NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Fulvestrant for untreated locally advanced or metastatic oestrogen-receptor positive breast cancer

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Fulvestrant for untreated locally advanced or metastatic oestrogen-receptor positive breast cancer

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Pre-meeting briefing

Fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer [ID951]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

1

Key issues: clinical effectiveness

- What are the current treatment options for people with hormone receptor-positive, human epidermal growth factor receptor-negative, locally advanced or metastatic breast cancer who have received no prior (including adjuvant) endocrine therapy?
- Who would receive an aromatase inhibitor (AI) in current clinical practice, and who would receive tamoxifen?
- Would fulvestrant be of particular value for any specific group (e.g. people unable to have AIs or unable to tolerate any oral endocrine therapies)?
- What are the committee's conclusions on the clinical trials and clinical results for fulvestrant?
  - quality, inclusion criteria and risk of bias in the trials
  - the results of fulvestrant vs anastrozole in FIRST compared to FALCON for progression-free survival and overall survival
- Direct trial data is only available to compare with anastrozole and the company carried out an indirect comparison with letrozole and tamoxifen; in clinical practice are the AIs usually regarded as having a class effect?

2

Breast cancer: hormone receptor-positive, locally advanced or metastatic

- Breast cancer arises from the tissues of the ducts or lobules of the breast
  - **Locally advanced**: describes tumours that are larger than 5 cm in size, or have grown into the skin or muscle of the chest or nearby lymph nodes
  - **Metastatic:** describes disease that has spread to another part of the body, such as the bones, liver, or lungs
- Endocrine (hormone) receptor positive breast cancer is the most prevalent form of the disease – about 70% are oestrogen-receptor positive (ER+)
- 15 to 25% of breast cancers are human epidermal growth factor-receptor positive (HER2+) which tend to grow more quickly than breast cancers that do not express HER2 – usually treated with targeted therapies such as trastuzumab
- **Common symptoms:** swelling of all or part of a breast, breast or nipple pain, nipple retraction and/or discharge, thickening of nipple or breast
- **Prevalence:** 46,083 people diagnosed (2015), and approximately 9,753 deaths from breast cancer in England (2015)
  - Approximately 13% of women with invasive breast cancers have locally advanced or metastatic disease when they are diagnosed

3

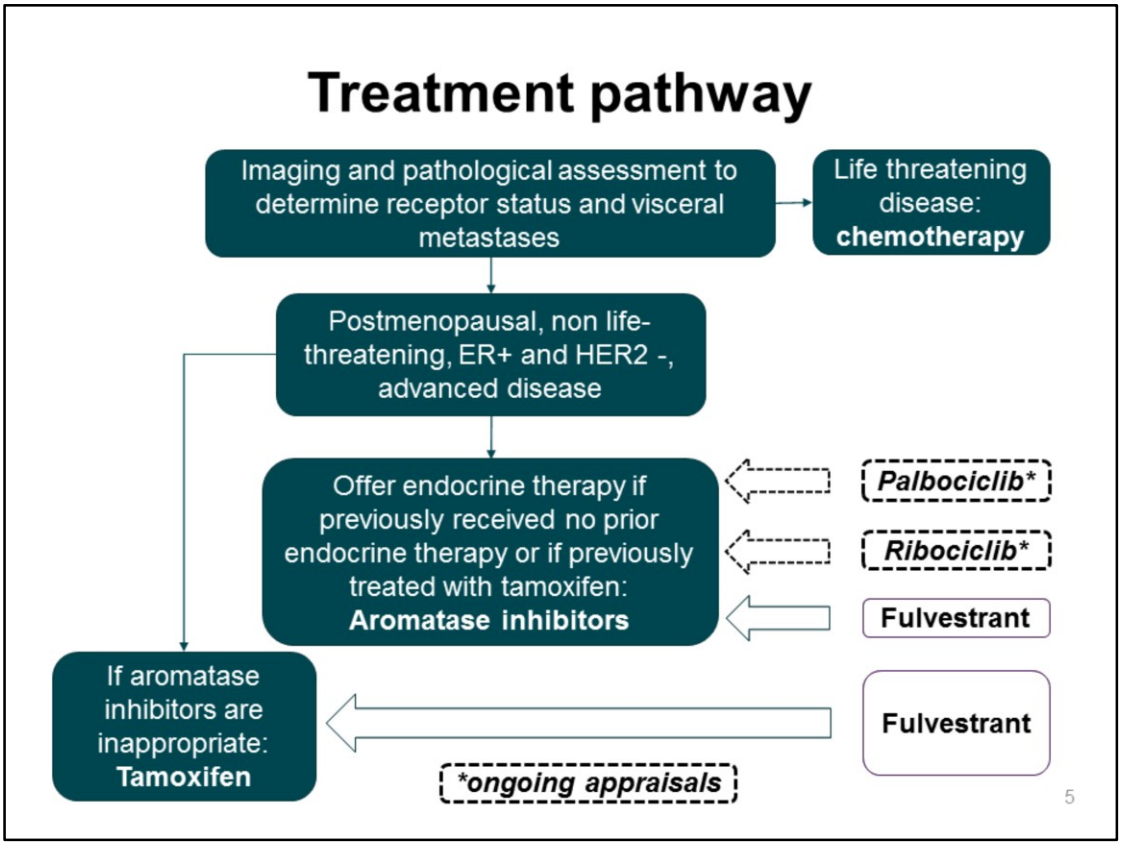
See section 3 of the company's submission and 2.1 of the ERG report for full details on the health condition

