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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Fulvestrant for the treatment of locally advanced or metastatic breast cancer

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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Fulvestrant for the treatment of locally advanced or metastatic breast cancer

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All authors read and commented on draft versions of the ERG report.

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Abbreviations

ABC	advanced breast cancer
AE(s)	adverse event(s)
AI(s)	aromatase inhibitor(s)
AO(s)	anti-oestrogen(s)
CBR	clinical benefit rate
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CONFIRM	Comparison of Faslodex™ in Recurrent Metastatic Breast Cancer
CR	complete response
CSR	clinical study report
EBC	early breast cancer
EMA	European Medicines Agency
EPAR	European Public assessment Report
ER / ER+	oestrogen receptor / oestrogen receptor positive
ERG	Evidence Review Group
FACT-B	Functional Assessment of Cancer Therapy - Breast
FDA	Food and Drug Administration
FINDER	Faslodex™ Investigation of Dose evaluation in Oestrogen Receptor-positive advanced breast cancer
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRQoL	health related quality of life
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
LABC/MBC	locally advanced or metastatic breast cancer
LYG	life years gained
MS	manufacturer's submission
NICE	National Institute for Health and Clinical Excellence
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression- free survival
PgR / PgR+	progesterone receptor / progesterone receptor positive
PR	partial response
PSA	probabilistic sensitivity analysis
QALY	quality adjusted life years
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours

SAE(s)	serious adverse event(s)
SD	stable disease
SmPC	Summary of Product Characteristics
STA	single technology appraisal
TTP	time to progression
vs	versus
WTP	willingness to pay

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost-effectiveness evidence submitted to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE from AstraZeneca UK Ltd in support of the use of fulvestrant 500mg (Faslodex^{TM}) for the treatment of postmenopausal women with oestrogen receptor positive, locally advanced or metastatic breast cancer.

Fulvestrant has a marketing authorisation in Europe. It is licensed for the treatment of postmenopausal women with oestrogen receptor positive, locally advanced (LABC) or metastatic breast cancer (MBC) for disease relapse on or after adjuvant anti-oestrogen (AO) therapy, or disease progression on therapy with an AO.

The European Commission approved a change in the licensed dose of fulvestrant from 250mg to 500mg monthly in October 2010. It did so principally on the basis of results from the CONFIRM study, which compared the two doses of fulvestrant in patients who had received prior endocrine therapy, not limited to AO therapy.

In clinical practice, fulvestrant therapy is most likely to be employed if the disease has relapsed after, or progressed during, aromatase inhibitor (AI) therapy. Patients may, or may not have received a previous AO. An application to extend the licensed indication to include patients who have failed on AI therapy was rejected by the European Commission in 2010. Therefore there is some disparity between licensed use and place in therapy as currently used in clinical practice.

1.2 Summary of submitted clinical-effectiveness evidence

The main source of clinical evidence described in the manufacturer submission (MS) is derived from the phase III CONFIRM trial, supported by two dose-ranging phase II trials, FINDER-1 and FINDER-2.

The CONFIRM trial is an international, multi-centre, double-blind, parallel-group randomised controlled trial (RCT) that included 736 patients who had previously received an AO or an AI for adjuvant treatment for early breast cancer (EBC) or for advanced breast cancer (ABC). It compared fulvestrant 500mg with fulvestrant 250mg.

FINDER-1 was a multicentre, parallel-group, double-blind phase RCT conducted in Japan. A total of 143 patients were recruited from 40 centres and randomised 1:1:1 to one of three treatment arms; fulvestrant 500mg, fulvestrant 250mg or fulvestrant 250mg with a loading dose.

FINDER-2 was a multicentre, international, double-blind phase II RCT conducted in seven European countries and Canada. A total of 144 patients were recruited from 34 centres and randomised on a 1:1:1 ratio to receive either fulvestrant 500mg, fulvestrant 250mg or fulvestrant 250mg with a loading dose.

Not all patients had previously received an AO in accordance with the European Union (EU) licence in these three trials, some patients having received an AI for EBC or for ABC, i.e. a mixed population. In CONFIRM, the manufacturer conducted pre-planned subgroup analyses for those whose last endocrine therapy was an AO (post-AO group) or an AI (post-AI group). All three trials excluded patients who had had two or more lines of previous endocrine therapy for LABC/MBC. As such, patients who had received both an AO and an AI for ABC were not eligible for inclusion.

Median time to progression (TTP) was the primary outcome in CONFIRM. The definition of TTP included disease progression or death; this definition is commonly referred to as progression-free survival (PFS). Median TTP/PFS was statistically significantly longer in the overall mixed population for the fulvestrant 500mg arm than the 250mg arm (6.5 vs 5.5 months; hazard ratio [HR]=0.80; 95% CI: 0.68 to 0.94; p=0.006). Improved TTP/PFS was also reported for the post-AO population (8.6 vs 5.8 months; HR=0.76; 95% CI: 0.62 to 0.94; p=0.013) and the post-AI population (5.4 vs 4.1 months; HR=0.85; 95% CI: 0.67 to 1.08; p=0.195); these findings were only significant for the post-AO population.

Secondary outcomes reported in CONFIRM included objective response rate (ORR), clinical benefit rate (CBR) and overall survival (OS). The results suggested that there were no significant differences between the two arms of the trial for these outcomes in the mixed population or post-AO and post-AI subgroups. Nevertheless, OS was numerically greater in the fulvestrant 500mg group compared to the 250mg group (25.1 vs 22.8 months). The log rank analysis suggests that there may be a trend for improved OS for patients in the fulvestrant 500mg group compared with those in the fulvestrant 250mg group (HR=0.84 [95% CI 0.69 to 1.03]; p=0.091). The ERG notes that the OS data from the trial were not mature, with 51% of mortality events occurring at the time of primary data cut off for TTP/PFS. The manufacturer stated that it plans to re-analyse the OS data when 75% of all patients have died.

The primary outcome in the FINDER-1 and FINDER-2 trials was ORR with secondary outcomes also including CBR and TTP. The findings from these trials broadly support the use of fulvestrant 500mg over 250mg as demonstrated in the CONFIRM trial.

The manufacturer conducted a network meta-analysis to compare fulvestrant 500mg with the comparators listed in the final scope issued by NICE. Eight trials were included which enabled a comparison of fulvestrant 500mg to fulvestrant 250mg, anastrozole and letrozole. The findings suggest that fulvestrant 500mg may improve OS when compared to fulvestrant 250mg, anastrozole or letrozole but the findings were not statistically significant. Statistically significant improvements were however reported for TTP/PFS for fulvestrant 500mg when compared to either fulvestrant 250mg or anastrozole.

It was not possible to compare adverse events (AEs) experienced in the fulvestrant 500mg group comprehensively to any other group of patients other than those who received fulvestrant 250mg. There were no apparent differences in AEs between patients receiving different doses of fulvestrant.

The manufacturer provided limited health related quality of life (HRQoL) data comparing fulvestrant 500mg vs fulvestrant 250mg; no statistically significant differences in HRQoL were identified.

1.3 Summary of submitted cost-effectiveness evidence

In the absence of any relevant UK economic evaluations, the manufacturer submitted a *de novo* economic evaluation of fulvestrant 500mg (vs fulvestrant 250mg, anastrozole and letrozole) as a second-line hormonal treatment in postmenopausal women with oestrogen positive, LABC/MBC for disease relapse on or after adjuvant AO therapy, or disease progression on therapy with AO. The manufacturer constructed an EXCEL-based cost-utility model, based on a time-in-state model structure in order to analyse the differences in health benefits, measured in quality adjusted life years (QALYs), and costs between the relevant competing interventions. There are three mutually exclusive health states represented in the model: pre-progression, post-progression and death. The perspective adopted in the economic evaluation was that of the NHS and Personal Social Services (PSS) and costs and benefits were discounted at 3.5% per annum.

In studies of patients who have failed on an AO in which the hormone receptor status of the disease has been confirmed to be positive in ≥70% of patients, there is direct clinical effectiveness evidence comparing fulvestrant 500mg with fulvestrant 250mg from the CONFIRM trial and from FINDER-1 and FINDER-2; however there are no direct clinical effectiveness data comparing fulvestrant 500mg with the other comparators listed in the final scope issued by NICE using these criteria. The manufacturer therefore uses a network meta-analysis approach to generate clinical effectiveness data for use in the economic evaluation.

The results of the manufacturer's base case economic evaluation yields an incremental cost-effectiveness ratio (ICER) of £31,982 per QALY gained for the comparison of fulvestrant 500mg vs letrozole with incremental costs of £12,239 and incremental QALYs of 0.383; based on an incremental ranking of technologies, there is extended dominance for anastrozole and fulvestrant 250mg. The manufacturer showed the ICERs to be robust when subjected to extensive deterministic and probabilistic sensitivity analysis (PSA). The manufacturer also considers exemestane as a comparator in a scenario analysis (broader patient population) and yields an ICER of £38,566 per QALY gained for the comparison of fulvestrant 500mg vs letrozole; based on an incremental ranking of technologies, there is extended dominance for exemestane, anastrozole and fulvestrant 250mg.

[redacted]

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

The manufacturer cites evidence from a large, well-designed trial (CONFIRM) of the clinical benefit of fulvestrant 500mg vs fulvestrant 250mg as a treatment for LABC/MBC following treatment failure with endocrine therapy. The evidence is supported by two phase II trials (FINDER-1 and FINDER-2) and a network-analysis, the conduct of which is well documented in the MS.

Survival estimation aside, the manufacturer's submitted economic model was well constructed and the ERG only identified a few errors in the estimation of costs and benefits.

1.4.2 Weaknesses

Clinical

The only direct comparison of fulvestrant 500mg is with fulvestrant 250mg. Since the European Commission approved the 500mg dose of fulvestrant in March 2010, fulvestrant 250mg no longer has an EU licence and its use at this dose is therefore diminishing in the UK.

While the CONFIRM trial was a large, well-designed trial, the trial population described does not fully match the licensed indication for fulvestrant 500mg as some patients whose last endocrine therapy was an AI were included in the trial. This is largely because of changes in clinical practice in which AIs are commonly now used earlier in the treatment pathway instead of tamoxifen. It is

arguably therefore a limitation of the scope for this STA rather than a weakness of the CONFIRM trial.

Given it is only through the base case network meta-analysis that a relevant comparison between fulvestrant 500mg vs anastrozole and letrozole is possible, the ERG considers that greater emphasis on describing and interpreting the results of the network meta-analysis in the clinical section of the MS would have been helpful.

The base case network meta-analysis was unable to include exemestane as a comparator due to a lack of any relevant trials where ≥70% of patients had hormone receptor positive ABC in a post-AO population.

It was not possible to compare comprehensively the types of AEs experienced by patients receiving fulvestrant 500mg with those receiving AIs due to differences in the reporting practices of different trials.

The MS states (pg 24): "It has been assumed for the purpose of this submission that there has been no adjuvant switch strategies initiated." In the NHS in England and Wales patients are commonly treated using a 'switch strategy'.

Economics

The economic evaluation relies on the use of the clinical effectiveness results from the base case network meta-analysis. The ERG considers that the base case network meta-analysis has two main flaws. Firstly, the manufacturer uses the mixed population data from the CONFIRM trial instead of data from the post-AO population only; fulvestrant 500mg does not appear to have a statistically significant TTP/PFS benefit in post-AI patients and the post-AO and post-AI subgroups appear to be heterogeneous populations. Secondly, the manufacturer uses a log-normal distribution as a basis for estimating pre-progression survival gain and the ERG considers that this approach is inappropriate and leads to an overestimation of TTP/PFS benefit.

1.4.3 Areas of uncertainty

From evidence submitted to the European Medicines Agency (EMA), around two-thirds of post-AO patients and around one-third of post-AI patients in the CONFIRM trial received their last endocrine therapy as part of adjuvant therapy. It is therefore unclear whether the reported improvement for TTP/PFS in the post-AO group over the post-AI group is influenced by where along the treatment sequence the majority of patients received fulvestrant rather than by whether the last prior treatment was an AO or an AI.

[redacted]

1.5 Key issues

The MS states that all patients in the CONFIRM trial received fulvestrant as a second-line treatment. The ERG notes that the definition of first-line treatment in the CONFIRM trial and MS comprises prior endocrine therapy for EBC **or** LABC/MBC.

The population in the CONFIRM, FINDER-1 and FINDER-2 trials and as stipulated in the EU licence and the scope issued by NICE reflect the assumption that first-line treatment for women with breast cancer (EBC or LABC/MBC) is usually an AO (e.g. tamoxifen). Clinical practice is changing in the UK; increasingly many postmenopausal women now receive AIs as their first-line treatment (for EBC and LABC/MBC). Fulvestrant is most likely to be employed if the disease has relapsed after, or progressed during, AI treatment. An application to extend the licensed indication to include patients who have failed on AI therapy was rejected by the European Commission in 2010. Therefore there is some disparity between the licensed use of fulvestrant and its place in therapy as currently used in clinical practice.

Exemestane has correctly been excluded as a comparator in the base case network meta-analysis since the only potentially relevant trial (EFECT) included a population of post-AI patients. However, exemestane is included in the network meta-analysis described in Scenario A which expands the patient population to include post-AO or post-AI patients and allows the entry of studies where ≥50% of patients had hormone receptor positive ABC.This means that the clinical and cost effectiveness of fulvestrant 500mg vs exemestane in post-AO patients is unknown.

The manufacturer has argued that a log-normal distribution should be assumed for all treatments for the TTP/PFS network meta-analysis. However, the ERG considers that the log- normal distribution poorly matches the CONFIRM data, and cannot be justified for other trials featured in the network. A different analytic approach has been used by the ERG based on a two-phase hazard model, which suggests significantly improved TTP/PFS for fulvestrant 500mg compared to all comparators (fulvestrant 250mg, anastrozole and letrozole).

In the economic model, the ERG identified several minor issues that require correction/modification relating to drug wastage, calculation of health state and adverse events costs, use of discounting method and estimation of utility values. However, none of these changes substantially impacts on the size of the revised ICERs. When the ERG makes minor amendments to the manufacturer's economic

model the revised ICER for fulvestrant 500mg vs anastrozole is approximately £30,000 per QALY gained

[redacted] However, the ERG's approach to network meta-analysis does lead to significant changes in the size of the estimated ICERs. Using the post-AO population, the ERG's revised ICER for fulvestrant 500mg vs anastrozole is approximately £35,000 per QALY gained

[redacted]

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problems

In the context section of the MS (Section 2) the manufacturer describes a number of key issues relating to the underlying health problem and associated risk factors.

The manufacturer identifies that over 40,000 women were diagnosed with breast cancer in England and Wales in 2006 while the total number of women with advanced breast cancer (ABC) in England was estimated to be 10,786 in 2009.[1] The MS states that 5% of women presenting with *de novo* breast cancer have advanced disease with distant metastases and it is estimated that around 35% of those presenting with early or localised breast cancer will eventually develop metastatic breast cancer (MBC).[1] Treatment is determined by the extent of disease and a variety of other prognostic factors, including age and hormone receptor status.[2]

As stated in the MS, it has long been acknowledged that many breast cancers are hormone dependent and that hormonal manipulation can affect the progress of the disease. The most important factor determining response to hormonal manipulation is the presence of the oestrogen receptor (ER) in the target tissue.[3] In postmenopausal women with hormone receptor positive disease (i.e. those who are either ER+ or progesterone receptor positive [PgR+]), early breast cancer (EBC) is often treated by a combination of surgery and radiotherapy and, as reducing circulating oestradiol levels has been shown to produce a beneficial effect, adjuvant endocrine therapy is common following surgery. Postmenopausal women with hormone receptor positive disease who present with ABC are generally treated with a sequence of endocrine therapies before receiving cytotoxic chemotherapy. Endocrine therapies used in practice may include steroidal aromatase inhibitors (AIs) (anastrozole or letrozole), non-steroidal AIs (exemestane), ER antagonists (anti-oestrogens (AOs) such as tamoxifen or fulvestrant) and less commonly progestogens (megestrol acetate), either as monotherapy or in combination with another therapy.

In summary, therefore, the MS provides an accurate overview of the underlying health problem, including epidemiology, prognosis and treatment objectives for postmenopausal women with oestrogen receptor positive (ER+), LABC/MBC.

2.2 Critique of manufacturer's overview of current service provision

In the decision problem (MS Section 4) and the context section of the MS (MS Section 2) the manufacturer describes a number of key issues relating to current service provision.

Reducing circulating oestradiol levels has been shown to produce a beneficial effect in women with breast cancer. Therefore the manufacturer notes that endocrine therapy is the mainstay of treatment for postmenopausal women with ER+ breast cancer. Tamoxifen has been the most widely used endocrine therapy for breast cancer in postmenopausal women but despite its demonstrated efficacy, *de novo* or acquired resistance may occur during treatment. In some patients, the disease progresses during tamoxifen therapy because tumour growth may be stimulated by tamoxifen, due to its partial agonist activity on the ER.[4] The NICE guidelines for ABC[1] recommend an AI for the treatment of postmenopausal women with ER+ breast cancer and no prior history of endocrine therapy and for the treatment of postmenopausal women with ER+ breast cancer previously treated with tamoxifen.

It is also stated in the MS that fulvestrant 250mg is well tolerated and has been shown to demonstrate efficacy in women whose breast cancer had progressed following AO therapy.[5, 6] The manufacturer acknowledges that the 2009 NICE clinical guidelines for ABC[1] did not make any recommendations on the clinical or cost effectiveness of fulvestrant; the ERG notes that fulvestrant 500mg was not licensed at the time of publication. The manufacturer explains that the NICE guidelines[1] recommended that evidence was required to determine the optimal sequence of alternative hormone treatment to AIs once a patient progresses.

The manufacturer proposes the use of fulvestrant as a possible alternative in the treatment pathway to receiving a first or second AI (Figure 1) since it is a competitive ER antagonist with an affinity comparable to oestradiol which blocks the trophic actions of oestrogens without any partial agonist (oestrogen-like) activity. It is also the only AO which acts directly on the ER and lacks cross-resistance with tamoxifen.[7] Fulvestrant is licensed for the treatment of postmenopausal women with ER+ LABC/MBC for disease relapse on or after adjuvant AO therapy, or disease progression on therapy with an AO. Thus the ERG notes that according to the EU licence women who have not received an AO previously should not be considered for fulvestrant.

The ERG further notes that the EU licence states previous AO therapy may have been for EBC or ABC, thus the NICE guidelines for EBC/ LABC[8] are also relevant, although these are not referred to in the MS. These guidelines[8] state that: "Current practice is to give low-risk patients tamoxifen for five years." Women who are considered to be at higher risk of disease recurrence should be offered anastrozole or letrozole as their adjuvant therapy.[8] Thus, according to the EU licence, fulvestrant may be offered as first-line therapy to women with ABC if they had received an AO during their treatment

for EBC. The ERG notes that such patients are still labelled as second-line in the MS and economic model (see also Figure 1).

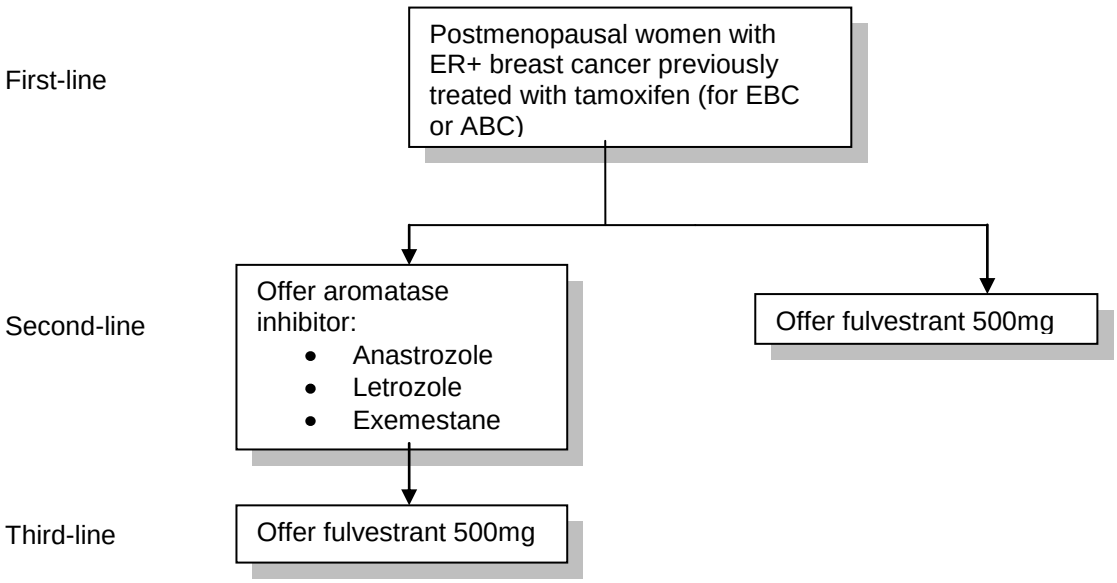

Figure 1: Proposed modification to the treatment algorithm for sequential systemic therapy for women with ER+ advanced breast cancer in the MS

Currently in clinical practice, the ERG believes that fulvestrant is highly unlikely to be offered as a first-line therapy for LABC/MBC; rather it is likely to be considered following treatment with an AI, or a sequence of AIs and/**or** tamoxifen (Figure 2). It is important to note the **or** in the last sentence as currently, some patients treated for LABC/MBC in clinical practice may not have actually received tamoxifen before being considered for fulvestrant. The ERG notes that a submission[9] to the EMA Committee for Medicinal Products for Human Use (CHMP) by the manufacturer to extend the indication of fulvestrant to include patients who had failed on AIs was rejected in October 2010. However, the CHMP considered it acceptable to include relevant data on patients who have failed on prior AO and AI therapy by subgroup in Section 5.1 of the Summary of Product Characteristics (SmPC)[10] as they considered the information may be helpful for the prescriber. These subgroup data derived from the CONFIRM[11] trial are also referred to in Section 4 of the ERG report.

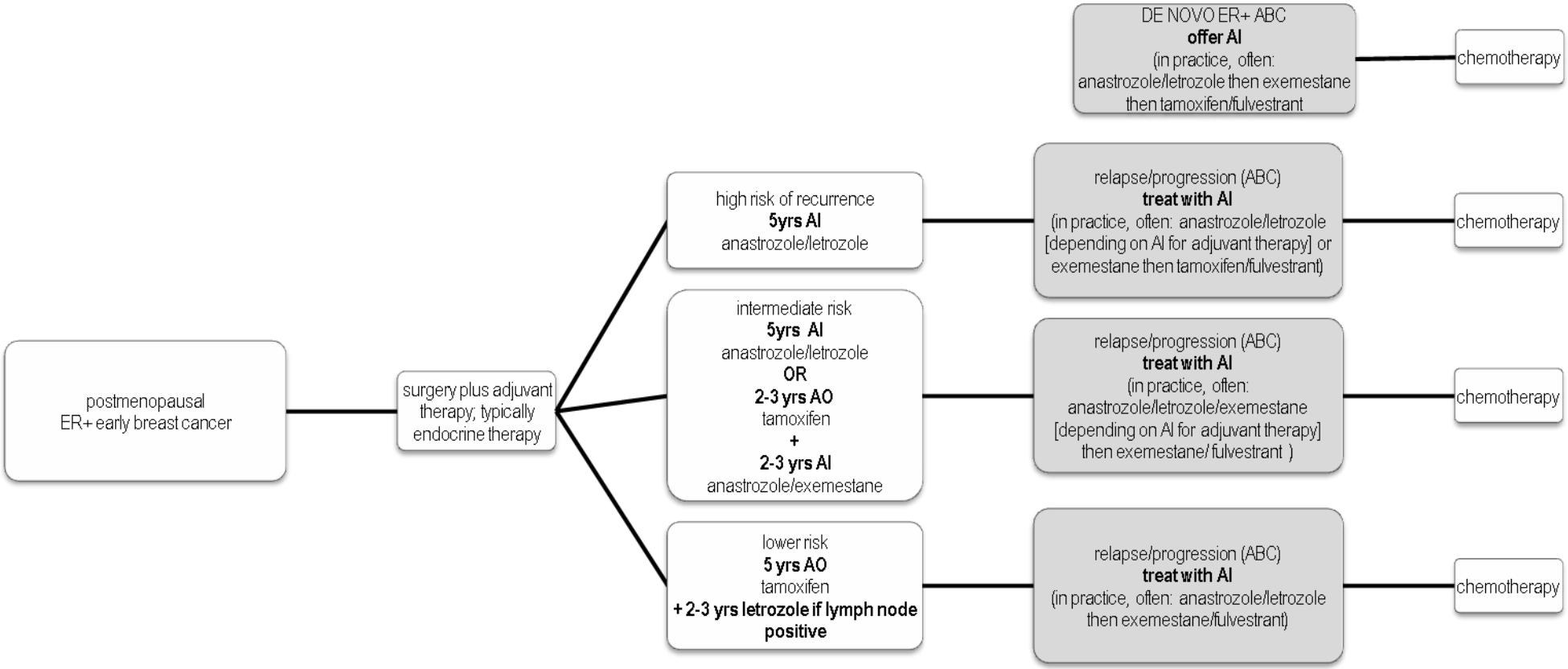

Figure 2: Current treatment pathway for women with ER+ advanced breast cancer based on NICE clinical guidelines and clinical practice

The ERG notes that with the exception of the FIRST[12] trial which considered fulvestrant as a first-line treatment for ABC, data on clinical benefit derived from differing positioning of fulvestrant in the sequence of treatment has mostly been derived from reports from single centres;[13-17] exceptions being a report on the multicentre Belgian compassionate use programme[18] and a retrospective follow-up of the pivotal 020 and 021 fulvestrant 250mg trials.[19] While all of these studies appear to support the assumption that fulvestrant is capable of inducing a response to treatment no matter where along the treatment pathway fulvestrant is offered, the further down the sequence that it is offered, the less likely patients are to respond to treatment. The studies also suggest that following treatment with fulvestrant, a further response is still possible following treatment with another endocrine therapy, regardless of whether the patient had responded to fulvestrant.

The manufacturer also recognises that in the NHS fulvestrant is typically used later in the treatment sequence after tamoxifen and an AI have both been used. It is also argued that the single-centre study reported on by Steger et al[15] demonstrated that earlier use of fulvestrant resulted in better clinical benefit rates for patients. The manufacturer therefore proposes that fulvestrant may be a suitable treatment for any line of treatment for patients with ABC providing they have previously received tamoxifen (Figure 1).

In addition to treatment with tamoxifen and/or AIs, guidelines for EBC/LABC published by NICE,[8] also recommend a "switch strategy" for some patients who start their adjuvant treatment with tamoxifen. After 2 to 3 years of treatment with tamoxifen, anastrozole or exemestane are recommended for patients who are not considered low risk for disease recurrence, who are intolerant of tamoxifen, or for whom tamoxifen is contraindicated. For women with lymph node-positive ER+ early invasive breast cancer, after 5 years of treatment with tamoxifen, a further 2 to 3 years of treatment with letrozole is recommended. Despite these switch strategies being recommended by NICE and commonly occurring in clinical practice in England and Wales, the manufacturer states that for the purpose of this submission, it is assumed that there has been no adjuvant switch strategies initiated.

