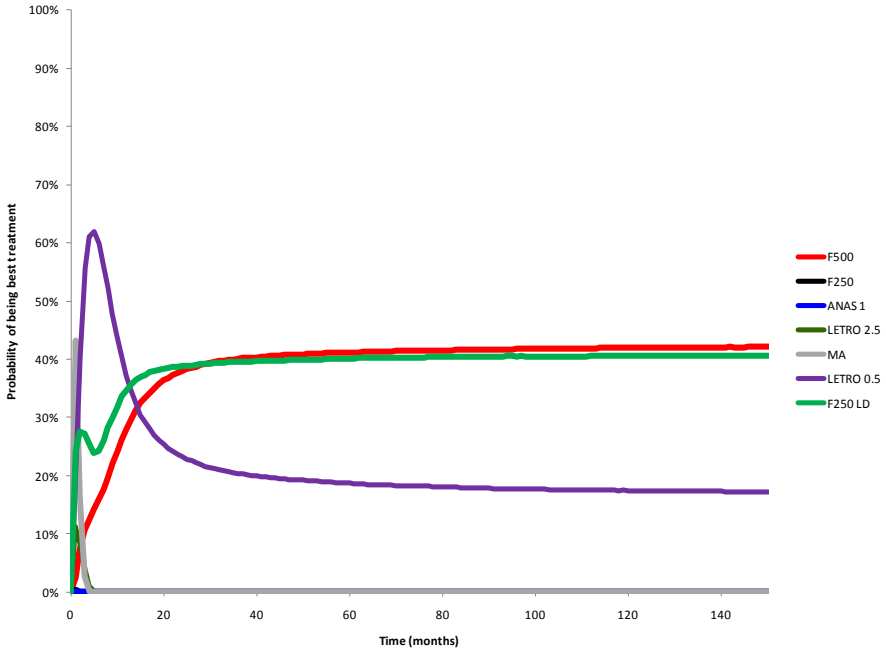
Table 6: Network meta-analysis TTP results: Difference in log normal parameters for treatment alternatives versus fulvestrant 500 mg

Treatment	Difference in scale			Difference in log shape		
	Estimate	2.5th percentile	97.5th percentile	Estimate	2.5th percentile	97.5th percentile
Fulvestrant 250mg LD*	-0.02	-0.30	0.26	-0.30	-0.75	0.29
Fulvestrant 250mg	-0.23	-0.29	-0.17	-0.23	-0.28	-0.12
Anastrozole 1mg	-0.32	-0.44	-0.21	-0.20	-0.17	0.16
Megestrol acetate 40mg*	-0.25	-0.40	-0.09	-0.01	-0.44	-0.03
Letrozole 0.5mg*	0.05	-0.15	0.25	-0.23	-0.39	0.15
Letrozole 2.5mg	-0.18	-0.38	0.01	-0.12	-0.26	0.26

* Excluded from the economic model

The probability of each treatment being the best over time in terms of TTP is presented in Figure 2 based on the results of the network meta-analysis for TTP. This probably was calculated using the number of times the treatment had the highest rank based on the proportion of patients with progression over time. The probability of Fulvestrant 500mg being the best treatment increased over the first 30 months and then remained the highest from 30 months onwards. It should be noted that all treatments included in the network meta-analysis are presented since the probability of being best depends on the number of treatment included, although the loading dose of Fulvestrant 250mg and Letrozole 0.5mg were not included in the economic model as these treatment doses were not of interest.

Figure 2: Probability of being the best treatment based on TTP network meta-analysis



F500=Fulvestrant 500mg; F250=Fulvestrant 250mg; F250LD=Fulvestrant 250mg+ loading dose; Anas 1=Anastrozole 1mg; MA=Megestrol acetate 40mg 4 times daily; Letro 0.5=Letrozole 0.5mg; Letrozole 2.5=Letrozole 2.5mg;

Response to B7: Overall survival

In order to compliment the network meta-analysis results for overall survival presented versus the common comparator (Fulvestrant 250mg) (Pg. 116 of the submission), Table 7 presents the results versus Fulvestrant 500mg for the base case analysis (CONFIRM, Howell 2005 (pooled analysis of Howell 2002 and Osborne 2002), Buzdar 1998, and Buzdar 2001). Table 8 presents the probability that each treatment is best[1].