Fulvestrant (*Faslodex*)

UK marketing authorisation	*Treatment of oestrogen-receptor positive, locally advanced or metastatic breast cancer in postmenopausal women:* • ***not previously treated with endocrine therapy*** (indication of interest for appraisal, CHMP positive opinion adopted June 2017) • *with disease relapse on or after adjuvant anti-oestrogen therapy, or disease progression on anti-oestrogen therapy (*not recommended under NICE technology appraisal 239*)*
Class of drug	**Selective Oestrogen Receptor Degrader (SERD):** oestrogen receptor (ER) antagonist that binds to the ER in a competitive manner with affinity comparable to that of oestradiol and downregulates the ER protein in human breast cancer cells
Administration and dosage	500mg given intramuscularly into the buttocks as two 5 mL injections, one in each buttock on days 1, 15, 29 and once monthly thereafter (until disease progression)
Cost	The current list price per pack of 2 × 5-mL (250-mg) prefilled syringes is £522.41 Total expected acquisition cost for an average course of treatment is £15,841 plus administration and monitoring costs of £2,458 (source: company model based on an average length of treatment of approx. 30 months)

4

See section 2 of the company's submission for full details on the technology.



Source: NICE clinical guideline CG81: advanced breast cancer: diagnosis and treatment and company's submission section 2

Patient perspective

- Living with breast cancer is difficult to come to terms with for the individual affected and their family
- Uncertainty in the length of survival after diagnosis – quality of life is as important
  - Physical impact varies depending on where the cancer has spread
- There are limited options for people with hormone receptor-positive breast cancer – aromatase inhibitors provide an alternative to chemotherapy and provide a better quality of life and additional survival
- Evidence shows that fulvestrant is as effective as current treatment and has a similar side-effect profile to aromatase inhibitors
- Fulvestrant provides another first-line option that may provide longer survival and may be suited to people who prefer the intramuscular administration

6

See patient expert statements for full details

Clinical expert view

- Current treatments are aromatase inhibitors – these are more effective than tamoxifen in locally advanced or metastatic breast cancer
  - Adherence to current oral treatments is poor – 25% do not take it in the adjunctive setting
  - An intramuscular injection may be more acceptable
- Fulvestrant is not frequently used because it is not yet licensed in this proposed setting but has been used where oral treatments are not tolerated
  - FALCON study shows that fulvestrant is well tolerated – similar profile to anastrozole
  - It will be prescribed, and the disease monitored, in secondary care but the intramuscular injection could be administered in either primary or secondary care

7

See clinical expert statements for full details

Decision problem

	NICE scope and company's submission
Population	Post-menopausal people with locally advanced or metastatic hormone receptor-positive breast cancer, who have not received endocrine therapy
Comparator(s)	• Aromatase inhibitors (such as anastrozole and letrozole) If aromatase inhibitors are not tolerated or are contraindicated: • Tamoxifen
Outcomes	• overall survival • progression free survival • response rate • adverse effects of treatment • health-related quality of life
Subgroups	• people with visceral disease • people with non-visceral disease

8

The ERG state that the decision problem from the scope is accurately reflected in the company's submission (see section 2.3 of the ERG's report).