Assuming the total number of women with ABC in England to be 10,786 in 2009[1] the manufacturer calculated the number of women with LABC/MBC would be 11,603 in 2011. Based on data from the West Midlands Cancer Intelligence Unit, 2009[20] it is estimated that 85% (n=9863) would be ER+. Of these women, endocrine therapy is believed to be an appropriate first-line therapy in 70% of instances (n=6904).[21] Based on data on file[22] the manufacturer believes that 32% (n=2209) of these women would then be eligible for fulvestrant based on the EU licence (i.e. women in whom disease progresses or relapses on or after AO therapy) although only 1% of these patients (n=27) are expected

to receive this; by 2015, the manufacturer has estimated that the market share for fulvestrant would rise to 8.5%, i.e. around 200 patients.

It was not clear from the MS on what evidence the current or projected market share was based. The ERG sought clarification on this issue and the manufacturer responded that the 1% was 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 the manufacturer 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 treatment with AIs. The market share forecast, however, takes account of the low usage of fulvestrant 250mg in its licensed population (i.e. post-AO therapy) since its launch in 2004.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

In the MS (p29), the manufacturer presents the decision problem issued by NICE and the manufacturer's rationale for any deviation from this.

Table 1 Decision problem and manufacturer's responses

Final scope issued by NICE[21]	Decision problem addressed in the submission	Rationale if different from the scope	ERG comment
Population Postmenopausal women with oestrogen receptor positive locally advanced or metastatic breast cancer, whose disease progresses or has relapsed while on or after endocrine (anti-oestrogen) therapy	***Base case analysis:*** Postmenopausal women with oestrogen receptor positive locally advanced or metastatic breast cancer, whose disease progresses or has relapsed while on or after endocrine (anti-oestrogen) therapy*. ***Secondary analysis:*** Postmenopausal women with oestrogen receptor positive LABC/MBC, whose disease progresses or has relapsed while on or after endocrine (anti-oestrogen) or AI therapy* * The inclusion of the post-AI group did not alter the result in favour of fulvestrant 500mg and considering that CONFIRM[11] was the licensing trial and powered for the total population it was considered most appropriate to include the total population	In the base-case analysis, based on the licensed population for fulvestrant 500mg, no published clinical data is available for the comparator, exemestane. As a result, a secondary analysis is presented in Section 6.7.9, where clinical data is available for exemestane.	The ERG considers that the mixed population in the CONFIRM[11] trial is heterogeneous; post-AO and post-AI patients should be treated separately (in line with the EU licence); it is acknowledged that this results in reduced power in CONFIRM[11] A significant proportion of women only received prior endocrine therapy for EBC and therefore received fulvestrant as first-line treatment for ABC; the ERG believes that currently in clinical practice for ABC, fulvestrant is most likely to be used later in the treatment sequence
Intervention Fulvestrant at its licensed dose of 500mg	Fulvestrant at its licensed dose of 500mg	-	-

Final scope issued by NICE[21]	Decision problem addressed in the submission	Rationale if different from the scope	ERG comment
Comparator(s) • Monotherapy or combination regimens of the following anti-oestrogen (endocrine) treatments: • Low-dose (250mg) fulvestrant every four weeks plus loading dose • AIs (anastrozole, exemestane, letrozole)	***Base case analysis***: fulvestrant 250mg (one monthly), anastrozole and letrozole ***Secondary analysis:*** fulvestrant 250mg, anastrozole, exemestane and letrozole	The dosing schedule of fulvestrant 250mg is based on the previous SmPC (once monthly). In the base-case analysis, based on the licensed population for fulvestrant 500mg, no clinical data is available for the comparator, exemestane. As a result, a secondary analysis is presented in Section 6.7.9, where clinical data is available for exemestane.	Exemestane is only included as a comparator in scenario A which allows data from post- AI populations to be included in the network meta-analysis
Outcomes The outcome measures to be considered include: • OS • PFS • ORR • AE • HRQoL	The outcome measures to be considered include: • OS • PFS • ORR • AE • HRQoL	PFS in the model is based on TTP from the CONFIRM[11] trial which included death. This definition of progression is commonly referred to as PFS (Saad et al, 2010)[23] ORR is not routinely assessed in England and therefore was not considered clinically relevant to include in the model	The outcome measures are appropriate
Economic analysis • The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and Personal Social Services perspective.	• Cost-effectiveness presented as incremental cost per quality-adjusted life year (QALY) • Time horizon: lifetime (13 years) • Perspective: NHS and Personal Social Services	-	-

Final scope issued by NICE[21]	Decision problem addressed in the submission	Rationale if different from the scope	ERG comment
Subgroups to be considered None	None	No appropriate subgroup was identified. The analysis of TTP in CONFIRM[11] included 12 pre-specified subgroups, chosen to investigate the consistency of any treatment effect across 6 covariates, which are potential prognostic factors for TTP. The treatment effect was consistent across all subgroups analysed	In view of the fact that not all patients in the CONFIRM[11] trial had received an AO as per the EU licence, the ERG requested additional *post-hoc* subgroup analyses for patients who had been previously treated with an AO only, AI only and an AO and AI

3.1 Population

The patient population defined in the scope by NICE[21] accurately reflects the population for whom the EU licence for fulvestrant 500mg applies. However, the patient population addressed by the direct evidence[11, 24, 25] in the MS is a broader population than this in that it includes patients who failed on a previous endocrine therapy which may have been an AO or an AI. Use of clinical effectiveness data from the broader mixed population in the CONFIRM[11] trial is justified by the manufacturer on the grounds that a subgroup analysis of patients based on their last treatment resulted in similar treatment effects for time to progression (TTP)/progression-free survival (PFS) in both those whose last endocrine therapy was an AO or AI. Considering that CONFIRM,[11] the trial on which the majority of the evidence in the MS is based, was the trial used to gain approval from the EMA CHMP and this was powered for the total population, the manufacturer therefore considered that inclusion of the mixed population in their submission was most appropriate. The ERG notes that when the population is split into post-AO and post-AI populations, the effects for TTP/PFS are statistically significant for patients whose last endocrine therapy was an AO but not for those for whom it was an AI. Thus, using the clinical effectiveness data from the mixed population is likely to result in a conservative estimate of any clinical benefit from fulvestrant 500mg. More problematically, this also suggests that the post-AO and post-AI populations may be heterogeneous populations. This appears to be confirmed when data from the EMA CHMP EPAR[9] are considered in which patients in the post-AO group were typically younger than those in the post-AI group (median 58 vs 64 years), had fewer previous endocrine therapies (3% vs 27% had two prior therapies) and had not been treated with adjuvant therapy for EBC (66% vs 33%). The ERG therefore believes the base case network meta-analysis and economic evaluation that is based upon this should be limited to the post-AO population for two reasons. Firstly, including the mixed population introduces a greater degree of heterogeneity into the indirect evidence derived from the network meta-analysis; secondly, the post-AI population is not an

EMA licensed population. It is acknowledged that this results in reduced power of the CONFIRM[11] trial but that the benefits of this approach (reduced heterogeneity) outweigh this.

The MS did not state how many patients in the CONFIRM[11] trial had previously ever received an AO. Data were however provided by the manufacturer for patients who received an AO for EBC, an AO for ABC and for patients whose last treatment was an AO or an AI. Whereas 57.5% had last received an AO, if it is assumed that the patients who previously received an AO as treatment for either EBC or ABC are mutually exclusive, then the maximum proportion of patients who may have ever received an AO was 77%. The ERG requested additional data from the manufacturer to identify those patients who had received only an AO, only an AI or an AO and an AI, at any time point, for EBC only or for ABC. As suggested from the data originally available in the MS, the data confirm that [redacted] had ever received an AO (including [redacted] who had received both an AO and AI; [redacted] had received AOs only, which it is noted is a similar proportion to those whose last treatment was an AO).

As noted above in Section 2.2, in clinical practice in the UK, patients would rarely be considered for fulvestrant as a first-line therapy for LABC/MBC. The MS does not provide data on how many lines of endocrine therapy patients in the CONFIRM[11] trial had previously received. However, these data were provided in the Clinical Study Report (CSR)[11] and discussed in the EMA European Public Assessment Report (EPAR).[9] It was evident from these data (Figure 3) that, of patients whose last endocrine therapy was an AO, 66% had not received endocrine therapy for ABC, i.e. the majority of patients received fulvestrant as first-line therapy for their LABC/MBC, which is unlikely to reflect current clinical practice in the UK. In the group of patients whose last endocrine therapy was an AI, the proportion of patients who had not received endocrine therapy for ABC was 33% i.e. the majority of patients were receiving fulvestrant as a second-line treatment for LABC/MBC.

Data on the number of previous lines of endocrine therapy for EBC **or** ABC in the EMA CHMP EPAR[9] reported the majority of patients whose last treatment was an AO (96%) or an AI (73%) had received only one previous endocrine therapy; all other patients had received two lines (except one patient who had received none and had therefore in fact violated the inclusion criteria). It should be noted that while patients receiving first-line fulvestrant for LABC/MBC in the CONFIRM[11] trial may not reflect the patient population who would currently receive fulvestrant in NHS clinical practice today, it is nevertheless a patient population compatible with that stated in the decision problem and the EU licence.

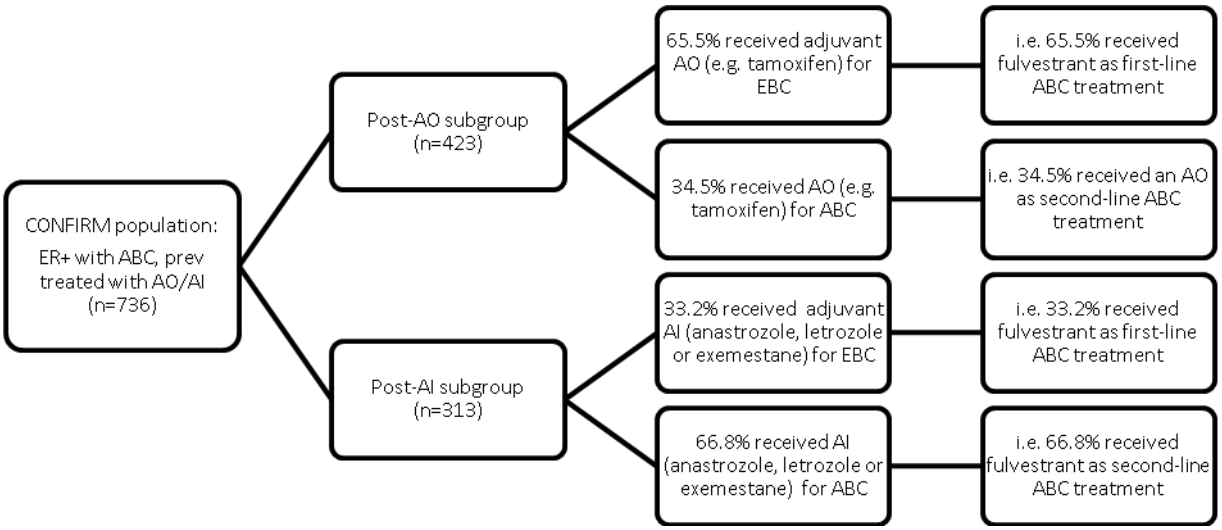

Figure 3 Lines of previous endocrine therapy for LABC/MBC in the CONFIRM trial

3.2 Intervention

Fulvestrant is indicated for the treatment of postmenopausal women with ER+, LABC/MBC for disease relapse on or after adjuvant AO therapy, or disease progression on therapy with an AO. It received its first marketing authorisation from the EMA at a dose of 250mg on the 10th March 2004. It received its current marketing authorisation for 500mg on the 9th of April 2010. A further request for a variation to the market authorisation for fulvestrant for an extension of the licensed indication to include patients who have failed on aromatase inhibitor therapy was rejected by the EMA in October 2010.

The higher dose entails fulvestrant being administered at 500mg each month, with an additional 500mg dose given 2 weeks after the initial dose and supersedes the previous dose of 250mg. Fulvestrant 500mg should be administered as two consecutive 5ml injections by slow intramuscular injection (1-2 minutes/injection), one in each buttock. There are no additional tests or investigations needed for the use of fulvestrant. According to the MS, the average length of course of treatment is 14 months. This is derived from the time-to-progression clinical endpoint in the network meta-analysis rather than the CONFIRM[11] trial.

3.3 Comparators

In the COMFIRM[11] trial (and in the network meta-analysis) fulvestrant 500mg is compared to fulvestrant 250mg. Fulvestrant 250mg was the originally approved dose as a result of showing non-inferiority to anastrozole in two Phase III trials.[5, 6] Aromatase inhibitors were also included as comparators in the network meta-analyses and in the economic evaluation. The ERG believes AIs to be the most appropriate comparators to fulvestrant 500mg since they are the most frequently used

endocrine therapy for LABC/MBC, particularly where an AO has previously been used. The ERG considers that as much emphasis should have been placed on the interpretation of results from the network meta-analyses in the clinical section of the MS as on interpretation of the results from the CONFIRM[11] trial; without the results of the network meta-analyses it is impossible to determine whether fulvestrant is more clinically effective than any other therapy. It is further noted that even using indirect evidence, it is not possible to compare fulvestrant 500mg with exemestane in a post-AO population. Section 4.1.3 explores the reasons for this in further detail.

3.4 Outcomes

The manufacturer has addressed all the outcomes stated in the scope issued by NICE;[21] these include OS, TTP/PFS, objective response rate (ORR), adverse events of treatment (AEs) and health-related quality of life (HRQoL). The ERG notes that although OS is considered to be the most robust outcome in trials of cancer treatments, very few trials of treatments for MBC employ OS as the primary endpoint; indeed the CONFIRM[11] trial from which the majority of the evidence in the submission is derived, specified TTP/PFS as its primary outcome. The definition of TTP used in the MS includes disease progression or death from any cause and is more commonly known as PFS.[23] The manufacturer states that objective response is not routinely assessed in England and was therefore not considered to be clinically relevant and is not included in the economic model; the ERG agrees that the most meaningful outcomes from the CONFIRM[11] trial in relation to both the network meta-analysis and the model are OS and TTP/PFS. Detailed comparison data for AEs was only available for fulvestrant 500mg vs fulvestrant 250mg in the MS. Adverse events were reported inconsistently across the trials included in the network meta-analysis and so additional AE data for the economic was derived by the manufacturer from a network meta-analysis of serious adverse events (SAEs). Health-related quality of life data were collected in a subgroup (n=144) of English and Spanish language speaking patients within the CONFIRM[11] trial. Since the data were collected using a disease-specific instrument (Functional Assessment of Cancer Therapy questionnaire [FACT-B[26]]), these data were unsuitable for use in the manufacturer's economic model.

3.5 Time frame

In CONFIRM,[11] the mean duration of treatment was 10.4 months in the fulvestrant 500mg group. The ERG notes that this differs to the mean duration of treatment of 14 months derived from the results of the network meta-analysis. In the CONFIRM[11] trial the MS reports that 378/736 (51.4%) of the patients had died (175 [48.3%] in the fulvestrant 500mg group and 203 [54.3%] in the fulvestant 250mg group) at the time of the primary data cut off point for TTP/PFS (February 2009).

The mean duration of follow-up in the CONFIRM[11] trial was not provided in the MS. However, on request, the manufacturer reported this to be 9 months (9.9 and 8.1 months for the fulvestrant 500mg

and 250mg groups respectively). For the reporting of AEs, the manufacturer reported the mean duration of follow-up to be 9.2 months (10.3 and 8.2 months for the fulvestrant 500mg and 250mg groups respectively).

In the manufacturer's economic model, the time horizon was 12.5 years.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

Table 2 provides an outline of the manufacturer's approach in terms of key background/clinical information and its location within the MS. Its purpose is to signpost the reader to the main areas of background/clinical information within the MS.

Table 2 Key information in the MS: background, context and clinical effectiveness

Key information	**Section in the MS**
Description of the technology	A
Context	2
Equity and equality	3
Statement of decision problem	4
Literature search	5
Search strategies	5.1 Appendix 2 and 4 and 6
Study selection	5.2
Summary of methodology and study characteristics of relevant RCTs	5.3 Appendix 3
Summary of methodology and study characteristics for indirect comparisons	5.7.1 to 5.7.2.12, 5.7.4 to 5.7.5
Critical appraisal of relevant RCTs	5.4 and 5.7.2.15 Appendix 3 and 5
Results: efficacy and tolerability from direct evidence	5.5
Results: efficacy and tolerability from indirect evidence	5.7.6
Adverse events	5.9
Interpretation of clinical evidence	5.10

4.1.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate.

The manufacturer described the literature searches conducted in January 2010. The ERG is confident that all major electronic databases were searched including MEDLINE, EMBASE, MEDLINE (R) In-Process and the Cochrane Library. All clinical abstracts for the past 2 years from relevant American Society of Clinical Oncology, the National Cancer Institute, and the San Antonio Breast Cancer Symposium were reviewed. The manufacturer provides a clear description of the searches carried out to identify primary relevant research in Appendix 2 of the MS. The comprehensive search strategy used drug names and no language restrictions were adopted. The ERG considers the search strategy to

be appropriate. The ERG conducted its own searches for direct evidence in support of fulvestrant 500mg in October 2010 and again in May 2011 (MEDLINE only) and is confident that all relevant studies were identified by the manufacturer.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The MS provides a detailed report of the inclusion/exclusion criteria applied to the selection of potentially relevant studies. These are described in Table 3. An important exclusion criterion is highlighted by the manufacturer in relation to the proportion of patients in RCTs with ER+ status. The manufacturer stated that some flexibility was required concerning the ER+ status of trial patients as, due to practical reasons it was necessary to have a comparator, other than fulvestrant 250mg, for use in the submission. Key opinion leaders and clinicians were consulted on this issue and no firm criteria with a solid rationale based on evidence could be decided upon. A number of issues were discussed including: only including trials from recent years or excluding trials that had a certain percentage of documented ER- status patients. Since the understanding of the role of ER status in outcomes has developed over time, it was not possible to identify a date that was not completely randomly chosen and as no evidence based rationale could be found for an alternative criteria, given ER status is definitely a variable that effects outcomes, it was decided by the manufacturer that at least 70% of the patient population should have a documented ER+ receptor status. The plan was to reassess this criterion should substantial heterogeneity be detected. The ERG agrees that this was a sensible approach to take. Thus, overall, the ERG is satisfied with the clinical-effectiveness literature review process as described in the MS.

Table 3 Inclusion/Exclusion criteria for clinical effectiveness review

Inclusion criteria	**Population** Postmenopausal women with locally advanced or metastatic breast cancer who had Previously received anti-oestrogen treatment either for EBC or ABC, documented ER+ receptor status of 70% or more **Interventions** Fulvestrant 250mg, fulvestrant 500mg, 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** 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 interest as identified at the scoping workshop (fulvestrant 250mg, fulvestrant 500mg, anastrozole, megestrol acetate, exemestane, letrozole, medroxyprogesterone acetate) **Outcomes** None **Study design** Any 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

4.1.3 Table of identified studies. What studies were included in the submission and what were excluded.

Direct comparisons

The search conducted by the manufacturer identified three randomised controlled trials (RCTs[11, 24, 25] which compared fulvestrant 500mg to fulvestrant 250mg for inclusion in the review (Table 4). The majority of the evidence considered in the MS is appropriately derived from CONFIRM[11] which was the only phase III trial and the largest of the three trials; there were 762 patients in CONFIRM[11] compared to 143 and 144 (92 and 93 respectively excluding the patients who received the fulvestrant 250mg loading dose which was not an identified comparator in the scope[21]) in FINDER-1[24] and FINDER-2[25] respectively. The ERG is confident that all relevant trials comparing fulvestrant 500mg to a relevant comparator are included in the MS.

All three trials[11, 24, 25] excluded patients who had had two or more lines of previous endocrine therapy for ABC. As such, patients who had received both tamoxifen (or other AO) and an AI for ABC were

not eligible for inclusion. However, patients were permitted to have had previous endocrine therapy for EBC.

Indirect comparisons

Three other comparators (anastrozole, letrozole and exemestane) were identified in the final scope[21] issued by NICE. The inclusion of the additional studies resulted in eight[5, 6, 11, 24, 25, 27-29] trials in a network (the additional five[5, 6, 27-29] studies are summarised in Table 5), enabling fulvestrant 500mg to be compared with anastrozole and letrozole. Due to the absence of clinical trial data in a post-AO population in which ≥70% of patients had confirmed hormone receptor positive stats, it was not possible to include exemestane as a comparator in the base-case network meta-analysis. Thus in order to inform the decision problem outlined in the scope,[21] a secondary scenario analysis (using studies with a wider patient population) was undertaken by the manufacturer as part of the economic analysis in order to evaluate the cost effectiveness of fulvestrant 500mg vs exemestane.

The ERG notes that one of these studies (Buzdar et al 1996/98)[28] pools analyses from two separate trials[30, 31] comparing megestrol acetate (which was not a comparator in the scope[21]) to two different anastrozole doses; one trial was based in North America[30] and the other trial was conducted in the rest of the world.[31] This approach to pooling data from two separate trials of the same intervention/comparator from conducted in North America and the rest of the world is similar to the approach taken to comparing fulvestrant 250mg with anastrozole in the 020[5] and 021[6] studies, although a key difference was that the megestrol acetate trials were identical in their design, unlike 020[5] and 021[6] which were open-label and double-blind studies respectively. Therefore the ERG agrees that these megestrol acetate trials[30, 31] should be considered as a single study whereas it is appropriate to consider 020[5] and 021[6] separately.

Inclusion/exclusion criteria for the scenario analysis (Section 5.3.12) were the same as for the base-case analysis except for the fact that trials including a post-AI population were allowed into the network, and the ER+ criteria was further relaxed to documented general hormone receptor positive status (i.e. ER+ or PgR+) of at least 50% of patients. Based on these new criteria for this analysis, the EFECT[32] trial which compared a fulvestrant 250mg loading dose with exemestane in a post-AI population was now eligible. In addition, three other trials[33-35] were now eligible as ≥50% patients had hormone receptor positive ABC; these compared letrozole to megestrol acetate[33] and to aminoglutethimide [34] and compared exemestane to megestrol acetate.[35]

Table 4 RCTs comparing fulvestrant 500mg vs 250mg

Trial	Population	Study arms	References
CONFIRM	• Histological/cytological confirmation of breast cancer • Documented ER+ status of primary or metastatic tumour tissue, according to the local laboratory parameters • Prior treatment with an endocrine agent • Measurable disease as per Response Evaluation Criteria In Solid Tumours (RECIST) criteria OR bone lesions, lytic or mixed (lytic and sclerotic), in the absence of measurable disease as defined by RECIST • Postmenopausal woman • WHO performance status ≤2	• Fulvestrant 500mg (n=362) • Fulvestrant 250mg (n=374)	• Clinical study report[11] • Di Leo et al 2010[36]
FINDER-1	• Histological/cytological Confirmation of breast cancer (from either primary or metastatic tumour) • Documented ER+ status of primary or metastatic tumour tissue, defined as ≥10% positive staining by Immunohistochemistry • Prior treatment with an endocrine agent • Measurable disease as per RECIST criteria • Postmenopausal women • WHO performance status ≤2	• Fulvestrant 500mg (n=47) • Fulvestrant 250mg (n=45) • Fulvestrant 250mg loading dose (n=51)	• Clinical study report[24] • Ohno et al 2010[37]
FINDER-2	• Histological/cytological Confirmation of breast cancer (from either primary or metastatic tumour) • Documented positive ER status (ER +ve) of primary or metastatic tumour tissue, defined as ≥10% positive staining by immunohistochemistry • Prior treatment with an endocrine agent • Measurable disease as per RECIST • Postmenopausal women • WHO performance status ≤2	• Fulvestrant 500mg (n=46) • Fulvestrant 250mg (n=47) • Fulvestrant 250mg loading dose (n=51)	• Clinical study report[25] • Pritchard et al 2010 [38]

Table 5 Additional trials identified for the network meta-analysis

Trial	Population	Study arms	References

Trial	Population	Study arms	References
Lundgren 1989	• Women with ABC who had been previously treated with tamoxifen either in the advanced or adjuvant setting	• Megestrol acetate • Aminoglutethimide	• Lundgren et al 1989[29]
Buzdar 1996/98*	• Postmenopausal women • Progressed while receiving tamoxifen or other AO therapy for ABC or relapsed during or after receiving adjuvant tamoxifen treatment • WHO performance status ≤2	• Anastrozole 1mg (n=263) • Anastrozole 10mg (n=248) • Megestrol acetate (n=253)	• Buzdar et al 1996[28] * • Buzdar et al 1998[39] * • Jonat et al 1996[31] • Buzdar et al 1997a[30] • Buzdar et al 1997b[40] *

Trial	Population	Study arms	References
Buzdar 2001	• Postmenopausal women • Histologically or cytologically confirmed breast cancer who presented with either locally advanced or locoregionally recurrent disease or had metastatic disease • Tumors were required to be ER+ and/or PgR+ • Unknown status of ER and PgR was acceptable for study entry if no assay had been conducted • Patients had either relapsed while receiving continuous adjuvant AO therapy or had relapsed within 12 months of stopping adjuvant AO therapy that had been administered for at least 6 months • Patients also eligible if they progressed while receiving first-line AO therapy for advanced disease	• Megestrol acetate • Letrozole 0.5mg • Letrozole 25mg	• Buzdar et al 2001[27]
020	• Postmenopausal women with LABC/MBC • Objective evidence of disease recurrence or progression on adjuvant endocrine therapy or following first-line endocrine therapy for advanced disease • Histological or cytological proof of breast cancer, • Presence of at least one measurable or evaluable lesion, tumours with evidence of hormone sensitivity (i.e. prior sensitivity to hormonal therapy or known ER or progesterone receptor positivity) • Life expectancy of >3 months • WHO performance status ≤2 • No prior fulvestrant or AI therapy	• Fulvestrant 250mg (n=222) • Anastrozole 1mg (n=229)	• Howell et al 2002[5] • Robertson et al 2003[12] * • Mauriac et al 2003[41] * • Howell et al 2005[42] *

Trial	Population	Study arms	References
021	• Postmenopausal women with LABC/MBC • Objective evidence of disease recurrence or progression on adjuvant endocrine therapy or following first-line endocrine therapy for advanced disease • Histological or cytological proof of breast cancer, • Presence of at least one measurable or evaluable lesion, tumours with evidence of hormone sensitivity (i.e. prior sensitivity to hormonal therapy or known ER or progesterone receptor positivity) • Life expectancy of >3 months • WHO performance status ≤2 • No prior fulvestrant or AI therapy	• Fulvestrant 250mg (n=206) • Anastrozole 1mg (n=194)	• Osborne et al 2002[6] • Robertson et al 2003[12] * • Mauriac et al 2003[41] * • Howell et al 2005[42] *

* Combined analysis of two trials, one based in North America and the other in the rest of the world

4.1.4 Details of any relevant studies that were not included in the submission?

The manufacturer did not identify any relevant studies that were excluded from the systematic review described in the MS. The ERG is not aware of any relevant studies that were excluded. Three other studies are however worth noting.