Table 7: Network meta-analysis results: HR relative to Fulvestrant 500 mg

	HR	2.5th percentile	97.5th percentile
Anastrozole 1mg	1.22	0.94	1.56
Megestrol acetate *	1.56	1.09	2.22
Letrozole 0.5mg*	1.23	0.80	1.88
Letrozole 2.5mg	1.43	0.94	2.19

* HR >1 favours fulvestrant 500mg, **Excluded from the economic model

Comment [HM1]: Please can we add a footnote to state whether a HR < 1 favours fulvestrant or is it a HR> 1?

[1] Best = probability of treatment having the most advantageous effect on the outcome assessed (that is, either the most benefit or the least harm.

Table 8: Network meta-analysis results: Probability of each treatment being the best

Treatment	Probability of being best[1]
Fulvestrant 250mg	2%
Fulvestrant 500mg	78%
Anastrozole 1mg	3%
Megestrol acetate *	0%
Letrozole 0.5mg*	15%
Letrozole 2.5mg	2%

* Excluded from the economic model

SECTION C - Clarifications of the economic data

C1. Please provide Product-limit survival tables (e.g. using SAS LIFETEST procedure or equivalent) from analysis of CONFIRM trial data for the following outputs:

a) Time to progression (TTP)

b) Overall survival (OS)

c) Post-progression survival (PPS)

d) Time on treatment (TOTx)

by treatment arm (Fulvestrant 500mg vs. Fulvestrant 250mg)

and

by whether or not patients were previously treated at any time with an AI

(i.e. 4 outputs x 2 treatment arms x 2 prior use of AIs = 16 K-M analyses)

In each case please provide a table of results showing for each event time:

- Time of event from baseline (days)
- Product-limit estimate of survival proportion
- Standard error of survival proportion
- Number of patients failed
- Number of patients remaining at risk

Response to C1: [**Commercial in confidence**]

[redacted]

SECTION D - Clarifications of the number of patients eligible to receive fulvestrant

D1. In section 7 of the MS, the manufacturer provides estimates for patients eligible for fulvestrant from 2011 up to 2015. Please clarify whether it is assumed if any of the patients may have also received an AI as well as an AO.

Response to D1: To estimate the number of eligible patients for fulvestrant therapy in section 7 of the Manufacturer's submission, it was assumed that in 32% of women, with oestrogen-receptor positive advanced breast cancer and for whom endocrine therapy is appropriate, their disease progresses or relapses while on, or after, other anti-oestrogen (i.e. tamoxifen) therapy (Data on File (FAS/004/AUG10). Of this eligible population, there may be some patients that have received an aromatase inhibitor prior to the anti-oestrogen therapy. However, this is expected to be minimal as patients are not commonly switched from an aromatase inhibitor to an anti-oestrogen therapy in routine clinical practice, except where tolerability issues arise.

Comment [HM2]: Why was 32% assumed? Please provide an appropriate reference for this assumption.

D2. According to section 7.1 of the MS, a total of 2,209 patients are potentially eligible for fulvestrant 500mg, out of a population of 11,603 patients, i.e. around a fifth of all patients. In section 7.3, the MS states that the market share for fulvestrant is anticipated to be 1.0% in 2011 (22 patients), rising to 8.5% in 2015 (193 patients). Please clarify why the market share is anticipated to rise to 8.5%.

Response to D2: The market share assumption used in the manufacturer's submission for fulvestrant 500mg is based on internal forecasts for fulvestrant's licensed population and on the assumption that fulvestrant receives a positive NICE recommendation. The expected uptake is based on market research and the historical usage of fulvestrant 250mg. Market research with UK oncologists commissioned by AstraZeneca provided evidence that there would be a relatively low uptake of fulvestrant 500mg in the indication under review as part of the NICE submission. A significant proportion of current fulvestrant 250mg usage is third or fourth line use after aromatase inhibitors. The market share forecast, however, takes account of the low usage of fulvestrant 250mg in its licensed population (i.e. post-oestrogen therapy) since its launch in 2004.

SECTION E – References

E1. Please provide in electronic format, copies of all documents cited in the references, in particular those that are not available in the public domain.

Response to E1: All outstanding references have now been provided.