Clinical effectiveness evidence

9

Randomised controlled trials: fulvestrant 500mg

Trial	Population	Comparator	Primary outcome	Key secondary outcomes
FIRST phase II, open-label, multicentre non-inferiority (Asia, Europe, North and South America, South Africa) N=233 enrolled, 205 randomised	Postmenopausal women with HR+, advanced BC: • 75% had no previous endocrine therapy • HER2 status – positive:19%; negative: 47% unknown: 34%	anastrozole (1mg tablet daily)	Clinical benefit rate (CBR)	Time-to-progression (TTP) Overall survival (OS)
FALCON* phase III, double-blind, multicentre, superiority study (Europe, North and South America) N=524 enrolled, 462 randomised	Postmenopausal women with ER+ and/or PR+ BC: • no previous endocrine therapy • HER2 negative	anastrozole (1mg tablet daily)	Progression-free survival (PFS)	OS

*number of participants from the UK unknown; please note the definition of TTP is similar to PFS so the results can be assumed to be comparable

10

See section 4.2 to 4.6 of the company's submission for full details on the trials.

Outcome definitions

- CBR - CR (complete response), PR (partial response), or SD (stable disease) ≥24 weeks
- PFS – time from randomisation until objective disease progression, defined by RECIST (Response Evaluation Criteria In Solid Tumors) 1.1, surgery or radiotherapy to manage worsening of disease or death by any cause
- TTP – time from randomisation to the time of the earliest evidence of objective disease progression or death from any cause prior to documented progression

Inclusion criteria

Previous endocrine therapy was not an exclusion factor in the FIRST trial, unlike FALCON. (99.4% endocrine-naïve in FLACON; 74% in FIRST)

People could have received one line of cytotoxic chemotherapy for breast cancer but had to show progressive disease prior to enrolment, so participants in FALCON may not have been completely untreated.

ERG comments (see section 3.1.3 and 3.1.4 of the ERG report)