The FIRST[12] study (n=205) which compares fulvestrant 500mg with anastrozole was excluded. The aim of this study was to examine fulvestrant for first-line treatment of patients with ABC; patients may have received prior endocrine therapy for EBC provided it was completed more than 12 months before random assignment. Overall survival was not one of the endpoints studied. The ERG notes that in the trial 25% of patients received prior treatment; however, it is not known how many of these 51 patients had received an AO (as opposed to an AI). Thus the ERG agrees that this trial should have been excluded.

A study conducted in China (n=234)[43] was identified by the ERG comparing fulvestrant 250mg to anastrozole. However, this was only identified in the ERG's most recent search in May 2011 and since the paper was published 12 months after the manufacturer's search was completed, it could not have been identified by the manufacturer. This study contained no data on OS.

Finally, the ERG is aware of another study being conducted in China (NCT01300351) that is currently ongoing which, like the CONFIRM[11] trial, compares fulvestrant 500mg to fulvestrant 250mg. This is expected to enrol 220 patients by 2015 but again, does not plan to examine OS.

4.1.5 Description and critique of manufacturers approach to validity assessment

Direct comparisons

Three RCTs (CONFIRM,[11] FINDER-1[24] and FINDER-2[25]) formed the basis of the direct clinical effectiveness evidence described in the MS. Two of these trials[24, 25] were relatively small phase II dose-ranging trials. The majority of the direct evidence presented in the MS was therefore appropriately derived from the phase III CONFIRM[11] trial.

The CONFIRM[11] trial is an international, multi-centre, double-blind, parallel-group phase III RCT. The manufacturer has included a quality assessment of the CONFIRM,[11] FINDER-1[24] and FINDER-2[25] trials in the MS. The tables (with brief comments on the quality assessment responses from the ERG) can be found in Appendix 1.

In the CONFIRM[11] trial patients were stratified according to study centre. Patients were randomised by sequentially assigned randomisation codes (patient number), with each patient pack labelled with a randomisation code to fulvestrant 250mg or fulvestrant 500mg in a 1:1 ratio. The baseline characteristics for both arms of the CONFIRM[11] trial were generally comparable. The only considerable difference was in terms of radiotherapy as a treatment for advanced disease (69 patients in the fulvestrant 500mg group vs 102 patients in the fulvestrant 250mg group). Blinding was achieved by use of a placebo injection for the 250mg dose patients to ensure all patients received two injections; all study personnel were unaware of the randomised treatment until all decisions on the quality of the data from all patients had been made and documented. The occurrence of pre-specified AEs was similar across the two arms so the ERG is satisfied that the blinding is not compromised by AEs that may be considered to be characteristic of one treatment group. While the CONFIRM[11] trial was carried out in 17 countries (Belgium, Brazil, Chile, Colombia, Republic, Hungary, India, Italy, Malta, Mexico, Poland, Russia, Slovakia, Spain, US, Ukraine and Venezuela), the ERG notes that no patients were recruited from the UK. However, Dr Patrick Cadigan from the Royal College of Physicians has commented that the settings for fulvestrant studies " reflect the conditions in UK current practice."[44] Clinical advice received by the ERG supports this statement.

Protocol deviations were also relatively comparable across the two groups [redacted]

[redacted]

FINDER-1[24] was a multicentre, parallel-group, double-blind phase II RCT conducted in Japan. A total of 143 patients were recruited from 40 centres, and randomised patients 1:1:1 to one of three treatment arms; 500mg fulvestrant, fulvestrant 250mg or fulvestrant 250mg with a loading dose. The method of randomisation was appropriate. Blinding was achieved through use of matching placebo injections, and all patients and personnel were unaware of treatment allocation. Patients across all arms were well balanced for key characteristics.

FINDER-2[25] was a multicentre, international, double-blind phase II RCT conducted in seven European countries (Belgium, Czech Republic, France, Hungary, Poland, Romania and Turkey) and Canada. A total of 144 patients were recruited from 34 centres on a 1:1:1 ratio to receive either: 500mg fulvestrant, fulvestrant 250mg or fulvestrant 250mg with a loading dose. The method of randomisation was assessed as adequate by the ERG, and blinding was successfully achieved through use of identical placebo injections to match each dose of fulvestrant. Baseline characteristics were well balanced across the treatment arms.

The ERG is therefore satisfied that patients were adequately randomised, that blinding was adequate, and in general, considered the all three trials[11, 24, 25] to be of good quality. However, the ERG notes that fulvestrant is currently most commonly used in clinical practice in England and Wales as a third or fourth line endocrine therapy for ABC, and then commonly after an AI; because fulvestrant was most commonly used as a first-line therapy for LABC/MBC in the post-AO group (see Section 3.1), then the generalisability of the population to clinical practice may be questionable.

Indirect comparisons

As noted above, the manufacturer also conducted a network meta-analysis. As with the CONFIRM,[11] FINDER-1[24] and FINDER-2[25] trials, which were included in this network meta-analysis, the manufacturer included a quality assessment of the additional five[5, 6, 27-29] trials to justify their

inclusion. The tables (with brief comments on the quality assessment responses from the ERG) can be found in Appendix 1.

It is important to note that with the exception of CONFIRM,[11] FINDER-1[24] and FINDER-2,[25] none of the patients in any of the other studies included in the base case network meta-analysis had received a prior AI. The ERG therefore sought clarification from the manufacturer that the populations were sufficiently similar so that it could be confidently assumed that the effect estimated in the CONFIRM[11] trial is generalisable to the patients in the other trials, i.e. that the assumption for "exchangeability of relative treatment effects" holds. The manufacturer responded that a global interaction test was performed to test whether the treatment effect for TTP/PFS was consistent across six pre-defined baseline covariate subgroups, including last endocrine therapy. The p-values indicated that there was insufficient evidence that the treatment effect is different between subgroups (including for post-AI and post-AO patients; Figure 4) and therefore the manufacturer argued there was no evidence to suggest the mixed population differed. However, the ERG's re-analysis of the CONFIRM[11] trial's TTP/PFS subgroup data indicates that for post-AI patients the higher dose of fulvestrant does yet yield a statistically significant TTP/PFS benefit compared to fulvestrant 250mg (log-rank test, p = 0.23) whereas for post-AO patients the difference in TTP/PFS is significant (log-rank test, p=0.012); these are consistent with the findings presented in the EMA CHMP EPAR[9] (see also Table 6 below). Alongside differences in the median age and differences in prior endocrine therapies received in these subgroups, the ERG therefore considered the population in the CONFIRM[11] trial to be heterogeneous. Thus it was not meaningful to treat the post-AO and post-AI patients as if they were similar. The ERG therefore believed that the network meta-analysis should only include the post-AO patients from CONFIRM;[11] ideally only post-AO patients from FINDER-1[24] and FINDER-2[25] would also be included but given the small size of these two trials and given no analyses were conducted for these subgroups in these trials, the ERG believes the impact of their inclusion on heterogeneity would be minimal. It is acknowledged by the ERG that by using a subgroup of the CONFIRM[11] trial, the power of the study is diminished. The ERG is of the view that the advantages of this approach (decreased heterogeneity) outweigh the disadvantages (reduced power of the CONFIRM[11] trial).

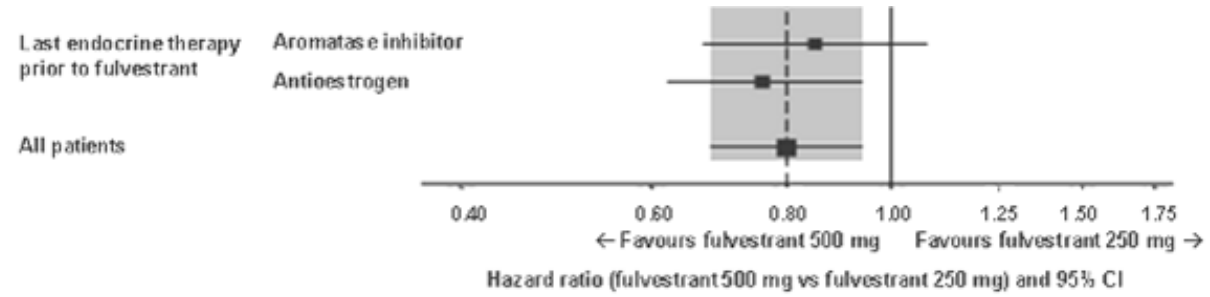

Figure 4 Forest plot of subgroup analysis of TTP/PFS by last endocrine therapy prior to fulvestrant in the CONFIRM trial

4.1.6 Description and critique of manufacturers outcome selection

Direct comparisons

Endpoints in the CONFIRM,[11] FINDER-1[24] and FINDER-2,[25] were evaluated according to RECIST criteria. All were standard outcomes used in trials of anti-cancer treatments and all were consistent with those (OS, TTP/PFS, ORR, AEs and HRQoL) specified in the scope issued by NICE[21] although not all trials planned to measure all endpoints; OS and HRQoL data was only collected in CONFIRM.[11] The ERG is satisfied that they are appropriate for the disease area.

The ERG notes that OS is regarded as the most reliable outcome in trials of anti-cancer treatments, but that it is rarely the primary outcome in trials in this area and setting. Overall survival was not formally analysed in CONFIRM[11] at the primary data cut-off for TTP/PFS as the event data were still considered immature. However, data for OS available at this time were presented in the MS, at which point there had been 378 (51%) deaths. Clarification sought from the manufacturer confirmed that 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 modelling of the deaths recorded on the database as of 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 2 months later.

Time to progression was the primary outcome of the CONFIRM[11] trial. No explicit definition was given for this choice in the MS although the manufacturer does note that it is the same definition that is commonly used for PFS; indeed, in the published paper[36] for CONFIRM,[11] PFS is cited as the primary outcome. This is defined as the time elapsing between the date of random assignment and the date of the earliest evidence of objective disease progression or death from any cause before documented disease progression.

Given FINDER-1[24] and FINDER-2[25] were dose ranging trials, the primary outcome for both these trials was ORR. The best overall objective response for each patient was categorised as a response (complete response [CR] or partial response [PR]) or a non-response (stable disease [SD], progressive

disease [PD], or not evaluable). Objective response rate was defined in CONFIRM[11] as the proportion of responders (CR and PR analysed in the "Evaluable for Response Set" i.e. those for whom objective response could be assessed). According to the EMA CHMP EPAR,[9] the reason for excluding patients from the "Evaluable for Response Set" in CONFIRM[11] was that there was no target lesion identified at baseline. Unlike in the CONFIRM[11] trial, all patients in FINDER-1[24] and FINDER-2[25] had measurable disease and were evaluated for ORR.

Clinical benefit rate (CBR) was a secondary outcome that was investigated in CONFIRM,[11] FINDER-1[24] and FINDER-2.[25] It was defined as the proportion of responders (CR or PR) plus those with SD ≥24 weeks in the intention to treat (ITT) population. Other secondary outcomes measured in CONFIRM,[11] FINDER-1[24] and FINDER-2[25] included duration of response (DoR), duration of clinical benefit (DoCB), AEs and HRQoL. Time to progression was also a secondary outcome in FINDER-1[24] and FINDER-2.[25]

Indirect comparisons

For the base-case network meta-analysis, data on two outcomes were collected: OS and TTP/PFS. Aside from the non-mature data from CONFIRM,[11] OS data were available from four[5, 6, 27, 28] other trials in the network meta-analysis. Time to progression/progression-free survival was assessed by seven[5, 6, 11, 24, 25, 27, 28] trials in the network meta-analysis.

4.1.7 Describe and critique the statistical approach used

Direct comparisons

The sample size calculation for CONFIRM,[11] was based on the primary outcome of TTP/PFS and assumed exponential survival times. It was driven by the number of required events. In order to detect a hazard ratio of ≤ 0.8 (or ≥ 1.25) for fulvestrant 500mg compared to fulvestrant 250mg, at a two-sided significance level of 5%, with 80% power, approximately 632 events were required to occur. It was anticipated that if 720 patients were recruited over a period of 36 months, then the required 632 events would be observed approximately 6 months after the end of treatment. In reality, 736 patients were recruited and 618 events had occurred when the analysis took place. The ERG notes that the required number of events for analysis was not achieved, however the difference in the number of events required and the number of events observed is small enough number to be of little concern.

Randomisation was stratified by institution site but not by any important prognostic factors. The ERG agrees that this was appropriate as in a trial with so many centres, according to ICH E9,[45] it is advisable to have a separate randomisation scheme for each centre and because of the size of the trial, it is expected that the two groups would be balanced with respect to any such prognostic factors.

For the primary outcome of TTP/PFS, the primary analysis was an unadjusted log-rank test. The treatment effect was estimated using the hazard ratio of fulvestrant 500mg versus fulvestrant 250mg, together with the 95% confidence interval (CI) and p- value. Kaplan-Meier plots were presented with estimates of the median TTP/PFS for each treatment group. The secondary analysis of TTP/PFS was a Cox proportional hazards model, which was adjusted for the following predefined covariates: progesterone receptor status (positive vs negative or unknown), visceral involvement (no vs yes), last endocrine therapy before fulvestrant (AO vs AI), age (< 65 years vs ≥ 65 years), measurable disease (no vs yes) and level of responsiveness to last endocrine therapy before fulvestrant (responsive vs poorly responsive or unknown). The results of this analysis were not presented in the MS, but are in the CSR[11] and they support the primary analysis. The primary and secondary analyses of TTP/PFS were carried out on the full analysis set (also known as the intention to treat population). An additional analysis based on the per protocol set (post-progression survival) was carried out using the log-rank test. Superiority was to be declared if the two-sided p-value for the treatment comparison was ≤ 0.05. This additional analysis was not presented in the MS but was in the CSR[11] and it supports the results of the primary analysis.

For the secondary endpoints, the nominal significance level of 0.05 was used. For OS, the log-rank test was to be performed when approximately 50% of patients had died, this occurred at the same time as the analysis of the primary endpoint. For ORR and CBR, a logistic regression model with treatment factor only was fitted. Results were expressed as an odds ratio together with a corresponding 95% CI. DoR and DoCB were summarised and Kaplan-Meier plots were produced with estimates of the median time for each treatment group. The Kaplan-Meier plots for DoR were not presented in the MS but can be found in the CSR[11]. For HRQoL endpoints, a longitudinal model with treatment and other covariates was used. For efficacy and HRQoL endpoints, summaries and analyses were carried out according to randomised treatment, where as for safety endpoints, summaries and analyses were carried out according to treatment actually received.

The ERG is satisfied with the statistical methodology utilised in the analyses of primary and secondary endpoints.

Several subgroup analyses were undertaken to assess the potential impact of the following factors:

- "ER+ and PgR+" vs"ER+ and PgR- or unknown" patients
- Visceral involvement (no vs yes)
- Last therapy prior to fulvestrant (post-AO vs post-AI)
- Response to last endocrine therapy received prior to fulvestrant (responsive vs not responsive)
- Age (< 65 years vs ≥ 65 years)

- Measurable disease (no vs yes)

According to the MS, all subgroups were predefined in the statistical analysis plan and were chosen to investigate the consistency of any treatment effect across six covariates that are potential prognostic factors for TTP/PFS.

The subgroup analyses by last therapy prior to fulvestrant raised an issue for the ERG. As highlighted in Section 3.1, the EU licence for fulvestrant 500mg is based on the patient having received previous AO therapy; it is not clear from the wording of the EU licence that eligibility for treatment is dependent on the last therapy received. While the ERG took the view that this was probably the case, the ERG considered it would also be useful for the data to be split by patients who had received an AO only, patients who had received an AI only and patients who had received both an AO and an AI. This was requested by the ERG in the clarification letter and the data were provided by the manufacturer and are presented in this report in Appendix 2.

According to the MS, the manufacturer did not consider it appropriate to perform a simple meta-analysis as the only comparator available if this method was to be adopted would be fulvestrant 250mg and whilst the manufacturer recognised that this was identified in the scope as a comparator, they felt that a more comprehensive picture with additional comparators would be obtained if a network meta-analysis was performed instead. The ERG does not understand why the manufacturer chose not to perform a simple meta-analysis for TTP/PFS alongside the network meta-analysis although accepts that a network meta-analysis was more meaningful to addressing the decision problem since it could consider a greater number of comparators than just fulvestrant 250mg.

Indirect comparisons

The network meta-analysis used a Bayesian approach and were performed using the WinBUGs software package using a Markov Chain Monte Carlo (MCMC) method known as Gibbs sampling. This approach combines a prior probability distribution that reflects a prior belief of the possible values of the pooled relative effects with a likelihood distribution of the pooled effect based on the observed data in the different studies to obtain a posterior distribution of the pooled relative treatment effect. Using the patient-level CONFIRM[11] dataset, the three most commonly used parametric distributions[46] in NICE technology appraisals (namely Weibull, log- logistic and log-normal) were evaluated for fit for TTP/PFS and OS. 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. The need to consider extrapolation was for the purpose of economic modelling (see Section 5).

For OS, the hazard ratios were assumed to be constant over time so the network meta-analysis was implemented by pooling the hazard ratios across interventions and extrapolating the OS using a

Weibull distribution. In the MS, the baseline OS curve was fitted based on fulvestrant 250mg using the CONFIRM[11] individual patient data and the pooled hazard ratios resulting from the network meta-analysis analysis were applied to the baseline curve. On inspection of the code that was used to implement the analysis in WinBUGs, the ERG noted that no adjustment had been made for the inclusion of the three arm trials. The ERG re-ran the analysis making this adjustment and found that it made little difference to the results.

For TTP/PFS, the manufacturer felt that it was inappropriate to assume that hazard ratios were constant over time and that it was therefore unsuitable to pool the hazard ratios. For that reason, they selected the log-normal distribution instead of the Weibull distribution that was used for OS. They used methodology developed by Ouwens[47] in which a simultaneous extrapolation and network meta-analysis of TTP/PFS curves for all the comparators were derived from all the available trials. This was done by relating the TTP/PFS Kaplan-Meier curves of each of the competing interventions directly to the parameters of the log-normal survival curves.

A fixed effects model was used to simultaneously extrapolate Kaplan-Meier curves over time by means of log-normal curves, to synthesize and to indirectly compare the different treatments. The shape and scale for the baseline (originally fulvestrant 250mg however the ERG requested the manufacturer to reanalyse with fulvestrant 500mg as the baseline as they believed this to be more appropriate) were calculated and were used as the anchor to obtain estimates for the shape and scale for the other interventions. The pooled TTP/PFS curves for each treatment were produced and the corresponding area under the curve was calculated to obtain a mean TTP/PFS for each treatment. Using this approach, the possible differences in both shape and scale of the log-normal curves within trial is taken into account without breaking randomisation.

While the ERG believes that the manufacturer has carried out a log-normal meta-analysis accurately, the ERG is not convinced that a log-normal distribution is appropriate for the CONFIRM[11] trial, nor for the other trials in the network. Section 5.5.4 explores this issue in further detail.

All the indirect comparisons used fulvestrant 250mg as the baseline comparator. The ERG considered it more appropriate to have estimates of the treatment effects relative to fulvestrant 500mg. Therefore the ERG requested that the manufacturer reanalysed the data fitting fulvestrant 500mg as the baseline comparator. These analyses were provided by the manufacturer, based on the same assumptions for the distribution of OS and TTP/PFS data.

Finally, as discussed in Section 4.1.5, the ERG believes that the network meta-analysis should have limited inclusion of patients from CONFIRM[11] to the post-AO subgroup.

4.1.8 Summary statement

The conduct of the systematic review in the MS generally appears to be complete and reasonable. The search strategy was appropriate and clearly reported. All relevant clinical trials published at the time of the search appear to have been identified. The validity of the trials to the decision problem, in particular CONFIRM,[11] the phase III trial from which much of the data on fulvestrant 500mg are derived, have been addressed by the manufacturer. In particular, the manufacturer provided a justification for its use of a mixed population in CONFIRM[11] based on subgroup analyses suggesting TTP/PFS was the same in both post-AO and post-AI groups. CONFIRM[11] was well-designed and the clinical outcomes reported in this RCT and supporting phase II trials[24, 25] address all the relevant outcomes outlined in the final scope issued by NICE.[21] The ERG believes that a meta-analysis of three trials would have been possible and could have been conducted for TTP/PFS although agrees that the network meta-analysis was more informative. The ERG is confident that the two most meaningful outcomes (OS and TTP/PFS) were selected for use in the network meta-analysis. The ERG does not consider that the use of the log-normal distribution for the network meta-analysis for TTP/PFS is appropriate or reliable. The ERG also believes that the post-AO population from CONFIRM[11] was a more appropriate population to include in the network meta-analysis rather than the mixed population, given the apparent heterogeneity in post-AO and post-AI populations, in light of the wording of the EU licence and given the fact that all trials for other comparators only included a post-AO population. It is accepted that FINDER-1[24] and FINDER-2,[25] which were included in the TTP/PFS analysis, also included post-AI patients but in view of the small numbers of patients in these trials, the ERG believes their inclusion is warranted since subgroup data for post-AO patients was not available for these two trials. The ERG also acknowledges that currently in clinical practice, fulvestrant is most likely to be considered by clinicians following treatment for LABC/MBC with an AI.

4.2 Summary of submitted evidence

4.2.1 Summary of results: efficacy

Direct comparisons

Because not all patients in CONFIRM[11] had received an AO (See Section 3.1), subgroup analyses were performed for patients whose last treatment was an AO or an AI. Other than the forest plot also reproduced in this ERG report (Figure 4; Section 4.1.5), these findings were not presented in the MS. They were however presented for the EMA CHMP[9] and reproduced in the SmPC[10] and are reproduced here (Table 6 and Table 7).

For the overall trial population (i.e. mixed population) and for patients whose last treatment was an AO, a significantly longer TTP/PFS was reported for patients receiving fulvestrant 500mg compared

with those receiving fulvestrant 250mg. The treatment effect (TTP/PFS) favouring fulvestrant 500mg was consistent across all of the pre-specified subgroups analysed (Figure 5). In terms of type of prior endocrine therapy, the difference in TTP/PFS between groups was only significant for patients whose last treatment was an AO, not for those who last received an AI (Table 6 and Figure 5). These findings were consistent with the *post-hoc* data analyses requested by the ERG where differences were significant for patients who had ever had an AO but not an AI (in confidence data presented in Appendix 2).

No other significant differences were reported between the two groups for any other outcome (Table 6 and Table 7). The log rank analysis indicates that there is a trend for improved OS for patients in the fulvestrant 500mg group compared with those in the fulvestrant 250mg group, however, this did not reach statistical significance (HR=0.84 [95% CI 0.69 to 1.03]; p=0.091). It should be noted that these data were currently immature at data cut off primary data cut off for TTP/PFS (51% of patients had died) and the manufacturer intends to conduct a formal analysis when 75% of patients have died.

Table 6 Summary of findings from the CONFIRM trial: TTP/PFS and OS

Outcome	Fulvestrant 500mg	Fulvestrant 250mg	Comparison between groups (Fulvestrant 500mg/Fulvestrant 250mg)		
	median (months)	median (months)	Hazard Ratio	95% CI	p-value
Time to progression/progression-free survival (TTP/PFS)					
All patients (mixed population) (n=736)	6.5	5.5	0.80	0.68 to 0.94	0.006
-Last prior treatment with an AO (n=423)*	8.6	5.8	0.76	0.62 to 0.94	0.013
-Last prior treatment with an AI (n=313)*	5.4	4.1	0.85	0.67 to 1.08	0.195
Overall survival (OS)					
All patients (mixed population) (n=736)	25.1	22.8	0.84	0.69 to 1.03	0.091
-Last prior treatment with an AO (n=423)*	27.9	25.9	0.85	0.65 to 1.13	0.264
-Last prior treatment with an AI (n=313)*	24.1	20.8	0.83	0.62 to 1.12	0.216

* Data for subgroups taken from EMA EPAR[9]

Table 7 Summary of findings from the CONFIRM trial: ORR and CBR

Outcome	Fulvestrant 500mg	Fulvestrant 250mg	Comparison between groups (Fulvestrant 500mg/Fulvestrant 250mg)				
	% of patients	% of patients	absolute difference	95% CI	Odds Ratio	95% CI	p-value
Objective response rate (ORR)[*a]							
All patients (mixed population) (n=501)	13.8	14.6	-0.8	-5.8 to 6.3	0.94	0.57 to 1.55	0.795
-Last prior treatment with an AO (n=296)[b]	18.1	19.1	-1.0	-8.2 to 9.3	-	-	-
-Last prior treatment with an AI (n=205)[b]	7.3	8.3	-1.0	-5.5 to 9.8	-	-	-
Clinical benefit rate (CBR)							
All patients (mixed population) (n=736)	45.6	39.6	6.0	-1.1 to13.3	1.28	0.95 to 1.71	0.100
-Last prior treatment with an AO (n=423)[b]	52.4	45.1	7.3	-2.2 to16.6	-	-	-
-Last prior treatment with an AI (n=313)[b]	36.2	32.3	3.9	-6.1 to15.2	-	-	-

[a] ORR was assessed in patients who were evaluable for response at baseline (i.e., those with measurable disease at baseline: 240 patients in the fulvestrant 500mg group and 261 patients in the fulvestrant 250mg group).

[b] Data for subgroups taken from EMA EPAR[9]

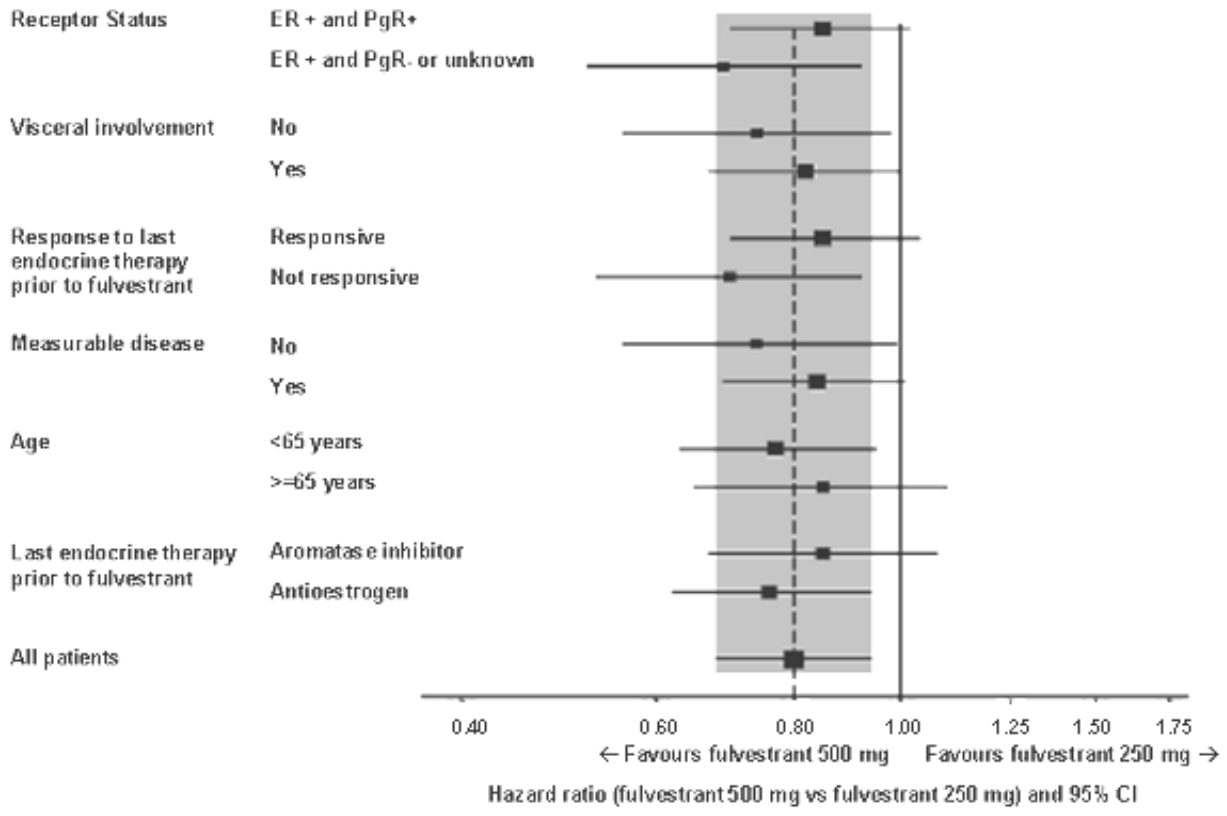

Figure 5 TTP/PFS subgroup analysis forest plot in CONFIRM

In terms of best objective response, most patients in both arms of CONFIRM[11] had SD (41% and 40% in the fulvestrant 500mg and 250mg arms respectively) or PD (43% vs 45%). A slightly greater proportion of patients in the fulvestrant 500mg group had a CR than in the 250mg group (2% vs <1%); however, a slightly lesser proportion had a PR (12% vs 14%). Median duration of response was numerically greater in the small number of patients (n=71) who experienced an objective response (19.4 vs 16.4 months; n=33 and n=38 respectively). Finally, the median DoCB, for the [redacted] patients who derived a clinical benefit, was also numerically greater in the fulvestrant 500mg group than the fulvestrant 250mg group ([redacted] vs [redacted] months respectively).

For the primary endpoint of ORR in FINDER-1[24] and FINDER-2,[25] fulvestrant 500mg and fulvestrant 250mg were similar in the former whereas in the latter, fulvestrant 500mg was numerically higher (Table 8). As in CONFIRM,[11] most responses were CR. Only two patients experienced a CR; both were in the fulvestrant 250mg group in FINDER-1.[24] Clinical benefit rates were numerically better in these same groups.

Table 8 Summary of findings from the FINDER-1 and FINDER-2 trials: ORR and CBR

Trial and outcome	Fulvestrant 500mg		Fulvestrant 250mg LD		Fulvestrant 250mg	
	% of patients	95% CI	% of patients	95% CI	% of patients	95% CI
ORR						
FINDER-1 (n=143)	10.6	3.5 to 23.1	17.6	8.4 to 30.9	11.1	3.7 to 24.1
FINDER-2 (n=144)	15.2	6.3 to 28.9	5.9	1.2 to 16.2	8.5	2.4 to 20.4
CBR						
FINDER-1 (n=143)	46.8	32.1 to 61.9	54.9	40.3 to 68.9	42.2	27.7 to 57.8
FINDER-2 (n=144)	47.8	32.9 to 63.1	47.1	32.9 to 61.5	31.9	19.1 to 47.1

LD=loading dose

In FINDER-1[24] median TTP was the same for fulvestrant 500mg and 250mg arms (6.0 months) and was numerically longer in the 250mg loading dose group (7.5 months). A similar number (and proportion) of progression events were also observed between groups: 31 (66%), 30 (67%) and 31 (61%) events respectively. In FINDER-2[25] the medians for TTP in the fulvestrant 500mg and fulvestrant 250mg loading dose treatment arms (6.0 months and 6.1 months, respectively) were numerically higher than the median TTP of the fulvestrant 250mg treatment arm (3.1 months). The proportions of progression events were also similar between the fulvestrant 500mg and 250mg loading dose arms (67%), being numerically higher in the 250mg group (75%).

Indirect comparisons

The manufacturer performed a network meta-analysis for two outcomes, OS and TTP/PFS.

The OS network meta-analysis analysis was based on five[5, 6, 25, 27, 28] trials as detailed in Table 9 below. Three of the identified trials (FINDER-1[24], FINDER-2[25] and Lundgren 1989[29]) were excluded from analysis because they did not include sufficient OS data.

Table 9 Evidence available for OS network meta-analysis

Trial	Fulvestrant 500mg	Fulvestrant 250mg	Anastrozole 1mg	Anastrozole 10mg	Megestrol acetate	Letrozole 0.5mg	Letrozole 2.5mg
CONFIRM	X	X					
020		X	X				
021		X	X				
Buzdar 1996/98			X	X	X		
Buzdar 2001					X	X	X

Note: 020 and 021 were pooled to give combined treatment effects; Buzdar 1996/98 is also the result of a pooled analysis

The findings reported in the MS suggested that fulvestrant 500mg may be the most efficacious treatment in terms of OS but this finding was not statistically significant since the 97.5th percentile exceeded the value of 1.0 (Table 10).

Table 10 Network meta-analysis OS results in the MS: Hazard Ratios relative to fulvestrant 250mg

Treatment	HR	2.5th percentile	97.5th percentile
Fulvestrant 500mg	0.84	0.69	1.03
Anastrozole 1mg	1.02	0.88	1.19
Megestrol acetate*	1.31	0.98	1.75
Letrozole 0.5mg*	1.03	0.71	1.51
Letrozole 2.5mg	1.20	0.83	1.74

*Excluded from the economic model

The TTP/PFS network meta-analysis was based on seven trials[5, 6, 11, 24, 25, 27, 28] as detailed in Table 11. Lundgren et al 1989[29] was excluded from the analysis because there was insufficient TTP/PFS data.

Since the log-normal distribution was selected for TTP/PFS, it was not appropriate to pool the hazard ratios; the proportionality and constancy of the hazard ratios cannot be assumed from a theoretical perspective. Alternatively, based on the methodology developed by Ouwens et al 2010,[47] a simultaneous extrapolation and network meta-analysis of TTP/PFS curves for all of the comparators were derived from the available RCTs. This was achieved by relating the TTP/PFS Kaplan Meier curves of each of the competing interventions directly to parameters of the log-normal survival curves.

Table 11 Evidence available for TTP/PFS network meta-analysis

Trial	Fulvestrant 500mg	Fulvestrant 250mg	Fulvestrant 250mg loading dose	Anastrozole 1mg	Anastrozole 10mg	Megestrol acetate	Letrozole 0.5mg	Letrozole 2.5mg
CONFIRM	X	X						
FINDER-1	X	X	X					
FINDER-2	X	X	X					
020		X		X				
021		X		X				
Buzdar 1996/98				X	X	X		
Buzdar 2001						X	X	X

The findings for TTP/PFS reported in the MS are presented in Table 12 and Table 13. These findings were not interpreted in the MS. However, at the ERG's request, the manufacturer provided the following interpretation of the TTP/PFS findings:

The difference in scale and shape parameters presented in Tables B35 and B36 [Table 12 and Table 13] describe the TTP/PFS curves for each intervention (MS 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/PFS) relative to the baseline comparator and to the other treatment presented.

The sign of the difference in scale shown in Table B36 [Table 13] indicates whether the treatment improves TTP/PFS more than the comparator i.e. 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/PFS than fulvestrant 250mg whereas Anastrozole 1mg results in significantly worse TTP/PFS than Fulvestrant 250mg. There were no statistically significant differences in TTP/PFS between the remaining treatments compared with fulvestrant 250mg.

Table 12 Network meta-analysis TTP/PFS results in the MS: fulvestrant 250mg (baseline comparator)

Treatment	Scale			Log shape		
	Scale	2.5th percentile	97.5th percentile	Log shape	2.5th percentile	97.5th percentile
Fulvestrant 250	1.676	1.600	1.750	-0.185	-0.344	-0.062

Table 13 Network meta-analysis TTP/PFS results in the MS: difference in log-normal parameters for treatment alternatives versus fulvestrant 250mg

Treatment	Difference in scale			Difference in log shape		
	Scale	2.5th percentile	97.5th percentile	Log shape	2.5th percentile	97.5th percentile
Fulvestrant 250mg loading dose	0.209	-0.047	0.503	-0.067	-0.639	0.402
Fulvestrant 500mg	0.229	0.167	0.293	-0.102	-0.185	-0.020
Anastrozole 1mg	-0.094	-0.189	-0.004	0.029	-0.109	0.173
Megestrol acetate 160mg*	-0.017	-0.162	0.131	0.222	0.033	0.405
Letrozole 0.5mg*	0.281	0.089	0.468	-0.004	-0.267	0.244
Letrozole 2.5mg	0.045	-0.140	0.231	0.108	-0.139	0.348

*Excluded from the economic model

As noted in Section 4.1.7, the ERG believes that it is more appropriate to have estimates of the treatment effects relative to fulvestrant 500mg than fulvestrant 250mg for both OS and TTP/PFS. The manufacturer provided revised estimates relative to fulvestrant 500mg in response to a request from the ERG.

The revised findings for OS with fulvestrant 500mg as the baseline comparator provided by the manufacturer are presented in Table 14. All hazard ratios favoured fulvestrant 500mg over the other treatments. The only difference that was found to be statistically significant was when fulvestrant 500mg was compared to megestrol acetate.

Table 14 Network meta-analysis OS results: Hazard Ratios relative to fulvestrant 500mg

Treatment	Hazard ratio*	95% CI
Fulvestrant 250mg	1.19	(0.97 to 1.45)
Anastrozole 1mg	1.22	(0.94 to 1.56)
Megestrol acetate	1.56	(1.09 to 2.22)
Letrozole 0.5mg	1.23	(0.80 to 1.88)
Letrozole 2.5mg	1.43	(0.94 to 2.19)

*HR > 1 favours fulvestrant 500mg

The ERG also requested that the manufacturer present the probability that each treatment is best (Table 15). These probabilities are calculated using the number of times the treatment had the highest rank based on the proportion of patients who die. The probability of fulvestrant 500mg being the best treatment is 78%.

Table 15 Network meta-analysis OS results: probability of each treatment being the best

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

The revised findings for TTP/PFS with fulvestrant 500mg as the baseline comparator provided by the manufacturer are presented in Table 16 and Table 17.

Table 16 Network meta-analysis TTP/PFS results: fulvestrant 500mg (baseline comparator)

Treatment	Scale		Log shape	
	Estimate	95% CI	Estimate	95% CI
Fulvestrant 500mg	1.90	(1.82 to 1.99)	-0.09	(-0.24 to 0.06)

Table 17 Network meta-analysis TTP/PFS results: difference in log-normal parameters for treatment alternatives versus fulvestrant 500mg

Treatment	Difference in scale		Difference in log shape	
	Estimate	95% CI	Estimate	95% CI
Fulvestrant 250mg loading dose	-0.02	(-0.30 to 0.26)	-0.30	(-0.75 to 0.29)
Fulvestrant 250mg	-0.23	(-0.29 to -0.17)	-0.23	(-0.28 to -0.12)
Anastrozole 1mg	-0.32	(-0.44 to -0.21)	-0.20	(-0.17 to 0.16)
Megestrol acetate	-0.25	(-0.40 to -0.09)	-0.01	(-0.44 to -0.03)
Letrozole 0.5mg	0.05	(-0.15 to 0.25)	-0.23	(-0.39 to 0.15)
Letrozole 2.5mg	-0.18	(-0.38 to 0.01)	-0.12	(-0.26 to 0.26)

The difference in scale and shape parameters describes the TTP/PFS curves for each intervention relative to the scale and shape parameters of the baseline comparator, fulvestrant 500mg. The curve for fulvestrant 500mg is above all the others indicating that it provides improved TTP/PFS compared to the other treatments. The sign of the difference in scale denotes whether the treatment improves TTP/PFS more than the comparator (if the difference in scale is positive then the treatment is better, if the difference in scale is negative the baseline comparator is better). If both limits of the confidence intervals have the same sign then the difference is statistically significant.

The results show that fulvestrant 250mg, anastrozole 1mg and megestrol acetate result in significantly worse TTP/PFS than fulvestrant 500mg. Fulvestrant 250mg loading dose, and letrozole 2.5mg result in worse TTP/PFS than fulvestrant 500mg but differences were not found to be statistically significant. Letrozole 0.5mg resulted in slightly better TTP/PFS than fulvestrant 500mg but again this difference was not found to be statistically significant.

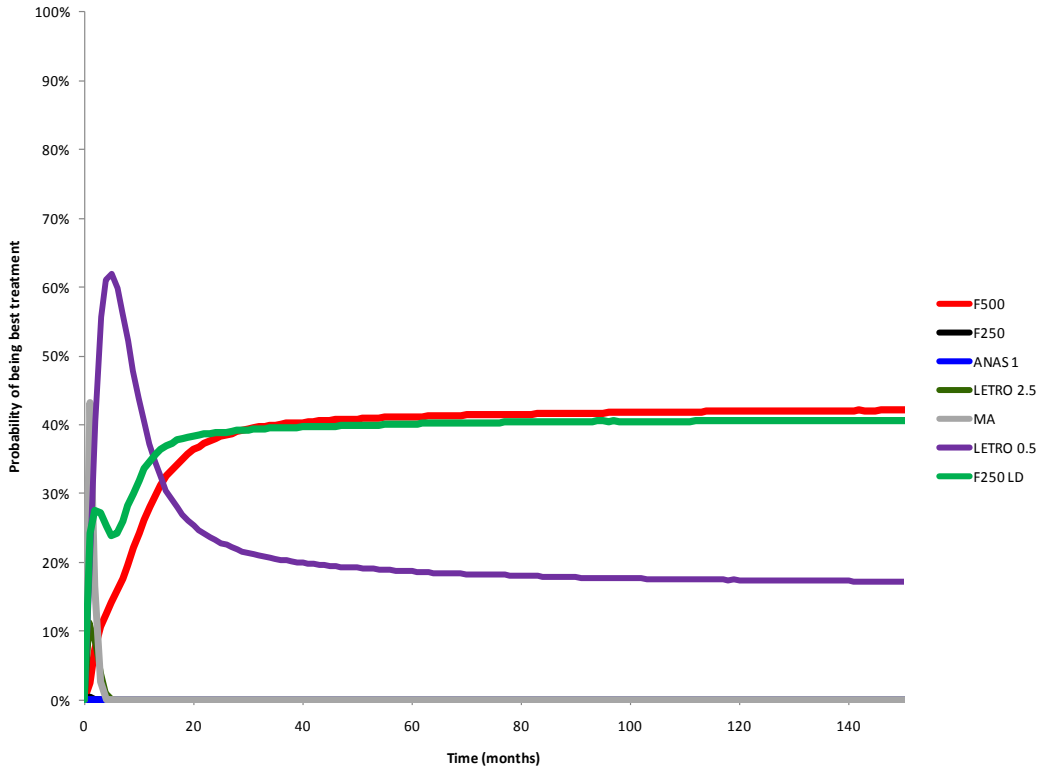

Figure 6 TTP/PFS network meta-analysis results: probability of each treatment being best

Figure 6 shows the probability of each treatment being the best over time. These probabilities were calculated using the number of times the treatments had the highest rank based on the proportion of patients that progressed over time. The probability of fulvestrant 500mg being best increased over the first 30 months and then remained the highest from this point onwards.

4.2.2 Summary of results: health related quality of life

Direct comparisons

A total of 145 women completed a baseline FACT-B questionnaire in CONFIRM.[11] This represented 82.3% of the 176 women randomly assigned in the countries that participated in the HRQoL sub-study (i.e. English speaking or Spanish speaking countries). No significant difference was detected between the two study arms.

Indirect comparisons

No HRQoL data were presented from the indirect comparisons.

4.2.3 Summary of results: adverse events

Direct comparisons

Consistent with the longer TTP/PFS for patients treated with fulvestrant 500mg in CONFIRM,[11] patients in this treatment group had a longer duration of exposure to fulvestrant than those in the fulvestrant 250mg group: mean 10.3 vs 8.2 months. A total of 2443 AEs were reported by 483 (66%) of the 735 patients in the Safety Analysis Set in CONFIRM[11]. Fifty-four patients (7%) reported a serious AE (SAE) including 11 patients (1%) who died due to an AE. Seventeen patients (2%) discontinued study treatment due to an AE. There were no notable differences between treatment groups in the incidence of AEs and overall the AEs observed in this study were consistent with the known safety profile of fulvestrant and there were no safety concerns emerging from this study.

A pooled analysis of safety from CONFIRM,[11] FINDER-1,[24] FINDER-2[25] and NEWEST[48] (a phase II study of postmenopausal women with newly diagnosed ER+ LABC randomised to fulvestrant 500mg or 250mg in the neoadjuvant setting). The most frequently reported AE in these patients was injection site pain followed by nausea, fatigue, hot flush and headache (Table 18). There were no important differences identified between the treatment groups from the reporting of these AEs.

Table 18 Commonly reported AEs in CONFIRM and pooled data (incidence ≥5% in either pooled group)[a]

Adverse event	Number (%) of patients, by treatment [b]			
	Fulvestrant 500mg		Fulvestrant 250mg	
	CONFIRM	Pooled	CONFIRM	Pooled
	500mg (n=361)	500mg (n=560)	250mg (n=374)	250mg (n=567)
Patients with any AE	243 (67.3)	393 (70.2)	240 (64.2)	387 (68.3)
Injection site pain	42 (11.6)	78 (13.9)	34 (9.1)	58 (10.2)
Nausea	35 (9.7)	57 (10.2)	51 (13.6)	79 (13.9)
Fatigue	27 (7.5)	54 (9.6)	24 (6.4)	40 (7.1)
Hot flush	24 (6.6)	49 (8.8)	22 (5.9)	49 (8.6)
Headache	28 (7.8)	45 (8.0)	25 (6.7)	41 (7.2)
Back pain	27 (7.5)	40 (7.1)	40 (10.7)	54 (9.5)
Arthralgia	29 (8.0)	38 (6.8)	29 (7.8)	36 (6.3)
Bone pain	34 (9.4)	37 (6.6)	28 (7.5)	30 (5.3)
Vomiting	22 (6.1)	33 (5.9)	21 (5.6)	32 (5.6)
Anorexia	22 (6.1)	32 (5.7)	14 (3.7)	20 (3.5)
Pain in extremity[c]	25 (6.9)	32 (5.7)	26 (7.0)	38 (6.7)
Cough	19 (5.3)	31 (5.5)	20 (5.3)	32 (5.6)
Diarrhoea	17 (4.7)	30 (5.4)	11 (2.9)	24 (4.2)
Asthenia	21 (5.8)	29 (5.2)	23 (6.1)	31 (5.5)
Hypertension	16 (4.4)	24 (4.3)	15 (4.0)	29 (5.1)
Nasopharyngitis	5 (1.4)	24 (4.3)	12 (3.2)	33 (5.8)

a Patients with multiple occurrences of the same event were counted only once per event.
b Pooled data: CONFIRM, FINDER-1, FINDER-2 and NEWEST.
c Following data queries to the investigational sites, it was confirmed that pain in extremity was not linked to injection site pain but was a distinct and separate AE.

Indirect comparisons

It was not possible to compare the incidence of specific AEs of fulvestrant 500mg with the other comparators (except fulvestrant 250mg) listed in the scope since in the other trials, in most cases, "common" AEs were reported, or alternatively AEs occurring in 'x%' of the population were reported; different reporting formats make it difficult to interpret comparisons across trials. In addition, the manufacturer argues that this method of reporting highlights the fact that the AEs associated with the treatments were relatively mild as AEs are typically reported in terms of Grades 3 and 4 for oncology treatments and this was not the case in most of the publications reviewed as there were simply not enough SAEs to report in this format. Serious adverse event data were not presented in the clinical section of the MS but were however presented in the economics section of the MS (Table 19).

Table 19 Network meta-analysis results for proportion of patients experiencing SAEs

Treatment	Proportion of patients suffering a serious adverse events	2.5% credible interval	97.5% credible interval
Fulvestrant 250mg	9.1%	6.4%	12.1%
Fulvestrant 500mg	10.2%	6.5%	15.0%
Anastrozole	6.4%	4.1%	9.7%
Letrozole	8.8%	3.6%	20.2%

4.3 Critique of submitted evidence syntheses

Direct comparisons

As noted in Section 4, the main trial in the MS (CONFIRM[11]) was well-designed and the clinical outcomes reported in this RCT cover the relevant outcomes outlined in the final scope issued by NICE[21] (OS, TTP/PFS, ORR, AEs and HRQoL). The ERG therefore believes the findings from this trial, which suggest a significant improvement in TTP/PFS for the fulvestrant 500mg group over the 250mg group, are likely to be robust for the mixed population. The findings from FINDER-1[24] and FINDER-2[25] broadly support these findings. However, for reasons highlighted above in Section 3.1 and Section 4.1.5, the ERG believes that findings for the post-AO group are more meaningful. Even for this group of patients, the ERG has concerns as 66% of patients in the CONFIRM trial had prior endocrine therapy as part of adjuvant therapy for EBC only. There exists the possibility that the improved findings in post-AO subgroup compared to the post-AI subgroup are attributable to the majority of these patients receiving first-line therapy for ABC compared to a minority (33%) in the post-AI group.

Indirect comparisons

As highlighted in Section 3.1 and again above, the ERG has concerns that the population of the CONFIRM[11] trial differs to that of the other trials included in the base case network meta-analysis carried out by the manufacturer; the CONFIRM[11] trial includes patients previously treated by either an AO or an AI whereas all other trials for OS include patients previously treated with an AO. While the ERG recognises that by using a subgroup of the CONFIRM[11] trial, the power of the study is diminished, the ERG re-ran the analysis using data from only those patients whose last endocrine treatment was an AO (n=423). The ERG's findings for OS with fulvestrant 500mg as the baseline comparator are presented in Table 20 and Table 21; the results are similar to the results obtained when the whole population of the CONFIRM[11] trial was included in the analysis. All hazard ratios still favour fulvestrant 500mg over the other treatments and it is still only found to be significantly better than megestrol acetate. Using the AO population only, the probability of fulvestrant 500mg being the best treatment was reduced slightly from 78% to 69%.

Table 20 Network meta-analysis results for OS (ERG analysis): Hazard Ratios relative to fulvestrant 500mg using only the post-AO subgroup of the CONFIRM trial

Treatment	Hazard ratios*	95% CI
Fulvestrant 250mg	1.18	(0.89 to 1.53)
Anastrozole 1mg	1.20	(0.86 to 1.61)
Megestrol acetate	1.54	(1.03 to 2.24)
Letrozole 0.5mg	1.22	(0.75 to 1.90)
Letrozole 2.5mg	1.43	(0.89 to 2.19)

*HR > 1 favours fulvestrant 500mg

Table 21 Network meta-analysis results for OS (ERG analysis): probability of each treatment being the best using only the post-AO subgroup of the CONFIRM trial

Treatment	Probability of being best
Fulvestrant 500mg	69%
Fulvestrant 250mg	5%
Anastrozole 1mg	5%
Megestrol Acetate	0%
Letrozole 0.5mg	19%
Letrozole 2.5mg	2%

The TTP/PFS network meta-analyses presented by the manufacturer relied strongly on the assumption that all trials follow a log-normal distribution and also include the mixed population from the CONFIRM[11] trial. As noted in Section 4.1.7, the ERG does not believe this to be true because data from the CONFIRM[11] trial show that there was a very large number of progression events around 90 days, followed by a period with relatively few new events. From 180 days onwards, there was a clear indication of a linear relationship between time and the cumulative TTP/PFS hazard. Thus the ERG proposes that a more accurate approach would be to model these two time points separately and to only include patients in the post-AO population from the CONFIRM[11] trial (see Section 5.5.4 for more detail).

For the first part of the analysis the ERG performed a network meta-analysis on the log-hazard ratios at 180 days. Log-hazard ratios and standard errors were calculated for each comparison within each trial using an approach by Parmar[49] which considers the numbers of patients at risk at the start of the trial and the probability of not experiencing an event at 180 days. Log-hazard ratios and standard errors were then incorporated into a fixed effects network meta-analysis making adjustments for the three armed trials. The results of this network meta-analysis are displayed in Table 22.

Table 22 Network meta-analysis results for TTP/PFS at 180 days (ERG analysis): hazard ratios relative to fulvestrant 500mg

Treatment	Hazard ratio*	95% CI
Fulvestrant 250mg	1.15	(0.96 to1.37)
Fulvestrant 250mg loading dose	1.06	(0.74 to1.48)
Anastrozole 1mg	1.20	(0.97 to 1.47)
Megestrol acetate	1.27	(0.97 to 1.64)
Letrozole 2.5mg	1.28	(0.94 to 1.70)

*HR > 1 favours fulvestrant 500mg

The results show that in the first 180 days after randomisation, fulvestrant 500mg provides a benefit in terms of TTP/PFS compared to all other treatments but none of the differences are statistically significant.

The ERG also calculated the probabilities of each treatment being the best over the first 180 days (Table 23). These probabilities were calculated using the number of times the treatments had the highest rank based on the proportion of patients that progressed during the first 180 days. The probability of fulvestrant 500mg being the best treatment is 56%.

Table 23 Network meta-analysis results for TTP/PFS at 180 days (ERG analysis): probability of each treatment being the best

Treatment	Probability of being best
Fulvestrant 500mg	56%
Fulvestrant 250mg	1%
Fulvestrant 250mg loading dose	38%
Anastrozole 1mg	1%
Megestrol acetate	1%
Letrozole 2.5mg	3%

For the second part of the analysis, the ERG performed a network landmark analysis of progression risk for patients who had not progressed during the first 180 days. This was based on the assumption that survival times after 180 days followed an exponential distribution. Log-hazard ratios and standard errors were calculated for each comparison within each trial using the same approach as before (Parmar[49]) but this time considering the numbers of patients at risk at 180 days (taken from published reports where available and estimated from within study data otherwise) and the probabilities of not experiencing an event at 30 day intervals thereafter. Log-hazard ratios and standard errors were then incorporated into a fixed effects network meta-analysis, making adjustments for the three armed trials as before. The results of this network meta-analysis are displayed in Table 24 below:

Table 24 Network meta-analysis results for TTP/PFS after 180 days (ERG analysis): hazard ratios relative to fulvestrant 500mg

	Hazard ratio*	95% CI
Fulvestrant 250mg	1.50	(1.11 to 1.97)
Fulvestrant 250mg loading dose	1.04	(0.49 to 1.96)
Anastrozole 1mg	1.62	(1.10 to 2.29)
Megestrol acetate	2.33	(1.39 to 3.64)
Letrozole 2.5mg	2.15	(1.02 to 4.01)

*HR > 1 favours fulvestrant 500mg

The results show that fulvestrant 500mg provides a statistically significant benefit in terms of TTP/PFS compared to all other treatments except for the fulvestrant 250mg loading dose; a very slight

benefit was still found for fulvestrant 500mg compared to the fulvestrant 250mg loading dose but this was not found to be statistically significant.

The results above should be interpreted with caution as they are hazard ratios for patients who survived to 180 days without progressing rather than overall TTP/PFS. The ERG also calculated the probabilities of each treatment being the best after the first 180 days (Table 25). These probabilities were calculated using the number of times the treatments had the highest rank based on the proportion of patients that progressed after the first 180 days. The probability of fulvestrant 500mg being the best treatment is 46%.

Table 25 Network meta-analysis results for TTP/PFS after 180 days (ERG analysis): probability of each treatment being the best

Treatment	Probability of being best
Fulvestrant 500mg	46%
Fulvestrant 250mg	0%
Fulvestrant 250mg loading dose	53%
Anastrozole 1mg	0%
Megestrol acetate	0%
Letrozole 2.5mg	1%

Taken together, the findings discussed above, as well as those originally submitted by the manufacturer, suggest that fulvestrant 500mg may result in improved OS when compared to all other comparators, although none of these findings are statistically significant. However, for TTP/PFS, when the log-normal distribution (as advocated by the manufacturer) is used, fulvestrant 500mg is significantly better than fulvestrant 250mg, megestrol acetate and anastrozole. When a two-part TTP/PFS model is employed (as advocated by the ERG), for the first 180 days (a period thought to be driven by protocol-driven activities and short-term events), there are no statistically significant differences between fulvestrant 500mg and the other comparators. However, after 180 days (which relates to the long-term patient experience), fulvestrant 500mg results in significantly improved TTP/PFS when compared to fulvestrant 250mg, megestrol acetate, anastrozole and letrozole.

4.4 Summary of submitted clinical effectiveness evidence

4.4.1 Clinical results

- The main source of clinical evidence described in the MS is derived from the CONFIRM[11] trial which includes 736 patients.
- Median TTP/PFS was statistically significantly longer in the mixed population and post-AO population for fulvestrant 500mg vs fulvestrant 250mg (6.5 vs 5.5 months and 8.6 vs 5.8 months respectively).
- Median TTP/PFS is not statistically significant in the post-AI population (5.4 vs 4.1 months).
- There were no statistically significant differences in terms of OS although the data have yet to mature; OS was numerically greater in the fulvestrant 500mg group compared to the 250mg group (25.1 vs 22.8 months). The log rank analysis indicates that there appears to be a trend for improved OS for patients in the fulvestrant 500mg group compared with those in the fulvestrant 250mg group, however, this did not reach statistical significance (HR=0.84 [95% CI 0.69 to 1.03]; p=0.091).
- Evidence from two supportive dose-ranging phase II trials (FINDER-1[24] and FINDER-2[25]) broadly support these findings.
- The base-case network meta-analysis for OS suggests fulvestrant 500mg improves survival when compared to fulvestrant 250mg, fulvestrant 250mg loading dose, megestrol acetate, anastrozole and letrozole; however, none of these findings are statistically significant.
- For TTP/PFS, the base-case network meta-analysis conducted by the manufacturer reports improved TTP/PFS for fulvestrant 500mg compared to fulvestrant 250mg, megestrol acetate and anastrozole.
- The TTP/PFS meta-analysis undertaken by the ERG suggests that after 180 days, fulvestrant significantly improves TTP/PFS when compared to fulvestrant 250mg, megestrol acetate, anastrozole and letrozole.
- Adverse events are broadly similar between fulvestrant 500mg and 250mg groups.

4.4.2 Clinical issues

- The only direct comparison is between fulvestrant 500mg and fulvestrant 250mg.
- The population included in CONFIRM[11] also includes patients who have not received a prior AO; the licence currently states they must have received a prior AO (although it is not clear to the ERG if this means ever received an AO or last received an AO).
- Two thirds of the patients who have received an AO appear to be receiving fulvestrant as a first-line treatment for LABC/MBC which may be a factor in the improved results for this subgroup compared to the post-AI group.
- It was not possible to compare fulvestrant 500mg with exemestane in a post-AO population.
- It is not possible to compare individual AEs experienced by those receiving fulvestrant 500mg with any comparator other than fulvestrant 250mg.

5 ECONOMIC EVALUATION

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by the manufacturer fulvestrant. The two key components of the economic evidence presented in the MS are (i) a systematic review of the relevant literature and (ii) a report of the manufacturer's *de novo* economic evaluation. See Table 26 for a summary of the key information points. The manufacturer also provided an electronic version of the EXCEL based economic model.

Table 26: Key information in the MS: economic evaluation

Key information	Section (MS)
Details of the systematic review of the economic literature	6
Model structure	6.2.2 to 6.2.5
Technology	6.2.7
Clinical parameters and variables	6.3.1 to 6.3.8
Measurement and valuation of health effects and adverse events	6.4.1 to 6.4.15
Resource identification, valuation and measurement	6.5.1 to 6.5.8
Sensitivity analysis	6.6.1 to 6.6.3
Results	6.7.6 to 6.7.11
Validation	6.8.1
Subgroup analysis	6.9.1 to 6.9.5
Strengths and weaknesses of economic evaluation	6.10.1 to 6.10.4
Assessment of factors relevant to other parties	7

5.2 Overview of manufacturer's cost-effectiveness review

The MS provides a brief description of the review of published cost-effectiveness evidence undertaken by the manufacturer. The databases searched and the search terms used appear to be reasonable and both inclusion and exclusion criteria are explicitly stated. The search by the manufacturer did not identify any relevant studies for inclusion in the review. Although there is no mention of searching within in-house databases for relevant studies, the ERG is confident that no relevant published studies are available for inclusion in the review.

The manufacturer did not identify any papers that had evaluated the cost effectiveness of fulvestrant as a hormonal treatment for women with LABC/MBC; however the MS included data extraction tables and quality assessment reviews of 19 full economic evaluations and two conference abstracts[1] that were considered relevant to inform the structure, assumptions and model inputs for the cost-

[1] Conference abstracts were not critically appraised due to lack of data in the abstracts

effectiveness analysis of fulvestrant as a hormonal treatment for the treatment of women with LABC/MBC.

5.3 Overview of manufacturer's economic evaluation

The manufacturer undertook a *de novo* economic evaluation of fulvestrant (500mg) as a hormonal treatment for women with LABC/MBC. In the base-case analysis, this economic evaluation provides the basis for the manufacturer's claim that fulvestrant (500mg) is cost effective compared with anastrozole, letrozole and fulvestrant (250mg) as a hormonal therapy for women with LABC/MBC. Exemestane is excluded from the base-case analysis as there are no published clinical trial data based on the inclusion criteria used for the network meta-analysis where 'at least 70% of the sample had a documented ER+ receptor status' or in which patients were being treated following treatment with an AO.

5.3.1 Description of manufacturer's economic model

The manufacturer constructed an EXCEL-based cost-utility model with a time-in-state model structure in order to analyse the differences in health benefits (measured in QALYs) and costs between the relevant competing interventions. Figure 7 provides a diagrammatical representation of the health states and the patient pathways in the submitted economic model.

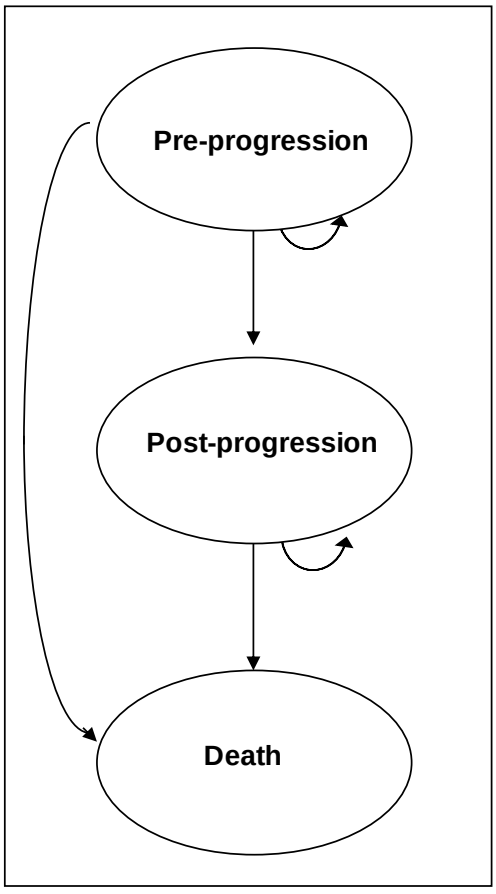

Figure 7 Schematic for cost-utility model for the second-line hormonal treatment of advanced breast cancer patients

Using the time-in-state approach, the proportion of patients transiting to the post-progression health state within a given cycle was estimated as the difference between the proportion of patients being alive at that time point and the proportion of patient being progression-free – i.e. the difference between OS and TTP/PFS. Given that there is an unproven relationship between TTP/PFS and OS for both fulvestrant (500mg) and the lower dose (250mg) that was previously marketed, the time-in-state approach allows both TTP/PFS and OS to be incorporated independently without requiring additional assumptions. If a Markov structure had been used it would have only been possible to model death after post-progression whereas the time-in-state approach allows the amount of time spent in each health state to be modelled explicitly, thereby avoiding this assumption.

There are three mutually exclusive health states represented in the model: pre-progression, post-progression and death. The pre-progression health state represents those patients that receive second-line hormonal therapy and are stable or responding to therapy. This health state is the starting point in the model and where patients are initiated on fulvestrant (500mg) therapy (in-line with the current marketing authorisation) or its competing alternatives. Patients in the pre-progression health state can then either die or if their disease progresses while on second-line hormonal therapy, they move to the post-progression health state. The duration of second-line hormonal treatment was assumed to be the same as the amount of time spent in the pre-progression health state given that the average duration of treatment was not consistently reported in the clinical trials. The post-progression health state captures a series of subsequent therapies and these can be broadly described in the following three groups: third-line hormonal therapy; chemotherapy, which is based on the patients receiving up to three lines of therapy; supportive palliative care. Patients in the post-progression state are assumed to remain in this state until death. The final absorbing health state in the model is death, which patients can move to from either the pre-progression or the post-progression health state. This captures death from any cause.

A monthly cycle length was adopted as this reflects the maximum length of time between doses of hormonal therapies and was also considered the shortest interval over which clinicians would observe a change in the course of the disease or symptoms in clinical practice.

5.3.2 Population

The patient group presented in the base-case analysis is made up of postmenopausal women with ER+ LABC/MBC for disease relapse on or after adjuvant AO therapy, or disease progression on AO therapy, as per the EU licence for fulvestrant 500mg. The manufacturer uses the results of the base case network meta-analysis to furnish the economic model with clinical effectiveness data. However, the base case network meta-analysis includes overall population data from the CONFIRM[11] trial which consists of a mixed population who had received an AO (57.5%) or an AI (42.5%) as their last therapy. This means that some of the clinical data used in the economic model submitted by the manufacturer are derived from patients who are excluded from the fulvestrant 500mg licensed population i.e. patients who had failed on an AI (last therapy); all other studies included in the base case network meta-analysis had received a prior AO.

5.3.3 Comparator technology

The main trial providing clinical evidence in support of fulvestrant 500mg is the CONFIRM[11] trial where fulvestrant 500mg is compared with fulvestrant 250mg. In the manufacturer's base case analysis economic evaluation, the manufacturer compares fulvestrant 500mg with fulvestrant 250mg, anastrozole and letrozole as per the scope using a network meta-analysis approach.

Exemestane is not included as a comparator in the manufacturer's base case economic evaluation as the only two clinical trials[32, 35] which evaluated exemestane did not meet the entry criteria into the base case network meta-analysis; exemestane is only included as a comparator in the manufacturer's economic evaluation when the inclusion criteria are relaxed to include studies in which patients who have failed AO and AI therapies and/or studies with ≥50% of patients with documented hormone receptor positive status are included (Scenario A).

5.3.4 Parameters and values

Table 27 presents a summary of the parameters and values used in the manufacturer's economic model.

Table 27: Parameters and values used in the economic model

	Value	Source	
Network meta-analysis HR OS (95% CI) vs fulvestrant 250mg			
Fulvestrant (500mg)	0.84 (0.69 to 1.03)	Network meta-analysis	
Anastrozole (1mg)	1.02 (0.88 to 1.19)	Network meta-analysis	
Letrozole (2.5mg)	1.20 (0.83 to 1.74)	Network meta-analysis	
Network meta-analysis TTP/PFS result			
Treatment	**Scale Scale (95% CI)**	**Log shape Median of posterior distribution (95% CI)**	
Fulvestrant (250)mg (***base line comparator***)	1.676(1.6 to 1.75)	-0.185	-0.344 to -0.062
	Difference in scale Scale (95% CI)	**Difference in log shape Scale (95% CI)**	
Fulvestrant (500mg)	0.229 (0.167 to 0.293)	-0.102	-0.185 to -0.020
Anastrozole (1mg)	-0.094 (-0.189 to -0.004)	0.029	-0.109 to 0.173
Letrozole (2.5mg)	-0.140 to 0.231	0.108	-0.139 to 0.348
Health state	**Utility value (SE)**	**Reference in MS**	**Justification**
Pre-progression	0.72 (0.014)	Lloyd et al	Most appropriate utility values available in relation to NICE reference case
Post-progression	0.44 (0.016)		
Death	0	n/a	Convention
Costs (drugs)	**Dose description, vial/pack**	**Price per vial/pack**	**Price per month (per 30.4 days)**
Fulvestrant (250mg)	1X5ml IM injection monthly, 50mg/mL, net price 5-ML (250mg)	£348.27	£348.27
Fulvestrant (500mg	2X5ml IM injection monthly + additional dose 2 weeks later, 2X50mg/mL, net price 5-ML (250mg)	£522.41	£522.41
Anastrozole (1mg)	1mg daily, 28-tablet pack	£68.56	£74.48
Letrozole (2.5mg)	2.5mg daily, 28-tablet pack	£84.86	£92.18
Costs (administration)	**Total cost for first month (per 30.4 days)**	**Total cost for subsequent months (per 30.4 days)**	
Fulvestrant (250mg)	£298	£79	
Fulvestrant (500mg)	£377	£79	
Anastrozole (1mg)	£193	£22	
Letrozole (2.5mg)	£193	£22	

5.3.5 Treatment effectiveness within the MS

In the manufacturer's base case economic evaluation, the clinical evidence is derived from a variety of sources. The key trial in support of the use of fulvestrant 500mg is the CONFIRM[11] trial which reports that fulvestrant 500mg is more clinically effective that fulvestrant 250mg in terms of TTP/PFS. The clinical data from the mixed populations in the CONFIRM,[11] FINDER-1[24] and FINDER-2[25] trials are used alongside other clinical trial data in the base case network meta-analysis; it is noted that the number of post-AI patients in the latter trial is small. In the base case network meta-analysis, the other included trials do not include mixed populations; the populations are made up of patients who have failed an AO. The manufacturer presents detailed information on how the network meta-analyses yield estimates of OS and TTP/PFS. The base case network meta-analysis presented by the manufacturer allows comparisons of fulvestrant 500mg with fulvestrant 250mg, anastrozole and letrozole (as per the final scope issued by NICE). The hazard ratios generated for OS and TTP/PFS are estimated using fulvestrant 250mg as the baseline; the manufacturer also provided estimates using fulvestrant 500mg as the baseline during the clarification process. The manufacturer selected a Weibull distribution for OS and a log-normal distribution for TTP/PFS. See Section 4.1.7 for a description and ERG's critique of the manufacturer's approach to network meta-analysis.

There are no data available for the comparison of fulvestrant 500mg vs exemestane in a post-AO population. The manufacturer is only able to consider exemestane as a comparator in a secondary analysis (Scenario A) which allows mixed population trials to be included in the evidence network meta-analysis.

5.3.6 Health related quality of life

Health related QoL data were collected from a subgroup of patients within the CONFIRM[11] study. In summary, pre-progression data were collected from 72 patients in each of the study arms at baseline using the FACT-B questionnaire (Functional Assessment of Cancer Therapy – Breast Cancer).[26] Only patients who lived in English and Spanish speaking countries were asked to complete the questionnaire as the questionnaire was readily available in these languages.

The manufacturer chose to use published pre-progression and post-progression utility values in the submitted economic model for two reasons. Firstly, NICE prefers the use of EQ-5D, a generic HRQoL instrument. Secondly, only baseline HRQoL data from a small subgroup had been collected during the CONFIRM[11] study.

A systematic literature review of utility studies in LABC/MBC was conducted as part of the systematic review of cost-effectiveness studies by the manufacturer; Table B58 in the MS provides a summary of the utility studies identified by the manufacturer. The manufacturer identified ten

potentially relevant sources of utility values; four sources of utility values were identified for hormonal therapies and six were identified for chemotherapy agents. The manufacturer considered that the data described by Lloyd et al[50] were the best utility data available for use in the economic model. The manufacturer acknowledges that the study by Lloyd et al[50] has a small degree of uncertainty given that the preferences are elicited from a relatively small sample of the general population in the UK and uses a standard gamble approach to utility estimation. Table 28 summarises the utility values used in the manufacturer's submitted economic model that were taken directly from the publication by Lloyd et al.[50]

Table 28: Summary of quality of life values for cost-effectiveness analysis

State	Utility value	Standard error	Reference in submission	Manufacturer's justification
Pre-progression	0.72	0.014	Lloyd et al 2006[50]	Most appropriate utility values available, in relation to NICE reference case
Post-progression	0.44	0.016	Lloyd et al 2006[50]	Most appropriate utility values available, in relation to NICE reference case
Death	0	n/a	n/a	Convention

5.3.7 Resources and costs

Resource use data sources

The manufacturer used up-to-date and relevant unit cost data for the valuation of resource use as described in the economic model. The two main published data sources are: NHS Reference Costs (2009/10, 2010/11)[51, 52] and the University of Kent Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2010.[53] In cases where unit costs were not identified in these sources, the unit costs reported by Karnon et al (2003)[54] were inflated to 2009/10 using the PSSRU Hospital and Community Health Services pay and price index.

The manufacturer conducted a systematic literature review of published sources of resource data relevant to the decision problem as part of the systematic review for cost-effectiveness publications. The literature search did not identify any relevant UK studies that contained sufficient information for use in the economic model.

The manufacturer used expert clinical opinion in order to estimate key resource use data. The following topics where included in the expert opinion questionnaire: treatment skipping, third-line hormonal therapy, chemotherapy regimens, post-progression treatment sequences and resource utilisation.

The key costing assumptions made in the economic evaluation are presented in Table 29. Full details of these assumptions and associated unit costs are presented in the MS (Section 6.5.5).

Table 29: Summary of key costing assumptions used in the economic evaluation

Assumption	Description
Resource use pre-progression	As no published UK resource-use data of cost-of-illness studies were identified in the literature review, the resource data were based on expert opinion in the UK
Cost during post-progression	Assumed to be the same cost per month for all treatments (therefore differences across treatments are only based on different amounts of time spent in post-progression health state), based on feedback from clinical experts
Treatments during post-progression	Assumed the treatment pathway involved one of the following four treatment pathways: A) Third line hormonal therapy + supportive palliative care B) Chemotherapy + supportive palliative care C) Third line hormonal therapy + chemotherapy + supportive palliative care D) Supportive palliative care
Treatment skipping (post-progression health state)	It was assumed that all patients received supportive palliative care. It was assumed that only a proportion of the patients received additional active treatments based on expert opinion
Resource use post-progression	For third line hormonal therapy, the resource use was assumed to be the same as during second line hormonal therapy For chemotherapy and palliative care the resource use was included in the total average cost per patient incorporated from the chemotherapy model For supportive and palliative care it was assumed that no active treatment were received and that resources were related to "Package B" as proposed by the chemotherapy model

[redacted]

5.3.8 Costs of adverse events

Grade 1 and Grade 2 AEs were not considered in the economic model as there are minimal costs and minor disutility implications associated with them. The manufacturer reports that it was not feasible to analyse the proportion of patients with Grade 3 or Grade 4 AEs as AEs were not consistently reported

across trials. However, the manufacturer did include SAEs in the model; it was concluded that there were sufficient data consistently reported across the RCTs used in the base case network meta-analysis for TTP/PFS and OS to conduct a network meta-analysis for SAEs. The model assumes that each SAE is associated with an average of 5 days in hospital at a cost of £321.02. Table 30 shows the proportion of patients with a SAE per treatment and the associated costs.

Table 30 Proportion of patients with a serious adverse event (based on network meta-analysis) and related costs per treatment (base-case)

Treatment	Proportion of patients with a serious adverse event	Cost of serious adverse events per treatment
Fulvestrant 250mg	9.1%	£145.94
Fulvestrant 500mg	10.2%	£164.20
Anastrozole	6.4%	£103.03
Letrozole	8.8%	£141.73

5.3.9 Perspective, time horizon and discounting

The economic evaluation was undertaken from the perspective of the NHS and Personal Social Services (PSS). The time horizon stated in the MS was 13 years (lifetime) and this was considered by the manufacturer to be adequate to capture complete differences between comparators (as per the NICE reference case). Both costs and benefits were discounted at 3.5% per annum.

5.3.10 Model validation

The MS (Section 6.8) states that the following measures were taken to check and validate the integrity of the model:

The agency that developed the model undertook an internal quality assurance of the model which involved checking the data inputs and referencing, choices of distributions, inclusion of uncertainty, cell calculations and the macros. Further tests were performed, which included extreme value testing and calculations by hand to ensure that the results were logical, consistent with input data, and made intuitive sense.

A health economist at AstraZeneca independently reviewed the model to access internal validity checks on the data inputs and calculations. At key stages during the development of the model, a clinician involved in regularly treating patients with breast cancer in England, was consulted to provide feedback on the clinical relevance of the modelling approach.

An advisory panel consisting of two independent health economists from academia and two oncologists were commissioned to critique the structure of the model, the key assumptions and data inputs. Furthermore, they validated the outputs of the network meta-analysis and the cost-utility model.

To evaluate whether the model outputs were consistent with the TTP/PFS and OS efficacy results for all the comparators available in the network meta-analysis, the time horizon of the model was restricted to 36 months and the results were compared to the observed network meta-analysis results. In summary, the modelled and the observed results from the network meta-analysis results appeared to show that the TTP/PFS is very similar for anastrozole and letrozole. The modelled results for fulvestrant 500mg and fulvestrant 250mg were lower than expected in comparison to the network meta-analysis results by approximately 0.7 months for fulvestrant 500mg and 0.4 months for fulvestrant 250mg. The manufacturer states that, as the model is under-estimating these results, it is expected that the model is under-estimating the QALY gain; thus the ICERs given by the model for fulvestrant 500mg vs anastrozole and letrozole may be lower in the base case.

5.3.11 Results included in manufacturer's submission

Results [redacted]

The ICERs for fulvestrant 500mg vs letrozole, anastrozole and fulvestrant 250mg are clearly shown in Table 31; both incremental cost per life year gained (LYG) and incremental cost per QALY gained estimates are presented.

Table 31 Manufacturer's base case results [redacted]: fulvestrant 500mg vs comparator

	Fulvestrant 500mg	Letrozole	Anastrozole	Fulvestrant 250mg
Technology acquisition cost	£7,956	£892	£687	£3,623
Other costs	£23,119	£17,944	£21,780	£21,980
Total costs	£31,075	£18,836	£22,467	£25,603
Total costs difference vs fulvestrant 500mg	n/a	£12,239	£8,608	£5,472
LYG	2.624	1.996	2.264	2.299
LYG difference vs fulvestrant 500mg	n/a	0.628	0.359	0.325
ICER (cost per LYG): fulvestrant 500mg vs comparator	**n/a**	**£19,488**	**£23,911**	**£16,688**
QALYs (discounted)	1.487	1.105	1.214	1.256
QALY difference vs. fulvestrant 500mg	n/a	0.383	0.274	0.232
ICER (cost per QALY): fulvestrant 500mg vs comparator	**n/a**	**£31,982**	**£31,461**	**£23,636**

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

The manufacturer performed an incremental analysis, ranking technologies in ascending order of total costs. As shown in Table 32 letrozole was associated with the least cost and fulvestrant 500mg with the highest cost. The base case results demonstrate that there is extended dominance for anastrozole and fulvestrant 250mg. The ICER of fulvestrant 500mg versus letrozole is £31,982 per QALY, with incremental costs of £12,239 and incremental QALYs of 0.383 associated with fulvestrant 500mg in comparison with letrozole.

Table 32 Manufacturer's base case ICERs [redacted]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Letrozole	£18,836	1.105	-	-	-	-
Anastrozole	£22,467	1.214	£3,631	0.109	£33,286	ED
Fulvestrant 250mg	£25,603	1.256	£3,136	0.042	£44,763	ED
Fulvestrant 500mg	£31,075	1.487	£5,472	0.232	£31,982	£31,982

QALYs=quality adjusted life years; ED= extended dominance

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5.3.12 Sensitivity analyses

Deterministic sensitivity analysis

The manufacturer uses tornado diagrams to illustrate the impact of varying the key inputs from their low and high values (95% CIs) on the ICERs for fulvestrant 500mg vs each of the comparators (i.e. anastrozole, letrozole and fulvestrant 250mg) (MS, Figure 35 to 37). [redacted] The key drivers of the cost-effectiveness results are summarised in Table 35.

[redacted]

Table 35 Summary of deterministic sensitivity analysis results [redacted]

Comparison	Variable	ICER range (Cost per QALY gained)
Fulvestrant 500mg vs letrozole	TTP/PFS for letrozole	£21,894 to £55,166
	Utility for pre-progression	£26,553 to £49,473
	Utility for post-progression	£27,691 to £38,331
	OS for letrozole	£30,700 to £40,781
	TTP/PFS for fulvestrant 500mg	£27,406 to £37,453
Fulvestrant 500mg vs anastrozole	TTP/PFS for anastrozole	£22,184 to £48,050
	Utility for pre-progression	£27,036 to £43,881
	TTP/PFS for fulvestrant 500mg	£25,386 to £39,416
Fulvestrant 500mg vs fulvestrant 250mg	TTP/PFS for fulvestrant 250mg	£17,880 to £31,625
	Utility for pre-progression	£20,122 to £33,862
	OS for fulvestrant 500mg	£12,281 to £25,913

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Scenario analyses

The manufacturer conducts six scenario analyses to assess the impact of key assumptions made in the base-case analysis. These are summarised in Table 37.

Table 37 Scenario descriptions

Scenario	Description
A	Expand patient population to post-AO/AI to enable entry of exemestane into network meta-analysis
B	Cost of administration of fulvestrant 500mg and 250mg using alternative proportions of administration in the primary care setting
C	Cost of post-progression using alternative mix of chemotherapies
D	Cost of post-progression eliminating treatment skipping
E	Discounting costs and benefits at 0% and 6%
F	Altering time horizon

Scenario A results are presented in Table 38.

[redacted] The results of Scenario A are presented here in full as exemestane is included as a comparator in the economic evaluation as the population of interest has been widened to include post-AO and post AI patients.

Table 38 Scenario A results [redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£) vs baseline (QALYs)	ICER (Cost/QALY)
Letrozole	£18,832	2.078	1.171	-	-	-	-	Reference
Exemestane	£19,804	2.114	1.180	£972	0.036	0.009	£105,272	ED
Anastrozole	£22,422	2.264	1.215	£2,618	0.151	0.035	£80,726	ED
Fulvestrant 250mg	£25,593	2.299	1.257	£3,171	0.035	0.041	£79,025	ED
Fulvestrant 500mg	£31,045	2.623	1.488	£5,452	0.324	0.231	£38,566	£38,566

ICER= incremental cost-effectiveness ratio; LYG=life years gained; QALYs=quality adjusted life years; ED=extended dominance; Incr.=incremental

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Probabilistic sensitivity analysis

[redacted] The manufacturer summarises the results of the probabilistic sensitivity analysis as follows (MS, Section 6.7.8): At a willingness to pay threshold (WTP) of £20,000 per QALY, there is a 2% probability of fulvestrant 500mg being a cost-effective versus fulvestrant 250mg, anastrozole or letrozole. This increases to 20% at a WTP threshold of £30,000 per QALY. At a WTP of £30,000 per QALY, anastrozole has a 34% probability of being cost-effective, while letrozole has a probability of 41% and fulvestrant 250mg has a probability of 5%.

[redacted]

5.4 Assessment of the manufacturer's economic model

This section summarises the ERG's assessment of the manufacturer's economic model against (i) NICE reference case checklist[55] and (ii) Drummond 10-point checklist.[56]

Table 41 shows how closely the manufacturer's submitted economic evaluation accords with the requirements for a base-case analysis set out in the NICE reference case checklist.[55] In summary, the manufacturer's base case economic evaluation described in the MS mostly matches the NICE reference case as set out in the NICE Methods Guide.[55] The decision problem listed exemestane as a comparator; however, the manufacturer was unable to include exemestane as a comparator in the base case economic evaluation due to lack of available clinical data in the eligible patient population.

Table 42 summarises the ERG's appraisal of the economic evaluation conducted by the manufacturer using the Drummond 10-point checklist.[56] In the main, the ERG considers the economic evaluation described in the MS to be well conducted; the ERG suggested only a few minor corrections related to cost (e.g. use of discounting, cost of drug wastage and re-estimation of AE costs) and a slight modification related to use of utility values. The ERG's main criticism was focussed on the derivation of the clinical effectiveness data for use in the economic model. The ERG is of the opinion that clinical results from the CONFIRM[11] trial do not support the use of fulvestrant 500mg in a post-AI population and that it is inappropriate to use the log-normal distribution to estimate pre-progression survival in the base case network meta-analysis.

Table 41: NICE reference case

Attribute	**Reference case**[55]	**Does the *de novo* economic evaluation match the reference case?**
Decision problem	The scope developed by the Institute	Yes - ok for the comparison of fulvestrant 500mg vs fulvestrant 250mg, anastrozole and letrozole. In order to compare fulvestrant 500mg vs exemestane the manufacturer had to broaden the patient population of interest to include patients for whom fulvestrant 500mg is not licensed
Comparator(s)	Alternative therapies routinely used in the NHS	Yes
Perspective costs	NHS and Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-effectiveness analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes
Synthesis of evidence on outcomes	Systematic review	The manufacturer used evidence from the results of systematic reviews and from pooled evidence using a network meta-analysis approach
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Partial. In the main, the manufacturer uses values from published literature that have been used in previous STAs. However, the ERG argues that a modification to the published values is required.
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes – sensitivity analysis, scenario analysis and probabilistic sensitivity analysis were all performed by the manufacturer

Table 42: Critical appraisal checklist

Item	Critical appraisal[56]	ERG comment
Was a well-defined question posed in answerable form?	Yes	The ERG notes the manufacturer's economic evaluation is focussed on second-line treatment i.e. after first-line tamoxifen in EBC **or** LABC/MBC.
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	The manufacturer used overall trial evidence from the key trial (CONFIRM) which included a mixed population in the base case network meta-analysis; this mixed population included patients (post-AI) for whom fulvestrant 500mg is not licensed. In addition, the ERG was not convinced by the log-normal distribution used to project pre-progression survival. The ERG re-estimated survival gains in the CONFIRM[11] trial and redid the network meta-analysis in the base case economic evaluation
Were all the important and relevant costs and consequences for each alternative identified?	Yes	The ERG's revised ICERs included an additional cost for drug wastage.
Were costs and consequences measured accurately in appropriate physical units?	Not always	The ERG considers the AE costs in the economic model to be overly simplistic; the ERG's recalculated AE costs are higher than the manufacturers AE costs
Were the cost and consequences valued credibly?	Yes	Up to date and relevant cost data sources were used by the manufacturer
Were costs and consequences adjusted for differential timing?	Yes	The ERG identified a minor inaccuracy with the discounting method applied by the manufacturer
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	The manufacturer presented (i) interventions and comparators form least to most expensive (ii) ICERs in comparison with baseline (iii) incremental analysis ranking technologies in terms of dominance and extended dominance
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Sensitivity analysis, scenario analysis and PSA were described in detail by the manufacturer
Did the presentation and discussion of study results include all issues of concern to users?	No	[redacted]

5.5 Detailed critique of manufacturer's economic model

5.5.1 Model structure

The manufacturer of fulvestrant has submitted an economic model of a basic design, which allocates living patients to one of two states – pre-progression and post-progression. Patients incur health care costs and accrue life years and health related utility in both states. The primary drivers of the model are the observed outcomes of the CONFIRM[11] clinical trial, modified by meta-analyses of data from other trials to incorporate the relative clinical effectiveness of comparator treatments.

The CONFIRM[11] trial results are not employed directly, but are represented by parametric models on pre-progression survival and OS, with post-progression survival represented as the difference between these modelled estimates. The reliability of the model therefore depends on answers to the following questions:

1) Is the model design appropriate for estimating differences in health outcomes between different treatments?

2) Do the parametric models adequately represent the data from which they were derived? Are the parametric models employed robust for projecting the available trial data for the remainder of patients' lifetimes?

Model design

The manufacturer's model is based on separate parametric models of the time from randomisation to disease progression (TTP/PFS) and OS. The manufacturer reports conducting comparative model-fitting exercises aimed at replicating each set of Kaplan-Meier product-limit survival estimates obtained from the CONFIRM[11] trial data. Three potential statistical distributions were compared (Weibull, log-logistic and log-normal), with log-normal being considered superior for modelling the TTP/PFS data and Weibull for modelling the OS data. Estimates of the number of patients alive in the post-progression state, are obtained in the submitted model by subtracting estimated numbers of pre-progression patients from the estimated numbers of patients alive at the same time.

This apparently simple approach to populating the model is not without potential problems. When different statistical functions are used to represent the two sets of data, or when the same function is used for both but does not satisfy proportional hazards criteria, it is possible for projected estimates of TTP/PFS to exceed the corresponding estimates of OS leading to negative estimates for the number of patients who are alive in the post-progression state, which is clearly unrealistic. This design flaw is implicitly acknowledged by the model developers by their use of a logical device which converts any such negative post-progression estimates to zero. However, there is no corresponding adjustment made to the OS estimate so the model allows the number of pre-progression patients to exceed the total number of patients alive. There are no checking mechanisms built into the model logic to indicate when such anomalies occur.

This difficulty arises from inherent complications in attempting to use parametric modelling directly to represent OS in an interventional clinical trial. The conventional parametric model functions available in proprietary statistical software all involve the assumption of a risk function which varies smoothly over time, without sudden alterations or discontinuities. However, the design of an interventional trial necessarily involves introducing an active agent for a period of time, and monitoring the condition of patients until a marked change in condition and prognosis occurs. Thus the mortality risk profile is most unlikely to follow a single consistent trajectory throughout the observation period: firstly risk can be expected to fall sharply as the new medication takes full effect, then continue at a relatively reduced rate whilst the treatment is effective, and finally once disease progression is reasserted and the medication is stopped, the risk is likely to rise sharply. In this case, the modellers assume that many patients will receive subsequent lines of medical treatment including cytotoxic therapy, so the risk profile is likely to become very complex and difficult to anticipate. Although a standard parametric model may be identified which appears to be a reasonable match to the available data, there must be serious uncertainty that projections of OS beyond the period of observation may be seriously over or under-estimated due to the complex risk changes that are likely to apply at later times.

An alternative approach to projective modelling is to consider modelling post-progression patient experience directly on the basis of the trial data, and then combine pre and post-progression estimates to obtain the likely best estimate of OS. This approach is not without its complexities, but avoids many of the pitfalls described here, and allows direct validation against the observed OS results available from the trial.

Thus the ERG concludes that the design of the manufacturer's model is inherently vulnerable to unintended errors, and that using a standard parametric model for OS calibrated from clinical trial data is unlikely to provide a robust basis for projecting survival beyond the observed data.

Parametric model performance

The results of the economic evaluation carried out by the manufacturer indicate that the majority of patient benefit within the model appears to arise during the pre-progression period due to extended estimates of TTP/PFS for patients receiving fulvestrant 500mg. It is therefore instructive to consider the extent to which the adopted log-normal parametric model of TTP/PFS corresponds to the trial data used in its calibration. Figure 8 shows a direct comparison of the fulvestrant 500mg model used in the submitted decision model and the Kaplan-Meier results obtained from the CONFIRM[11] trial. An initial view of the TTP/PFS survival plot (Figure 8-A) appears to suggest a reasonable match between data and model. However, the model residuals (Figure 8-B) indicate a non-random pattern of divergence with steadily increasing over-estimation of pre-progression survival for times greater than 18 months after randomisation. This is most clearly seen in the cumulative hazard plot (Figure 8-C) where the log-normal model shows a progressively decreasing gradient (i.e. reducing risk over time) while the trial data indicates a linear trend from 6 months onward (i.e. a fixed risk independent of time).

This discrepancy can be of considerable importance for decision analysis. When projecting a survival curve beyond the trial data for a lifetime, a long 'fat' tail to the distribution may accrue substantial additional estimates of incremental patient benefit which can exceed the incremental gain observed directly during the trial, and in some cases reverse it. Thus it is of critical importance that a parametric model intended for use in projecting patient outcomes should show good correspondence and absence of bias in the later stages of the data collection period. Indeed, since the early phase of the trial is dominated by protocol driven risk-modifying effects it is unlikely that a standard 'smooth' statistical function would ever be adequate to represent trial data over the whole period of observation.

Since the log-normal parametric modelling based on the CONFIRM[11] trial data is used to calibrate the estimates of patient experience for all comparators (via a network meta-analysis), the evident weakness of this aspect of the submitted model calls into question the reliability of all the economic results presented by the manufacturer.

The ERG concludes that the log-normal parametric model used fails to represent adequately the data on which it was calibrated, and therefore does not provide a robust basis for projecting the available trial data for the remainder of patients' lifetimes.

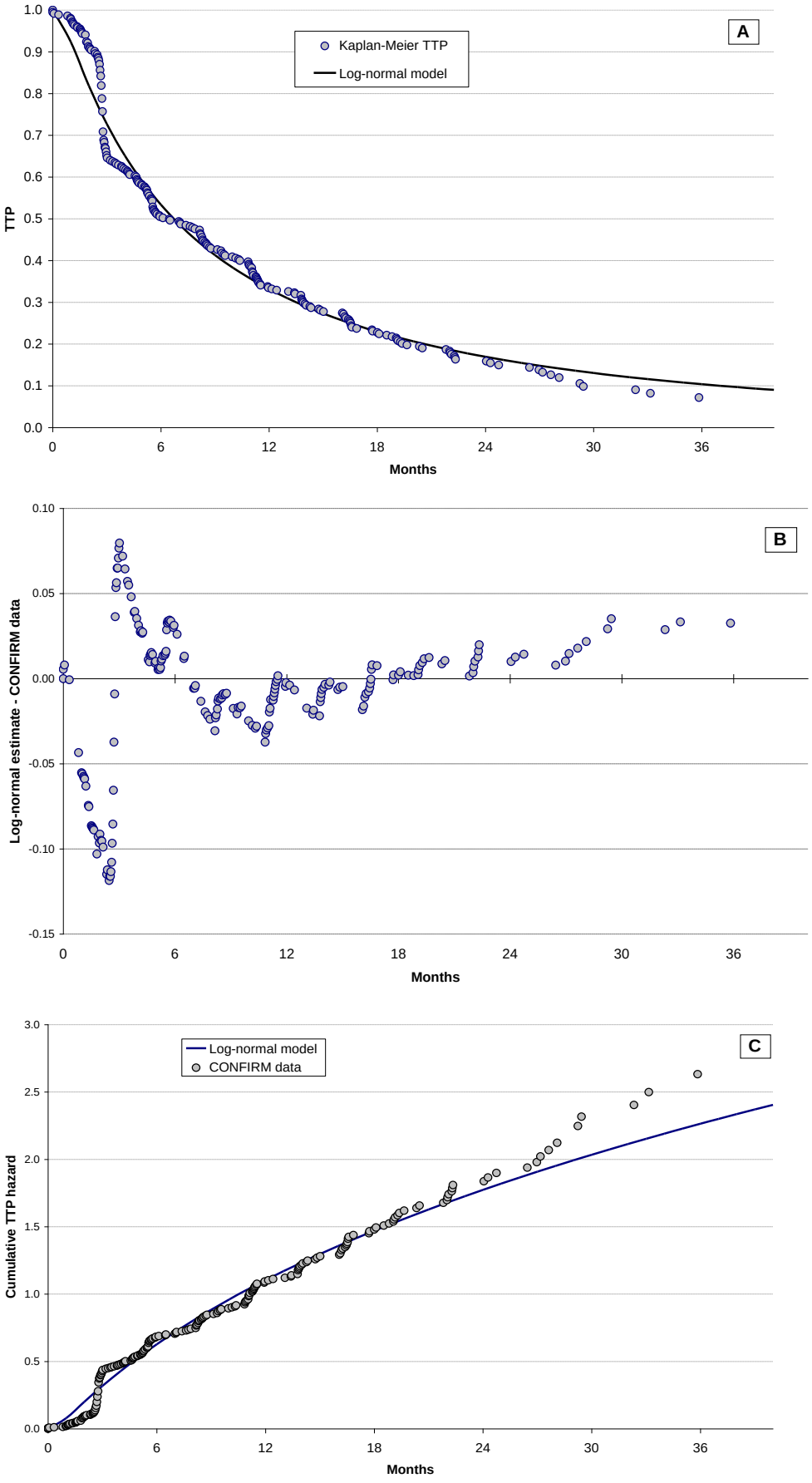

Figure 8 Comparison of CONFIRM TTP/PFS results (fulvestrant 500mg) and log-normal model

5.5.2 Costs

Drug acquisition costs

Although all unit costs use current list prices, and are correctly adjusted to the rate per calendar month, the manufacturer's model does not account for wastage of part-used dispensed packs at the time of progression. If a notional average of half a pack wastage cost is added per patient, the cost of prescribed anastrozole, letrozole and exemestane is increased by a small amount. This has the effect of reducing the incremental cost of fulvestrant against the comparators, and hence reducing estimated ICERs, though the size of this adjustment is small.

Health state costs: disease monitoring, supportive care and terminal care

The manufacturer has used expert opinion to construct a scheme for pre and post-progression health state costs. The ERG prefers to base such costs on the treatment pathways described in the NICE clinical guidelines for ABC[1] as used in a previous ERG STA report.[57]

There are several differences in the assumptions made in these two approaches to costing monthly costs in the pre-progression state. However, the overall monthly estimates are quite similar - £249.36 for the manufacturer and £242.94 using the ERG's approach. Applying the alternative cost estimate leads to a small increase in ICERs for fulvestrant.

For the post-progression state, the manufacturer appropriately applies the "Package 2" method from the NICE clinical guidelines for ABC[1] but the calculations do not appear to be accurate. The ERG has re-estimated the monthly cost at £760.94 rather than £808.33 used in the submitted model, leading to a small decrease in ICERs for fulvestrant.

The manufacturer omits the cost of terminal care on the grounds that all patients in the model die so there will be no incremental cost due to terminal care. Although this is generally a reasonable approximation, differential timing of death will lead to different discounting of costs in each treatment arm with the potential for a small contribution to incremental cost estimates.

Adverse event costs

The manufacturer limits consideration of drug-related AEs to SAEs rather than the more common practice of categorising AEs as Grade 3 and 4 AEs. This is because it is not possible to obtain details of graded AEs consistently for all the comparator drugs featured in the evidence network. Though regrettable, this is a reasonable compromise. By definition, all SAEs involve a non-elective hospital in-patient episode. The manufacturer uses a single cost obtained from a paper by Karnon et al[54] which is based on a simple average cost of all UK hospital admissions derived from the PSSRU cost report,[53] which the manufacturer has updated for NHS hospital inflation from 2000 prices to current prices. This approach is very simplistic and almost certainly inappropriate for costing AEs associated with treatment complications in ABC.

The ERG has calculated an alternative estimate by using a weighted average of four HRG average costs from the 2009/10 NHS Reference Costs[51] for non-elective (long stay) in-patient episodes using codes WA17V/W (Other admissions related to neoplasms with / without complicating conditions) and codes PA43A/45Z (Other neoplasms with length of stay of 1 day or more with complicating conditions, and febrile neutropenia with malignancy). Overall these episodes have a combined mean length of stay of 5.33 days at a mean cost of £3,147.14, which contrasts with the AE average cost of £1605.10 in the submitted model.

In addition the estimated AE costs are all assigned to the first cycle of treatment in the submitted model. This is accurate for chemotherapy restricted to a few cycles in the first year, but in this case some patients remain progression free for several years and remain at risk of treatment related events, so the costs of treating SAEs beyond the first year should be discounted.

Making these modifications nearly doubles the model costs for SAEs, increasing the ICERs for use of fulvestrant, though the increases are small since AE costs are generally a minor element of total costs.

5.5.3 Utility values

Calculation of utility values from model by Lloyd et al

The manufacturer has chosen to employ the Lloyd et al[50] mixed model analysis results to generate utility values for their economic model. This analysis has been used in previous NICE appraisals and probably represents the best source currently available. However, it is important to recognise that the age parameter in the published paper refers to the age of 100 participants in the valuation exercise, and not to the age of patients. For consistency with the standard UK EQ-5D tariff scores, the mean age should be set to 47, the mean age of the original York study.[58] Recalculating the expected utility values for patients in the stable, responder and progression states (without AEs) on this basis produces revised utility estimates consistently higher than those in the submitted model. The manufacturer argues that no account need be taken of the responder status of patients since objective response is not routinely assessed in UK practice. This would be relevant if we assume that the utility difference attributed to a complete or partial response is purely psychological. If however, we admit that response to therapy may have a clinical/physical aspect, then the absence of a response assessment does not mean that responses achieved in clinical trials are not informative in estimating utility values.

In fact response to therapy has been uniformly reported in the trial used in the evidence network, so it was possible for the ERG to recalculate utility scores for post-progression survival, and also for TTP/PFS incorporating trial reported response rates. This produced very similar TTP/PFS estimates across all trials and all therapies, such that it was concluded that a single pooled estimate was appropriate for use in this appraisal. The ERG estimated utility values are 0.7733 for time in the TTP/PFS state, and 0.4964 for time in the post-progression survival state. Very few SAEs were reported, and no significant differences between

therapies were found; therefore it is appropriate that disutilities for AEs are omitted from the model. Applying the recalculated scores to the manufacturer's model noticeably reduces the ICER for fulvestrant vs comparators by about £2,700 per QALY gained.

5.5.4 Survival estimation

As previously discussed in Section 4.1.7, the ERG is of the opinion that the data sources used in the network meta-analyses presented by the manufacturer do not support comparison of fulvestrant 500mg with other agents for patients who have failed on prior AI treatment, since important cited trials include very few patients who have ever received AI treatment. However, the manufacturer's base case evidence network is valid for patients previously treated with AO therapy. To allow recalibration of the manufacturer's model, data from the CONFIRM[11] trial specific to patients receiving prior AO therapy has been analysed by the ERG.

TTP/PFS projection in CONFIRM trial

The ERG has adopted a simple two-part model to all lifetime projections of TTP/PFS. This recognises that the timing of disease progression events in the early phase of the trial is largely governed by the scheduling of patient assessments as per the protocol. In the CONFIRM[11] trial these were set at 90 day intervals. The TTP/PFS Kaplan-Meier plot clearly shows a very large number of progression events around 90 days, followed by a period with relatively few new events. By the time of the second assessment (180 days) it was judged that all the patients who would derive no benefit from the allocated treatment would have been identified, and the drug would have achieved its full potency and effectiveness in reducing the risk of disease progression. From 180 days onwards, there was a clear indication of a linear relationship between time and the cumulative TTP/PFS hazard suggesting that an exponential long-term model would be appropriate for both treatment arms of CONFIRM.[11] Therefore, mean TTP/PFS was estimated as the area under the Kaplan-Meier plot (AUC) from randomisation to 180 days, to which was added the expected mean remaining lifetime in the pre-progression state for all patient remaining alive and progression free 180 days after randomisation. The results are shown in Table 43 and indicate an estimated gain of nearly 4 months prior to disease progression, almost all attributable to the reduced risk of progression after the first 6 months treatment with the higher dose of fulvestrant.

Table 43: ERG estimated TTP/PFS in CONFIRM trial

	AUC (0-180 days)		Projected (180+ days)		Total estimated TTP/PFS	
Treatment	**Days**	**Months**	**Days**	**Months**	**Days**	**Months**
Fulvestrant 250mg	129.8	4.26	175.1	5.75	304.9	10.02
Fulvestrant 500mg	137.4	4.51	289.4	9.13	415.2	13.64
Difference	7.60	0.26	114.3	3.37	110.3	3.62

Post-progression projection in CONFIRM trial

In response to a request by the ERG, the manufacturer provided details of post-progression survival in the CONFIRM[11] trial. Detailed analysis indicated that neither the dose of fulvestrant (250mg vs 500mg) nor the prior therapy received by patients (AO vs AI) had any effect on the survival of patients following disease progression whilst being treated with fulvestrant. Kaplan-Meier analysis revealed a consistent pattern involving a constant mortality risk for a period of about 250 days after progression, then a period of gradually increasing risk, then finally after 500 days, from post-progression onwards, a final phase with a higher constant mortality risk occurred. This appears to be consistent with patients being offered one or more additional lines of medical therapy, before active treatments are discontinued in favour of supportive and palliative care.

To estimate the expected mean post-progression survival per patient, the area under the survival curve (AUC) was calculated for the whole of the data set (regardless of regimen or prior treatment to minimise uncertainty in estimation), to which was added the anticipated mean survival beyond the trial data, based on a projected exponential model, calibrated on the Kaplan-Meier results for the final long-term period (500+ days). This resulted in a mean expected post-progression survival estimate of 567.9 days (18.7 months) made up of 520.4 days within the trial period and 47.4 additional projected days.

Overall survival projected in the CONFIRM trial

Overall survival has been estimated by the ERG by combining TTP/PFS and post-progression survival estimates. In order to achieve this it is necessary to estimate the proportion of progressing patients who die at the time of progression and therefore do not benefit from any post-progression survival. An analysis of fatality rates in the pre-progression phase split by regimen and by prior treatment showed that the small differences calculated were not statistically significant (χ^2= 0.195, p = 0.98). A further analysis indicated that there was no difference in fatalities occurring before or after 180 days (χ^2=0.10, p = 0.75). It was therefore decided to use the common overall pre-progression fatality rate of 9.21%.

On this basis the estimated OS for CONFIRM[11] patients previously AO treated is 820 days (26.96 months) when treated with fulvestrant 250mg, and 931 days (30.58 months) when treated with fulvestrant 500mg. In both cases the post-progression survival component of the estimate is 516 days (16.94 months). Thus the incremental survival gain attributable to the higher dose of fulvestrant is 110 days (3.62 months).

Estimated survival for comparators

In order to calculate compatible survival estimates for the base case analysis in post-AO patients, it was necessary for the ERG to revise the network meta-analysis presented by the manufacturer for TTP/PFS. Instead of the complex procedure necessary to accommodate the assumption of a log-normal baseline model distribution, it was only necessary to produce a simple hazard ratio for TTP/PFS at 180 days, and hazard ratios for the post-180 day exponential model parameter. The resulting ratios are shown in Table 44 and in Table 45.

Table 44: Network meta-analysis hazard ratios for TTP/PFS **at** 180 days (post-AO population)

	Comparator				
Treatment	**Fulvestrant 250mg**	**Fulvestrant 250mg LD**	**Anastrozole 1mg**	**Megestrol Acetate**	**Letrozole 2.5mg**
Fulvestrant 500mg	1.153 (0.964 to1.368)	1.064 (0.743 to1.483)	1.196 (0.965 to1.465)	1.273 (0.974 to 1.638)	1.276 (0.941 to1.695)
Fulvestrant 250mg		0.922 (0.676 to 1.233)	1.037 (0.920 to 1.162)	1.104 (0.905 to 1.333)	1.107 (0.867 to 1.391)
Fulvestrant 250mg LD			1.151 (0.822 to 1.568)	1.225 (0.843 to1.727)	1.228 (0.823 to 1.769)
Anastrozole 1mg				1.065 (0.908 to1.24)	1.067 (0.861 to 1.306)
Megestrol Acetate					1.002 (0.872 to 1.146)

Hazard Ratios > 1 favour the treatment; hazard ratios < 1 favour the comparator

Table 45: Network meta-analysis hazard ratios for exponential projection of TTP/PFS **after** 180 days (post-AO population)

	Comparator				
Treatment	**Fulvestrant 250mg**	**Fulvestrant 250mg LD**	**Anastrozole 1mg**	**Megestrol Acetate**	**Letrozole 2.5mg**
Fulvestrant 500mg	1.496 (1.114 to1.969)	1.038 (0.489 to 1.959)	1.62 (1.103 to 2.293)	2.327 (1.393 to 3.642)	2.149 (1.018 to 4.01)
Fulvestrant 250mg		0.694 (0. 35 to 1.244)	1.083 (0.851 to1.357)	1.555 (1.032 to 2.248)	1.437 (0.729 to 2.546)
Fulvestrant 250mg LD			1.732 (0.828 to 3.209)	2.488 (1.106 to 4.88)	2.298 (0.855 to 5.058)
Anastrozole 1mg				1.437 (1.037 to1.938)	1.327 (0.709 to 2.267)
Megestrol Acetate					0.924 (0.549 to 1.459)

Hazard Ratios > 1 favour the treatment; hazard fatios < 1 favour the comparator

5.5.5 Minor amendments and corrections

Discounting

A minor error was detected in the timing of discounting in the manufacturer's model. The formula used allowed the first 13 months of model costs and outcomes to be undiscounted (instead of 12), so that thereafter discounting was not correctly synchronised with calendar years. Since this affects both costs and outcomes, the net effect is only a very small increase in calculated ICERs.

5.6 Summary

The ERG has identified several minor issues that require correction/modification in the economic model relating to drug wastage, calculation of health state and adverse events cost, use of discounting method and estimation of utility values. More importantly, the ERG considers the data used to furnish the clinical effectiveness data in the economic model to be weak. The impact on the size of the estimated ICERs of these minor and major corrections/adjustments is explored in Section 6.

6 ADDITIONAL WORK UNDERTAKEN BY ERG

6.1 Survival estimation

6.1.1 Survival estimation: post-progression survival

In response to a request from the ERG, the manufacturer provided detailed Kaplan-Meier analysis results for post-progression survival, separately for patients who had previously received any AI treatment (AI patients) and those who had not (AO patients). A direct comparison of the post-progression survival experience in the four subgroups defined by type of prior therapy and trial arm was carried out and confirms that there is no statistical differences present post-progression (p= 0.704, log-rank test) as shown in Figure 9.

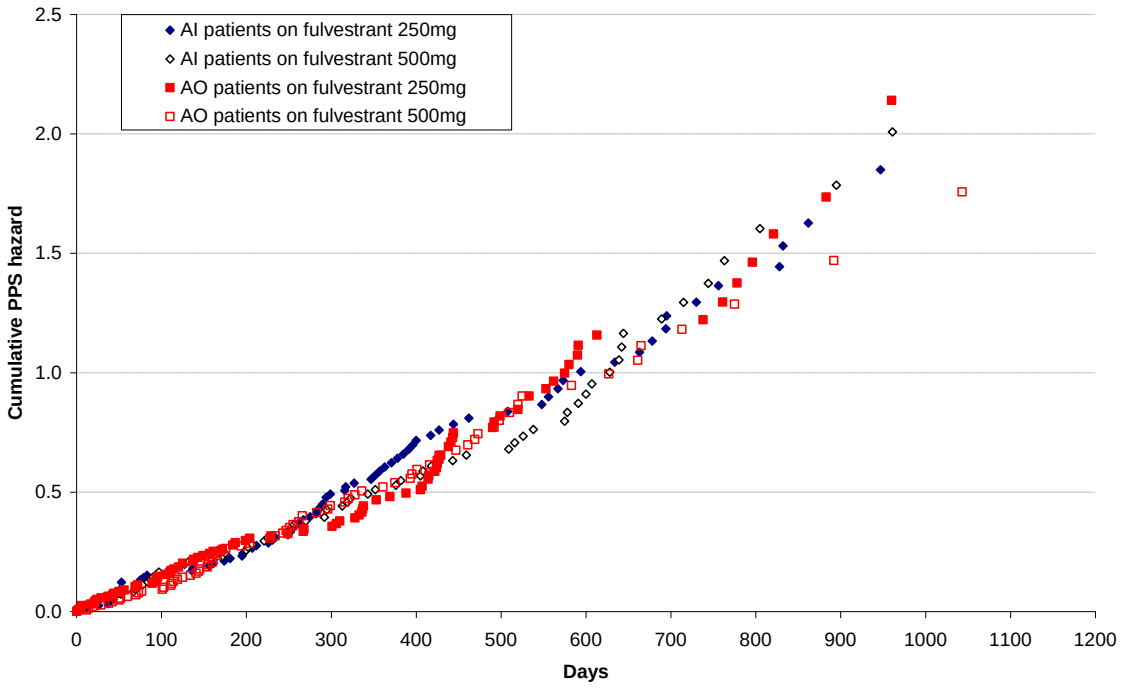

Figure 9 Comparison of CONFIRM post-progression survival results: by prior treatment and fulvestrant dose

In view of this close similarity of trends, a single combined Kaplan-Meier analysis was carried out (Figure 10) which indicated a stable pattern of post-progression mortality, with a long-term constant risk of death at any time beyond 500 days after disease progression.

Although these results can be used to project post-progression survival beyond the available trial data, the main consequence of this finding is that all differential benefit from use of the 500mg dose of fulvestrant is strictly limited to the pre-progression phase, provided that there is no difference in the proportions of trial

patients proceeding alive at progression into the post-progression phase. These proportions were examined and showed no significant difference was present ($\chi^2 = 0.195$, $p = 0.978$). Therefore, the ERG concluded that examination of the TTP/PFS data from CONFIRM[11] was sufficient to establish a reliable estimate of overall survival gain from use of 500mg of fulvestrant rather than 250mg.

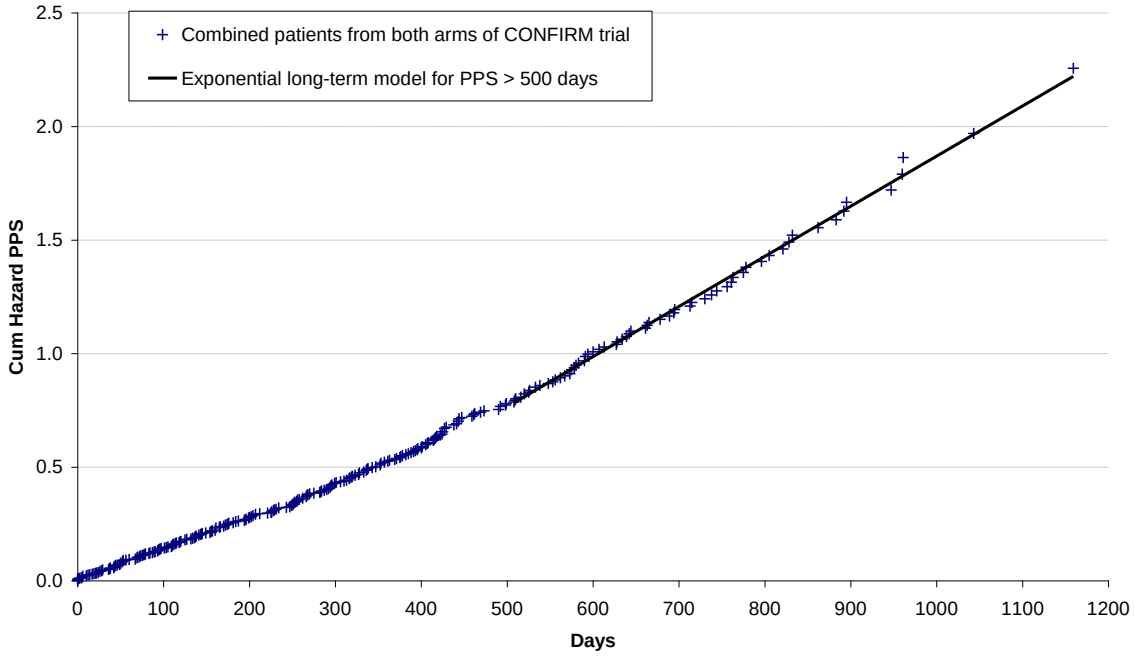

Figure 10 Combined post-progression survival data from CONFIRM trial and long-term exponential model

6.1.2 Survival estimation: time to progression/progression-free survival

In order to obtain consistent estimates of TTP/PFS across the range of comparator treatment, it is necessary to meta-analyse data from several clinical trials. The network of evidence identified by the manufacturer is designed to allow calibration of evidence for anastrozole, letrozole and exemestane against fulvestrant 500mg. However, the ERG has examined the populations of the various trials in the network and concluded that they are not compatible. In particular, the CONFIRM[11] trial includes patients who have received an AI treatment (AI) and who have not previously received an AI treatment (AO). The manufacturer's approach to meta-analysis implicitly assumes that both AI and AO patients gain similar benefits from fulvestrant. However, there is evidence from the CONFIRM[11] trial that patient outcomes are heterogeneous with respect to type of previous treatment, since AI patients appear to benefit considerably less than AO patients from fulvestrant treatment.

In most of the other trials in the manufacturer's evidence network the trial populations are predominantly AO patients (since AIs were not in widespread use at the time). Therefore the use of the evidence network may not be valid for the comparison of other treatments with fulvestrant 500mg. The ERG takes the view that an

assessment of cost effectiveness may still be made if the use of CONFIRM[11] data is restricted to the AO sub-population of the CONFIRM[11] trial, and exemestane is omitted as a comparator.

The ERG has analysed Kaplan-Meier data provided by the manufacturer in response to a clarification request, to consider the most appropriate way to estimate pre-progression survival from the CONFIRM[11] trial, and then estimate the parameters which would allow consistent inclusion of anastrozole and letrozole within the economic evaluation.

Figure 11 shows the TTP/PFS hazard plot for the two CONFIRM[11] trial arms, and in each it is apparent that the timing of protocol mandated patient assessments at 90 day intervals are influential on the reporting of progression events. However, it also appears that simple linear long-term trends are established after the first half-year and continue throughout the trial period. On this basis it was decided to split the estimation of TTP/PFS into two phases:

- the first 180 days from randomisation (up to the second trial assessment), in which the CONFIRM[11] Kaplan-Meier results would be used directly, and

- the remaining period (180+ days), which would be modelled using an exponential model calibrated using a landmark analysis.

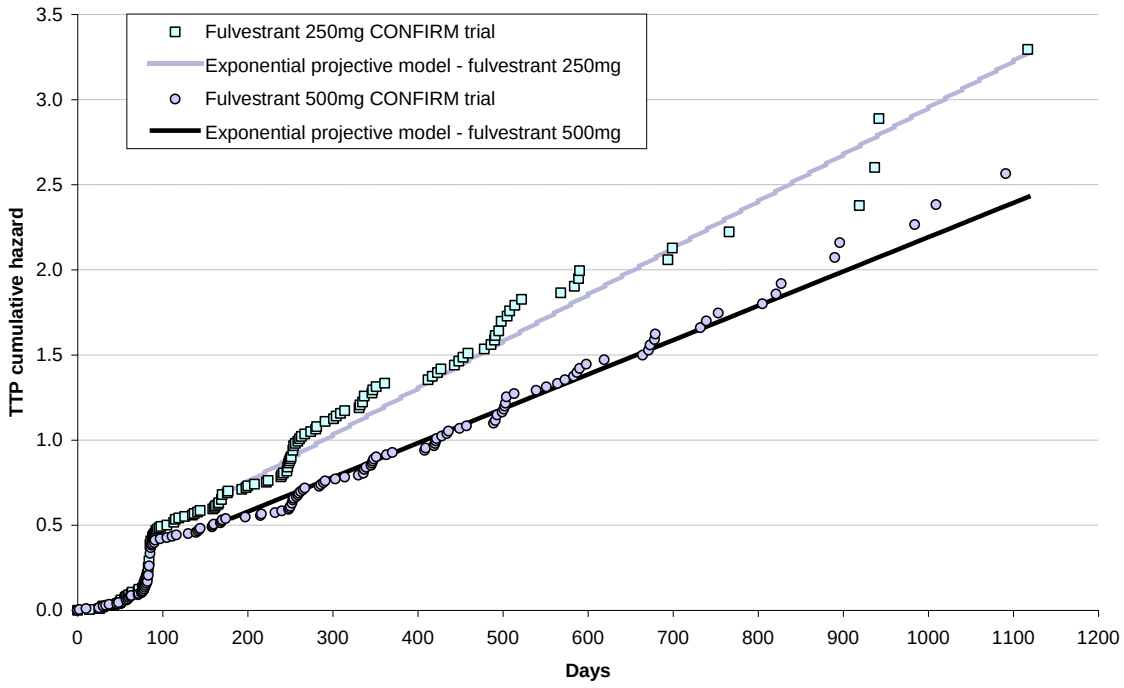

Figure 11 Kaplan-Meier hazard plot for TTP/PFS data for AO patients in the CONFIRM trial and long-term exponential models (180+ days)

The expected mean TTP/PFS was then estimated as 415.2 days for fulvestrant 500mg and 304.9 days for fulvestrant 250mg, indicating a gain in TTP/PFS (and hence in OS) of 110.3 days (95% confidence interval, 99.4 to 121.3days) or 3.63 months (3.27 to 3.98).

Separate hazard ratios were estimated using WinBUGs to estimate the hazard at 180 days, and the long-term exponential projection parameter for anastrozole and letrozole compared to fulvestrant 500mg.

6.1.3 Survival estimation: overall survival

In order to exemplify, in the manufacturer's model, the effects of these ERG outcome gains estimated for TTP/PFS, it was necessary to transfer these accurately to OS gains (since no post-progression survival advantage occurs). A compatible set of survival estimates (PFS, post-progression survival and OS) were prepared for fulvestrant 250mg patients, by calibrating a hazard ratio applied to the OS estimated for fulvestrant 500mg patients which generated an OS gain equal to the corresponding estimated TTP/PFS gain. This is an approximation but allows the timing of post-progression survival to be calculated without recourse to elaborate additional modelling. The same approach was used for anastrozole and letrozole: this appears fully justified in the case of anastrozole since key clinical trials comparing anastrozole with fulvestrant 250mg[5, 6] demonstrated very similar (and statistically non-significant) TTP/PFS and OS results. The approach is less clearly supported in the case of letrozole, where there are no trials which directly compare letrozole with any fulvestrant regimen. The OS hazard ratios employed were 1.130 for fulvestrant 250mg, 1.148 for anastrozole and 1.209 for letrozole.

6.2 Cost-effectiveness results using ERG model revisions

Eight separate modifications were made by the ERG to allow exploration of the impact of the various issues described above. Seven of these concern amendments or corrections to model logic or alterations to model parameter values. The eighth involves substituting effectiveness data from the AO sub-population from the CONFIRM[11] trial in place of those from the whole trial sample, to match more closely the populations in the other studies featured in the evidence network.

Detailed deterministic results are presented separately for the manufacturer's base case scenario using the whole CONFIRM[11] population and for the ERG's AO population. [redacted]

It was not possible within the time available for the ERG to produce probabilistic cost-effectiveness results without extensive modifications and testing of the model to incorporate uncertainty associated with the inclusion of the ERG alterations and additions made to the manufacturer's model.

6.2.1 Base case using full CONFIRM population

The full results for four treatments are shown in Table 46.

The ERG changes to the manufacturer's model to arrive at a revised base case do not affect patient survival, but increase modestly both mean estimated costs and utilities for all four treatments. [redacted]

The calculated deterministic ICERs suggest that the efficiency frontier passes through letrozole, anastrozole and fulvestrant 500mg which dominates fulvestrant 250mg. The ICERs for anastrozole vs letrozole and fulvestrant 500mg vs anastrozole are both close to £30,000 per QALY gained. [redacted]

6.2.2 ERG base case using AO-only CONFIRM population

Table 47 details the deterministic results based on the ERG's analysis of the AO-only subgroup of the CONFIRM[11] trial, and updating of the evidence network meta-analysis results. This suggests slightly increased lifetime survival estimates, but reduced incremental outcomes (life-years and QALYs). Anastrozole now appears to perform more strongly compared to letrozole (with much reduced incremental cost) and remains on the efficiency frontier [redacted]. [redacted] The ICER for fulvestrant 500mg vs anastrozole is nearly £35,000 per QALY gained [redacted]. Figure 12 and Figure 13 show the cost-effectiveness planes and efficiency frontiers using (i) full CONFIRM[11] population and manufacturer's effectiveness analysis (ii) AO-only CONFIRM[11] population and manufacturer's effectiveness analysis.

Table 46: Cost-effectiveness results using full CONFIRM population and manufacturer's effectiveness

Treatment / Result	Fulvestrant 500mg Survival (months)	Fulvestrant 500mg QALYs *	Fulvestrant 500mg Costs *	Fulvestrant 250mg Survival (months)	Fulvestrant 250mg QALYs *	Fulvestrant 250mg Costs *	Anastrozole Survival (months)	Anastrozole QALYs *	Anastrozole Costs *	Letrozole Survival (months)	Letrozole QALYs *	Letrozole Costs *
Manufacturer Base Case	**33.39**	**1.4872**	**£31,075**	**28.98**	**1.2557**	**£25,603**	**28.52**	**1.2137**	**£22,467**	**24.94**	**1.1046**	**£18,836**
Correct discounting logic	33.39	1.4840	£31,004	28.98	1.2531	£25,544	28.52	1.2111	£22,412	24.94	1.1024	£18,791
Include pack wastage	33.39	1.4872	£31,075	28.98	1.2557	£25,603	28.52	1.2137	£22,501	24.94	1.1046	£18,878
Revise PFS costs	33.39	1.4872	£31,654	28.98	1.2557	£26,025	28.52	1.2137	£22,842	24.94	1.1046	£19,229
Revise PPS costs	33.39	1.4872	£31,024	28.98	1.2557	£25,552	28.52	1.2137	£22,414	24.94	1.1046	£18,794
Include terminal care costs	33.39	1.4872	£32,011	28.98	1.2557	£26,578	28.52	1.2137	£23,446	24.94	1.1046	£19,847
Discount SAE costs	33.39	1.4872	£31,215	28.98	1.2557	£25,733	28.52	1.2137	£22,560	24.94	1.1046	£18,965
Revise utility values	33.39	1.6316	£31,075	28.98	1.3813	£25,603	28.52	1.3369	£22,467	24.94	1.2138	£18,836
ERG revised Base Case	**33.39**	**1.6280**	**£32,602**	**28.98**	**1.3784**	**£27,013**	**28.52**	**1.3341**	**£23,833**	**24.94**	**1.2114**	**£20,317**
Incremental results using ERG revised Base Case												
Fulvestrant 500mg vs *ICER (per QALY gained)*				+4.40	+0.2496 ***£22,393***	+£5,589	+4.87	+0.2939 ***£29,838***	+£8,769	+8.45	+0.4165 ***£29,492***	+£12,285
Fulvestrant 250mg vs *ICER (per QALY gained)*							+0.47	+0.0443 ***£71,774***	+£3,180	+4.05	+0.1670 ***£40,104***	+£6,696
Anastrozole vs *ICER (per QALY gained)*										+3.58	+0.1227 ***£28,664***	+£3,516
[redacted]												

analysis * discounted

Table 47: Cost-effectiveness results using AO-only CONFIRM population and ERG's effectiveness analysis

Treatment	Fulvestrant 500mg			Fulvestrant 250mg			Anastrozole			Letrozole		
Result	Survival (months)	QALYs *	Costs *	Survival (months)	QALYs *	Costs *	Survival (months)	QALYs *	Costs *	Survival (months)	QALYs *	Costs *
Manufacturer Base Case *(AO only population)*	**36.33**	**1.5460**	**£34,142**	**32.74**	**1.3535**	**£29,527**	**32.31**	**1.3301**	**£26,145**	**30.90**	**1.2537**	**£26,046**
Correct discounting logic	36.33	1.5425	£34,062	32.74	1.3506	£29,456	32.31	1.3272	£26,079	30.90	1.2511	£25,981
Include pack wastage	36.33	1.5460	£34,142	32.74	1.3535	£29,527	32.31	1.3301	£26,179	30.90	1.2537	£26,088
Revise PFS costs	36.33	1.5460	£34,664	32.74	1.3535	£29,911	32.31	1.3301	£26,513	30.90	1.2537	£26,359
Revise PPS costs	36.33	1.5460	£34,080	32.74	1.3535	£29,464	32.31	1.3301	£26,082	30.90	1.2537	£25,983
Include terminal care costs	36.33	1.5460	£35,054	32.74	1.3535	£30,470	32.31	1.3301	£27,092	30.90	1.2537	£27,005
Discount SAE costs	36.33	1.5460	£34,291	32.74	1.3535	£29,663	32.31	1.3301	£26,242	30.90	1.2537	£26,180
Revise utility values	36.33	1.7004	£34,142	32.74	1.4928	£29,527	32.31	1.4675	£26,145	30.90	1.3851	£26,046
ERG revised Base Case *(AO only population)*	**36.33**	**1.6966**	**£35,576**	**32.74**	**1.4896**	**£30,849**	**32.31**	**1.4644**	**£27,453**	**30.90**	**1.3822**	**£27,357**
Incremental results using ERG revised Base Case												
Fulvestrant 500mg vs *ICER (per QALY gained)*				+3.59	+0.2071 ***£22,828***	+£4,727	+4.03	+0.2323 ***£34,972***	+£8,123	+5.43	+0.3144 ***£26,137***	+£8,218
Fulvestrant 250mg vs *ICER (per QALY gained)*							+0.43	+0.0252 ***£134,703***	+£3,396	+1.84	+0.1074 ***£32,519***	+£3,492
Anastrozole vs *ICER (per QALY gained)*										+1.41	+0.0822 ***£1,162***	+£95
[redacted]												

* discounted

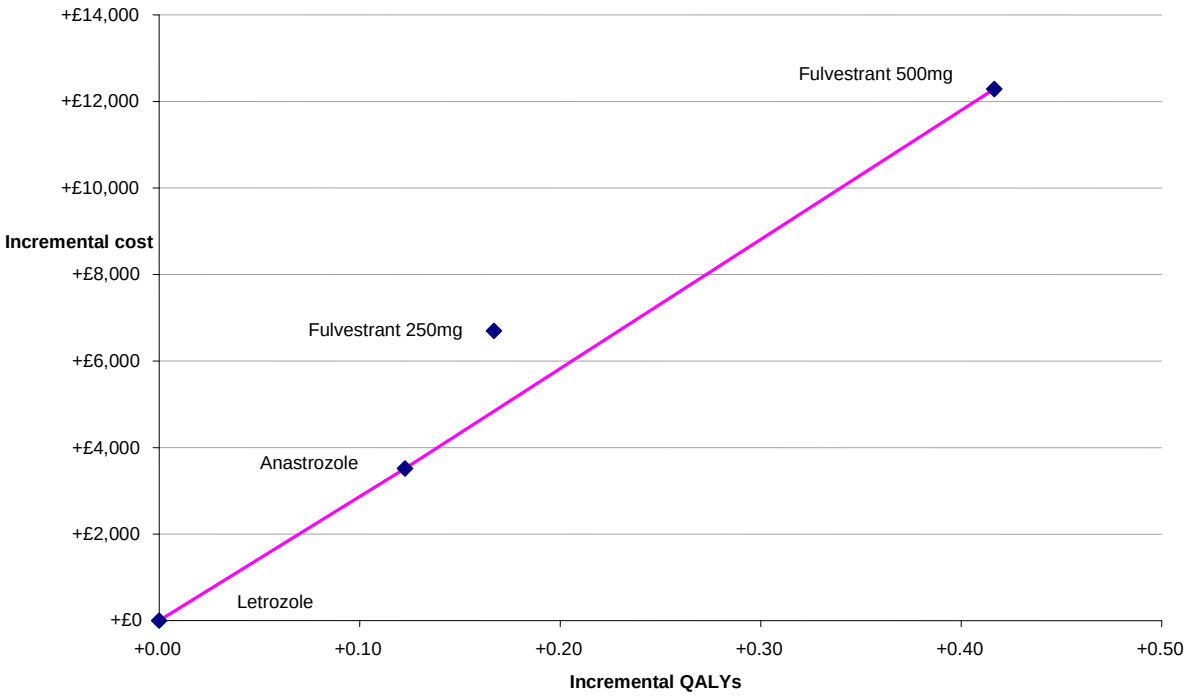

Figure 12: Cost-effectiveness plane and efficiency frontier using full CONFIRM population and manufacturer's effectiveness analysis

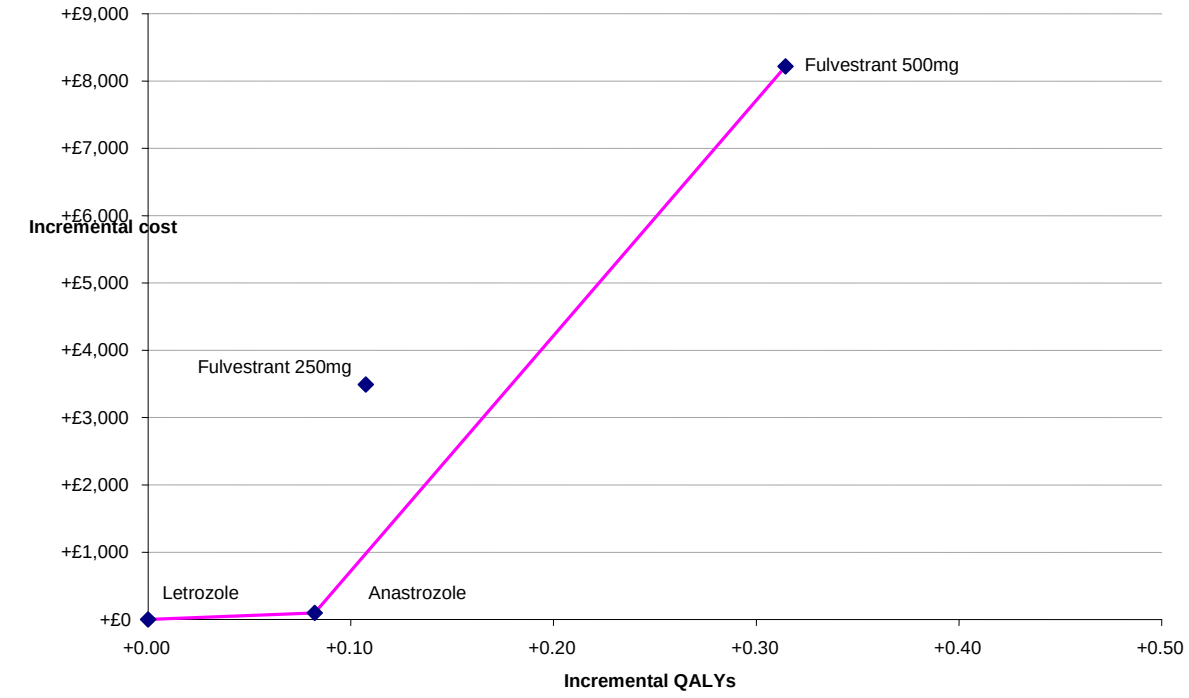

Figure 13: Cost-effectiveness plane and efficiency frontier using AO-only CONFIRM population and ERG's effectiveness analysis

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

The manufacturer presents the case for the use of fulvestrant 500mg compared to fulvestrant 250mg for patients with LABC/MBC from evidence from a large phase III trial (CONFIRM[11]) supported by evidence from the two smaller dose-ranging phase II trials (FINDER-1[24] and FINDER-2[25]). To enable comparisons with AIs, a network meta-analysis was conducted which included an additional five[5, 6, 27-29] trials.

In terms of direct evidence, for a mixed population of patients who had received either an AO or an AI as their last endocrine therapy, CONFIRM[11] reported significant improvements in terms of TTP/PFS for the fulvestrant 500mg arm over the 250mg arm. No significant differences were reported for other outcomes, including OS, ORR and CBR although there did appear to be a trend towards improved OS. No significant differences were reported in the phase II trials[24, 25] and so taken together, there appears to be evidence that fulvestrant 500mg is more efficacious than fulvestrant 250mg in a mixed population.

The scope issued by NICE[21] is compatible with the EU licence for fulvestrant 500mg in stipulating that patients must have failed a prior endocrine therapy with an AO. Therefore, the ERG believes a more appropriate population to consider is the post-AO subgroup. The subgroups of post-AO and post-AI patients appear to be heterogeneous populations in terms of their age, previous endocrine therapy received and in terms of their outcomes. That is, patients in the post-AO group appeared to be younger than those in the post-AI group (median 58 vs 64 years), and the majority of patients in the post-AO group were receiving fulvestrant as first-line treatment for ABC whereas the majority of patients in the post-AI group were receiving it as second-line therapy for ABC. Significant improvements in TTP/PFS between fulvestrant 500mg and 250mg were reported in the post-AO group but not in post-AI patients. An association between previous treatment (and possibly also age) and size of treatment effect would not be unexpected. The ERG notes that similar concerns were expressed by the oncology Scientific Advisory Group in the EMA EPAR,[9] who stated (pg 47):

> Currently, there is no strong pharmacologic rationale to assume that tumour characteristics would be substantially different in patients with disease progression after aromatase inhibitors compared to patients who progressed upon anti-estrogen therapy. However, there is also no strong rationale to exclude that such differences exist. One would need to confirm this through adequate clinical trials.

Concerning the CONFIRM trial, there are substantial differences between the two populations in terms of patient and disease characteristics (e.g., demographics, prior treatment) to make an extrapolation difficult.

In terms of indirect evidence, while much detail was provided in the MS about how the analysis was conducted, little was devoted to the interpretation of the findings in the clinical section of the MS. This is surprising given that the other comparators in this network meta-analysis include AIs which are not only used more often in clinical practice than is fulvestrant 250mg, but crucially are also recommended by NICE. The findings from analysis of seven[5, 6, 11, 24, 25, 27, 28] trials suggests that fulvestrant 500mg results in significantly improved TTP/PFS when compared to fulvestrant 250mg and anastrozole. While not statistically significant, there is also the suggestion of an improved benefit in TTP/PFS when compared to letrozole. A similar OS benefit is seen in five trials,[5, 6, 11, 27, 28] when compared to fulvestrant 250mg, anastrozole and letrozole.

However, there are a number of weaknesses with the network meta-analysis. First, the ERG believes a different approach (not using a log-normal distribution) is required for TTP/PFS based on events shown on the Kaplan-Meier curve for CONFIRM.[11] More importantly, because of heterogeneity between the post-AO and post-AI populations in CONFIRM,[11] the ERG also considered that only the post-AO subgroup from this trial should be included in the network meta-analysis. The approach advocated by the ERG examined TTP/PFS for the first 180 day by log-hazards and thereafter using a landmark analysis. Regardless of the approach used, it appeared that fulvestrant 500mg resulted in a significantly improved TTP/PFS compared to fulvestrant 250mg and anastrozole (albeit only after 180 days in all instances using the ERG approach). The ERG analysis also suggested that fulvestrant may result in significantly improved TTP/PFS after 180 days when compared to letrozole.

A weakness of both the manufacturer's and ERG's approaches to indirect comparisons has been the inability to consider exemestane as a comparator. This is because no relevant studies were identified in either a predominantly post-AO population or one in which the hormone receptor status of the disease has been confirmed to be positive in ≥70% of patients. The EFECT[32] trial does compare fulvestrant to exemestane but this is neither the licensed dose of fulvestrant nor in the licensed population, since patients receive a fulvestrant loading dose (500mg intramuscularly on day 0, 250mg on days 14, 28, and 250mg every 28 days thereafter) and had failed on prior-AI therapy.

It was not possible to compare comprehensively differences in AEs between fulvestrant 500mg and any other comparator aside from fulvestrant 250mg, where no notable differences between treatment groups

in the incidence of AEs were reported. The ERG further notes that previous studies have reported no notable differences between fulvestrant 250mg and anastrozole.[59] Limited HRQoL data were also presented, this being restricted to the comparison of fulvestrant 500mg vs fulvestrant 250mg in CONFIRM[11] in which no statistically significant differences were identified.

Taken together, the clinical evidence suggests that fulvestrant 500mg is an effective treatment option for postmenopausal women with ER+, LABC/MBC for disease relapse on or after adjuvant AO therapy for EBC, or disease progression on therapy with an AO with an ABC. However, the positive treatment effects in terms of TTP/PFS may be largely a result of the majority of patients in the post-AO group in CONFIRM[11] receiving fulvestrant as a first-line treatment for ABC. The ERG has doubts whether clinicians would prefer fulvestrant at this stage given it is administered intramuscularly compared to the oral administration of anastrozole and letrozole. Furthermore, the ERG believes that most clinicians would currently prefer to consider fulvestrant following treatment with an AI. However it is noted that this is a population beyond the scope of this STA, is not licensed by the EU, and is a population for whom the treatment effects have yet to be proven.

7.2 Summary of cost-effectiveness issues

The ERG identified several issues with model logic and parameter values which, when corrected, produced only minor alterations to the cost-effectiveness results and which do not materially impact on the decision problem. However, the ERG does not consider that an analysis which includes a substantial proportion of patients previously treated with an AI can be considered reliable since the CONFIRM trial data demonstrate that the patient population is heterogeneous and not compatible with the evidence network submitted by the manufacturer which largely excludes AI treated patients.

In addition, the ERG does not accept the manufacturer's approach to TTP/PFS survival projection using a log-normal parametric framework which performs poorly and is not consistent with the long-term trial experience. The ERG has adapted the submitted model to incorporate new survival estimates based on the AO-only subgroup of the CONFIRM trial and an alternative approach to projecting survival.

When the mixed (AI and AO) population is used without the ERG's survival analysis, the ICER for fulvestrant 500mg vs anastrozole is close to £30,000 per QALY gained [redacted]. When the AO-only population is used together with the ERG's survival analysis, the ICER for fulvestrant 500mg vs anastrozole is nearly £35,000 per QALY gained

[redacted].

7.3 Implications for research

The fact that some patients had received their previous endocrine therapy as adjuvant therapy for EBC and others had received it for treatment of ABC suggests that studies have so far examined a rather heterogeneous population, namely patients with *de novo* LABC/MBC, patients who are presenting having relapsed on endocrine therapy for EBC, and patients who have relapsed on endocrine therapy for ABC. Furthermore, it is apparent that of those relapsing, the majority of patients who had received an AO (96%) had received only one prior line of treatment whereas a greater proportion of those whose last treatment was an AI, albeit still a minority (27%), had received two lines of treatment. It may therefore be prudent for future studies to attempt to consider these populations of patients separately. In particular, given the current predominant use of AI as a treatment option before fulvestrant in clinical practice, further research into the treatment effects of fulvestrant following treatment with an AI is welcome. The ERG is aware that increasingly, trials in a post-AI population are being conducted and acknowledges that the CONFIRM[11] trial included a subgroup of such patients, the findings from which may inform future research.

8 REFERENCES

1. National Institute for Health and Clinical Excellence (NICE). Advanced breast cancer: diagnosis and treatment. 2009 [cited 11/03/2009]; Available from: http://www.nice.org.uk/Guidance/CG81.
2. Guarneri V, Conte PF. The curability of breast cancer and the treatment of advanced disease. Eur J Nucl Med Mol Imaging. 2004; 31 Suppl 1:S149-61.
3. Fisher B, Anderson S, Tan-Chiu E, Wolmark N, Wickerham DL, Fisher ER, Dimitrov NV, Atkins JN, Abramson N, Merajver S, Romond EH, Kardinal CG, Shibata HR, Margolese RG, Farrar WB. Tamoxifen and Chemotherapy for Axillary Node-Negative, Estrogen Receptor–Negative Breast Cancer: Findings From National Surgical Adjuvant Breast and Bowel Project B-23. Journal of Clinical Oncology. 2001; 19(4):931-42.
4. Wiebe VJ, Osborne CK, Fuqua SAW, DeGregorio MW. Tamoxifen resistance in breast cancer. Critical Reviews in Oncology/Hematology. 1993; 14(3):173-88.
5. Howell A, Robertson JF, Quaresma Albano J, Aschermannova A, Mauriac L, Kleeberg UR, Vergote I, Erikstein B, Webster A, Morris C. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2002; 20(16):3396-403.
6. Osborne CK, Pippen J, Jones SE, Parker LM, Ellis M, Come S, Gertler SZ, May JT, Burton G, Dimery I, Webster A, Morris C, Elledge R, Buzdar A. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2002; 20(16):3386-95.
7. Robertson JFR. Faslodex (ICI 182, 780), a novel estrogen receptor downregulator--future possibilities in breast cancer. The Journal of Steroid Biochemistry and Molecular Biology. 2001; 79(1-5):209-12.
8. National Institute for Health and Clinical Excellence (NICE). Early and locally advanced breast cancer: diagnosis and treatment. 2009 [cited 11/03/2009]; Available from: http://www.nice.org.uk/Guidance/CG80.
9. European Medicines Agency. Assessment Report For Faslodex (fulvestrant). Procedure No.: EMEA/H/C/000540/II/0018. 2010 [cited 09/06/2011]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000540/WC500098922.pdf.
10. AstraZeneca UK Ltd. Faslodex 250mg solution for injection. Summary of Product Characteristics. 2010 [updated 11/10/2010; cited 10/06/2011]; Available from: http://www.medicines.org.uk/EMC/medicine/14381/SPC/Faslodex++250+mg+solution+for+injection/.
11. AstraZeneca UK Limited. Comparison of Faslodex in Recurrent Metastatic Breast Cancer (CONFIRM) Clinical Study Report2009.

12. Robertson JF, Llombart-Cussac A, Rolski J, Feltl D, Dewar J, Macpherson E, Lindemann J, Ellis MJ. Activity of fulvestrant 500mg versus anastrozole 1mg as first-line treatment for advanced breast cancer: results from the FIRST study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010; 27(27):4530-5.
13. Cheung K, Owers R, Robertson JF. Endocrine response after prior treatment with fulvestrant in postmenopausal women with advanced breast cancer: experience from a single centre. Endocrine related cancer. 2006; 13(1):251-5.
14. Mlineritsch B, Psenak O, Mayer P, Moik M, Namberger K, Hauser-Kronberger C, Greil R. Fulvestrant ('Faslodex') in heavily pretreated postmenopausal patients with advanced breast cancer: single centre clinical experience from the compassionate use programme. Breast Cancer Research and Treatment. 2007; 106(1):105-12.
15. Steger GG, Gips M, Simon SD, Lluch A, Vinholes J, Kaufman B, Wardley A, Mauriac L. Fulvestrant ('Faslodex'): Clinical experience from the Compassionate Use Programme. Cancer treatment reviews. 2005; 31:S10-S6.
16. Vergote I, Robertson JF, Kleeberg U, Burton G, Osborne CK, Mauriac L. Postmenopausal women who progress on fulvestrant ('Faslodex') remain sensitive to further endocrine therapy. Breast cancer research and treatment. 2003; 79(2):207-11.
17. Wang J, Jain S, Coombes CR, Palmieri C. Fulvestrant in Advanced Breast Cancer Following Tamoxifen and Aromatase Inhibition: A Single Center Experience. The Breast Journal. 2009; 15(3):247-53.
18. Neven P, Paridaens R, Pelgrims G, Martens M, Bols A, Goeminne J, Vindevoghel A, Demol J, Stragier B, De Greve J, Fontaine C, Van Den Weyngaert D, Becquart D, Borms M, Cocquyt V, Van Den Broecke R, Selleslags J, Awada A, Dirix L, Van Dam P, Azerad M, Vandenhoven G, Christiaens M, Vergote I. Fulvestrant (Faslodex™) in advanced breast cancer: clinical experience from a Belgian cooperative study. Breast Cancer Research and Treatment. 2008; 109(1):59-65.
19. Robertson JFR, Howell A, Gorbunova VA, Watanabe T, Pienkowski T, Lichinitser MR. Sensitivity to further endocrine therapy is retained following progression on first-line fulvestrant. Breast Cancer Research & Treatment. 2005; 92(2):169-74.
20. West Midlands Cancer Intelligence Unit. All Breast Cancer Report: A UK analysis of all symptomatic and screen-detected breast cancers diagnosed in 2006 2009 [cited 08/06/2011]; Available from: http://www.wmpho.org.uk/wmciu/documents/All%20Breast%20Cancer%20Report%20pp.pdf.
21. National Institute for Health and Clinical Excellence. Fulvestrant for the treatment of locally advanced or metastatic breast cancer. London: NICE; 2010 [cited 2010 August]; Available from: http://guidance.nice.org.uk/TA/Wave23/15/Scope/pdf/English.
22. AstraZeneca UK Ltd. DOF: FAS-004-AUG10: Data on file 2010.
23. Saad ED, Katz A. Progression-free survival and time to progression as primary end points in advanced breast cancer: often used, sometimes loosely defined. Annals of Oncology. 2009; 20(3):460-4.
24. AstraZeneca UK Limited. Faslodex INvestigation of Dose evaluation in Estrogen Receptor-positive advanced breast cancer (FINDER 1) Clinical Study Report.
25. AstraZeneca UK Limited. Faslodex INvestigation of Dose evaluation in Estrogen Receptor-positive advanced breast cancer (FINDER 2) Clinical Study Report.

26. FACIT. FACT-B for patients with breast cancer. [cited 2011 April]; Available from: http://www.facit.org.
27. Buzdar A, Douma J, Davidson N, Elledge R, Morgan M, Smith R, Porter L, Nabholtz J, Xiang X, Brady C. Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2001; (14): Available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/473/CN-00349473/frame.html
28. Buzdar A, Jonat W, Howell A, Jones SE, Blomqvist C, Vogel CL, Eiermann W, Wolter JM, Azab M, Webster A, Plourde PV. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. Arimidex Study Group. Journal of Clinical Oncology. 1996; 14(7):2000-11.
29. Lundgren S, Gundersen S, Klepp R, Lønning PE, Lund E, Kvinnsland S. Megestrol acetate versus aminoglutethimide for metastatic breast cancer. Breast Cancer Research and Treatment. 1989; 14(2):201-6.
30. Buzdar AU, Jones SE, Vogel CL, Wolter J, Plourde P, Webster A. A phase III trial comparing anastrozole (1 and 10 milligrams), a potent and selective aromatase inhibitor, with megestrol acetate in postmenopausal women with advanced breast carcinoma. Arimidex Study Group. Cancer. 1997a; 79(4):730-9.
31. Jonat W, Howell A, Blomqvist C, Eiermann W, Winblad G, Tyrrell C, Mauriac L, Roche H, Lundgren S, Hellmund R, Azab M. A randomised trial comparing two doses of the new selective aromatase inhibitor anastrozole (Arimidex) with megestrol acetate in postmenopausal patients with advanced breast cancer. Eur J Cancer. 1996; 32A(3):404-12.
32. Chia S, Gradishar W. Fulvestrant: expanding the endocrine treatment options for patients with hormone receptor-positive advanced breast cancer. Breast. 2008; 17 Suppl 3:S16-21.
33. Dombernowsky P, Smith I, Falkson G, Leonard R, Panasci L, Bellmunt J, Bezwoda W, Gardin G, Gudgeon A, Morgan M, Fornasiero A, Hoffmann W, Michel J, Hatschek T, Tjabbes T, Chaudri HA, Hornberger U, Trunet PF. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1998; (2): Available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/634/CN-00147634/frame.html
34. Gershanovich M, Chaudri HA, Campos D, Lurie H, Bonaventura A, Jeffrey M, Buzzi F, Bodrogi I, Ludwig H, Reichardt P, O'Higgins N, Romieu G, Friederich P, Lassus M, Group LIT. Letrozole, a new oral aromatase inhibitor: Randomised trial comparing 2.5mg daily, 0.5mg daily and aminoglutethimide in postmenopausal women with advanced breast cancer. Annals of Oncology. 1998; 9(6):639-45.
35. Kaufmann M, Bajetta E, Dirix LY, Fein LE, Jones SE, Zilembo N, Dugardyn JL, Nasurdi C, Mennel RG, Cervek J, Fowst C, Polli A, di Salle E, Arkhipov A, Piscitelli G, Miller LL, Massimini G. Exemestane is superior to megestrol acetate after tamoxifen failure in

postmenopausal women with advanced breast cancer: Results of a phase III randomized double-blind trial. Journal of Clinical Oncology. 2000; (7): Available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/773/CN-00423773/frame.html
36. Di Leo A, Jerusalem G, Petruzelka L, Torres R, Bondarenko IN, Khasanov R, Verhoeven D, Pedrini JL, Smirnova I, Lichinitser MR, Pendergrass K, Garnett S, Lindemann JP, Sapunar F, Martin M. Results of the CONFIRM Phase III Trial Comparing Fulvestrant 250mg With Fulvestrant 500mg in Postmenopausal Women With Estrogen Receptor-Positive Advanced Breast Cancer. J Clin Oncol. 2010.
37. Ohno S, Rai Y, Iwata H, Yamamoto N, Yoshida M, Iwase H, Masuda N, Nakamura S, Taniguchi H, Kamigaki S, Noguchi S. Three dose regimens of fulvestrant in postmenopausal Japanese women with advanced breast cancer: results from a double-blind, phase II comparative study (FINDER1). Ann Oncol. 2010.
38. Pritchard KI, Rolski J, Papai Z, Mauriac L, Cardoso F, Chang J, Panasci L, Ianuli C, Kahan Z, Fukase K, Lindemann JPO, Macpherson MP, Neven P. Results of a phase II study comparing three dosing regimens of fulvestrant in postmenopausal women with advanced breast cancer (FINDER2). Breast Cancer Research & Treatment. 2010; 123(2):453-61.
39. Buzdar AU, Jonat W, Howell A, Jones SE, Blomqvist CP, Vogel CL, Eiermann W, Wolter JM, Steinberg M, Webster A, Lee D. Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma. Cancer. 1998; 83(6):1142-52.
40. Buzdar AU, Jonat W, Howell A, Plourde PV. ARIMIDEX: a potent and selective aromatase inhibitor for the treatment of advanced breast cancer. J Steroid Biochem Mol Biol. 1997b; 61(3-6):145-9.
41. Mauriac L, Pippen JE, Quaresma Albano J, Gertler SZ, Osborne CK. Fulvestrant (Faslodex) versus anastrozole for the second-line treatment of advanced breast cancer in subgroups of postmenopausal women with visceral and non-visceral metastases: combined results from two multicentre trials. European Journal of Cancer. 2003; 39(9):1228-33.
42. Howell A, Pippen J, Elledge RM, Mauriac L, Vergote I, Jones SE, Come SE, Osborne CK, Robertson JF. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma: a prospectively planned combined survival analysis of two multicenter trials. Cancer. 2005; 104(2):236-9.
43. Xu B, Jiang Z, Shao Z, Wang J, Feng J, Song S, Chen Z, Gu K, Yu S, Zhang Y, Wang C, Zhang F, Yang J. Fulvestrant 250mg versus anastrozole for Chinese patients with advanced breast cancer: results of a multicentre, double-blind, randomised phase III trial. Cancer Chemotherapy and Pharmacology. 2011; 67(1):223-30.
44. NCRI/RCP/RCR/ACP/JCCO. Professional organisation statement template: Joint statement from the NCRI/RCP/RCR/ACP/JCCO accompanying the Manufacturer's Submission. 2010.
45. ICH. E9: Statistical Principles for Clinical Trials. 1998 [09/06/2011]; Available from: http://private.ich.org/LOB/media/MEDIA485.pdf.
46. Guyot P, Ouwens M. The use of survival analysis for cost-effectiveness models: an evaluation of methods in NICE appraisals. Value in Health. 2009; 12(7):A231.

47. Ouwens M, Philips Z, Jansen J. Network meta-analysis of parametric survival curves. Research Synthesis Methods. 2010; 1:258-71.
48. Kuter I, Hegg R, Singer CF, Badwe R, Lowe E, on Behalf of the NEWEST Investigators. Fulvestrant 500mg vs 250mg: first results from NEWEST, a randomized, phase II neoadjuvant trial in postmenopausal women with locally advanced, estrogen receptor-positive breast cancer. Breast Cancer Research and Treatment. 2007; 106(Suppl1):S7.
49. Parmar M, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Statistics in Medicine. 1998; 17:2815-34.
50. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. British Journal of Cancer. 2006; 95:683-90.
51. Department of Health. NHS Reference Costs 2009-10. 2010 [cited 21/06/2011]; Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459.
52. Department of Health. NHS Reference Costs 2010-11. 2010 [cited 21/06/2011]; Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_122803.
53. Curtis L. Unit Costs of Health and Social Care 2010. Personal Social Services Research Unit, University of Kent; 2010; Available from: http://www.pssru.ac.uk/uc/uc2010contents.htm.
54. Karnon J, Jones T. A Stochastic Economic Evaluation of Letrozole versus Tamoxifen as a First-Line Hormonal Therapy: For Advanced Breast Cancer in Postmenopausal Patients. PharmacoEconomics. 2003; 21(7):513-25.
55. National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. London 2008; Available from: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf.
56. Drummond M, Stoddart G, Torrance G. Methods for the Economic Evaluation of Health Care Programmes. Oxford: 2nd Edition. Oxford University Press; 1997.
57. Greenhalgh J, Bagust A, Boland A, Oyee J, Trevor N, Dundar Y, Fleeman N, Davis H, O'Reilly S. Eribulin for the treatment of advanced or metastatic breast cancer: A Single Technology Appraisal: LRiG, The University of Liverpool 2011.
58. Kind P, Hardman G, Macran S. UK population norms for EQ5-D. The University of York, Centre for Health Economics: Discussion paper 172. York: The University of York, Centre for Health Economics; 1999 [cited 24/06/2011]; Available from: http://www.york.ac.uk/media/che/documents/papers/discussionpapers/CHE%20Discussion%20Paper%20172.pdf.
59. Bross PF, Baird A, Chen G, Jee JM, Lostritto RT, Morse DE, Rosario LA, Williams GM, Yang P, Rahman A, Williams G, Pazdur R. Fulvestrant in postmenopausal women with advanced breast cancer. Clinical Cancer Research. 2003; 9(12):4309-17.

9 APPENDICES

APPENDIX 1: QUALITY ASSESSMENT IN MANUFACTURER INCLUDED TRIALS

Direct comparisons

	CONFIRM	FINDER-1	FINDER-2
Was randomisation carried out appropriately?			
Manufacturer response	Yes	Yes	Yes
ERG comment	Agree	Agree	Agree
Was the concealment of treatment allocation adequate?			
Manufacturer response	Yes	Yes	Yes
ERG comment	Agree	Agree	Agree
Were the groups similar at the outset of the study in terms of prognostic factors?			
Manufacturer response	Yes	Yes	Yes
ERG comment	Agree	Agree	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?			
Manufacturer response	Yes	Yes	Yes
ERG comment	Agree	Agree	Agree
Were there any unexpected imbalances in drop-outs between groups?			
Manufacturer response	No	No	No
ERG comment	Agree	Agree	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?			
Manufacturer response	No	No	No
ERG comment	Agree	Agree	Agree
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?			
Manufacturer response	Includes all randomized patients, regardless of whether any study treatment was received	Includes all randomized patients, regardless of whether any study treatment was received	Includes all randomized patients, regardless of whether any study treatment was received
ERG comment	Agree	Agree	Agree

Indirect comparisons

	Buzdar 1996/98	020	021	Lundgren 1989	Buzdar 2001
Was randomisation carried out appropriately?					
Manufacturer response	Yes	Yes	Yes	Not stated	Yes
ERG comment	Agree	Unclear	Unclear	Agree	Unclear
Was the concealment of treatment allocation adequate?					
Manufacturer response	No -Open label for megestrol acetate, in addition to the fact that the dosing schedule differed for MA and anastrozole	No – open label study	Yes	Not stated	Yes
ERG comment	Agree	Agree	Unclear	Agree	Unclear
Were the groups similar at the outset of the study in terms of prognostic factors?					
Manufacturer response	Yes - Groups formed were well balanced with respect to demographic and pre-treatment characteristics. There appeared to be an imbalance in treatment allocation for the three groups however it was believed to be an artefact related to the large proportion of centres in the European trial in which the total number of patients was not divisible by six (allocated in blocks of 6 in European trial, compared with blocks of 3 in the US trial)	Yes	Yes	Yes	
ERG comment	Agree	Agree	Agree	Agree	Yes

	Buzdar 1996/98	020	021	Lundgren 1989	Buzdar 2001
Were the care providers, participants and outcome assessors blind to treatment allocation?					
Manufacturer response	No – open label study	No – open label study	Yes	Not stated	Yes
ERG comment	Agree	Agree	Agree The ERG notes that one statistician was not blinded	Agree	Agree
Were there any unexpected imbalances in drop-outs between groups?					
Manufacturer response	No	No	No	There are differences but the numbers are small so difficult to assess whether real differences or due to chance	No
ERG comment	Agree	Agree	Agree	Agree	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No
Manufacturer response	No	No	No	No	No
ERG comment	Agree	Agree	Agree	Agree	Agree

	Buzdar 1996/98	020	021	Lundgren 1989	Buzdar 2001
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?					
Manufacturer response	Calculations based on number randomised	The primary statistical analyses of the efficacy endpoints were conducted using all randomized patients on an intention-to-treat basis, and used response data as defined by the computer algorithm	The primary statistical analyses of the efficacy end points were conducted on an intention-to-treat basis, included all randomized patients, and used response data as defined by the computer algorithm. Secondary (supportive) statistical analyses were conducted on a per-protocol population (according to treatment received) and an intention-to-treat basis with a model that excluded baseline covariates	No - Calculations only involved evaluable patients who had been treated for > 8 weeks	ITT defined as the set of randomised patients who took at least one dose of trial medication. All patients, regardless of their length of treatment were included in the ITT analysis.
ERG comment	Agree	Agree	Agree	Agree	Agree

APPENDIX 2: POST-HOC ANALYSES REQUESTED BY THE ERG

The findings of the analyses presented by the manufacturer at the ERG's request are presented in [redacted] to [redacted]

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