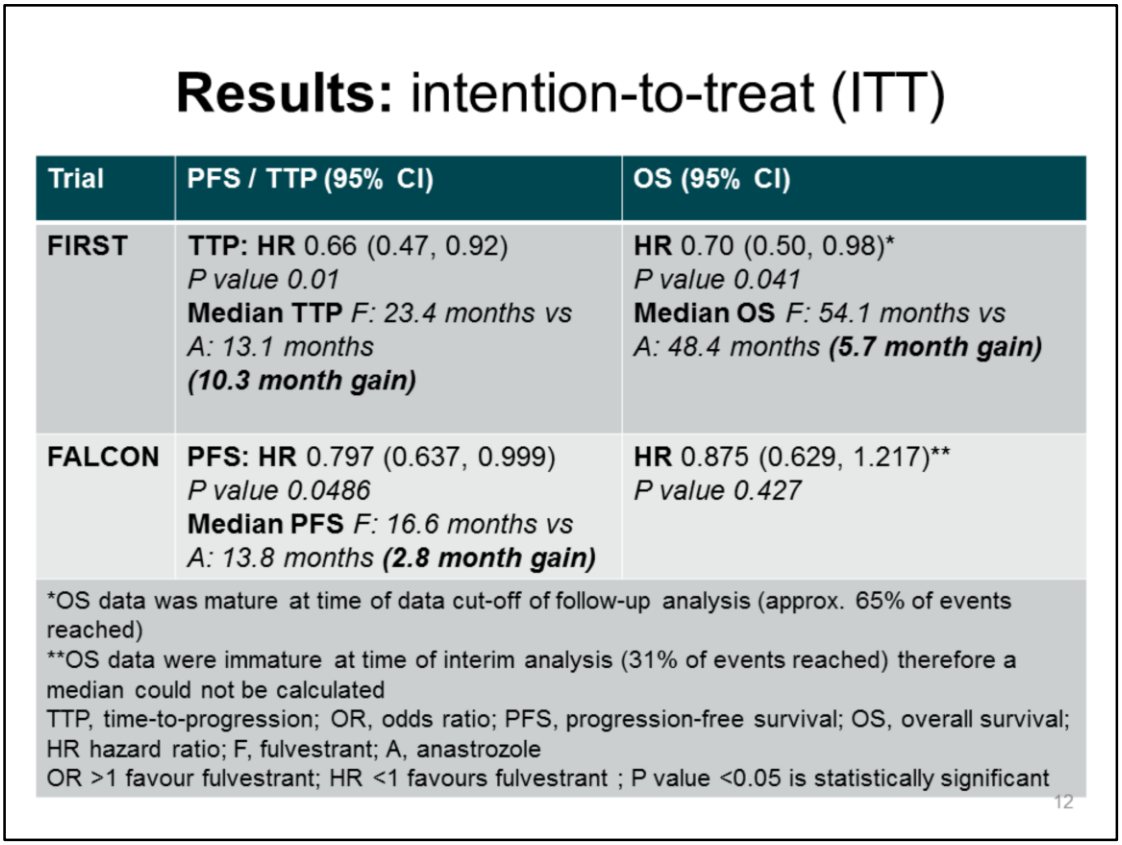
The ERG state that participants from the UK are included in both trials but the number of participants are not explicitly stated. The ERG also note that the fulvestrant arm of the FALCON trial contains a higher % of women with prior endocrine therapy completed more than 12 months prior to enrolment but this is unlikely to cause imbalance in the outcomes between the treatment arms.

The ERG state that both trials appear to be well conducted. However, FIRST may have a high risk of allocation concealment bias. There are also differences at baseline between the two arms in the trials. In FIRST there is a higher proportion of 'any visceral disease' in the anastrozole arm so people are expected to have a worse prognosis thereby favouring the fulvestrant arm. In FALCON there is a difference in the mean age but this is unlikely to have an impact on the outcomes.

Key baseline characteristics

Patient demographic and disease characteristics	FIRST		FALCON	
	Fulvestrant n=102 (%)	Anastrozole n=103 (%)	Fulvestrant n=230 (%)	Anastrozole n=232 (%)
HER2 status n (%)	2+/3+		Positive	
Positive	19 (18.6)	19 (18.4)	0	1 (<1)
Negative	48 (47.1)	49 (47.6)	230 (100)	231 (100)
Unknown	35 (34.3)	35 (34.0)	0	0
Site of disease n (%)				
Any visceral disease	48 (47.1)	58 (56.3)	135 (59)	119 (51)
Prior endocrine therapy n (%)				
None	73 (71.6)	80 (77.7)	228 (99.1)	231 (99.6)
Completed ≤12 months prior to randomisation	1 (1.0)	0	2 (1)	1 (<1)
Completed >12 months	28 (27.5)	23 (22.3)		

See section 4.5 of the company's submission and 3.1.3 of the ERG report for full details



See section 4.7 of the company's submission for full trial results and 4.8 of the company's submission for full subgroup analysis

Company: the overall survival data were immature at the time of the interim analysis for the FALCON trial. Mature OS results (when >=50% have died) will be available in approximately 2 years (2020).

The results are presented for the intention-to-treat (ITT) population which includes all participants from the point of randomisation

Subgroup analysis

Subgroup covariates were pre-defined in the FALCON trial but were conducted post-hoc for FIRST trial. Analyses were done to assess the impact on the treatment effect by adjusting for variables (covariates). These analyses included covariates such as receptor status, visceral involvement age, geographic region, bisphosphonate use at baseline etc.

The results show that the subgroup analysis is consistent with the overall results (unadjusted).
FIRST: TTP, HR 0.64 (0.46, 0.90) *P value 0.01;* **OS**, HR 0.70 (0.50, 0.98)

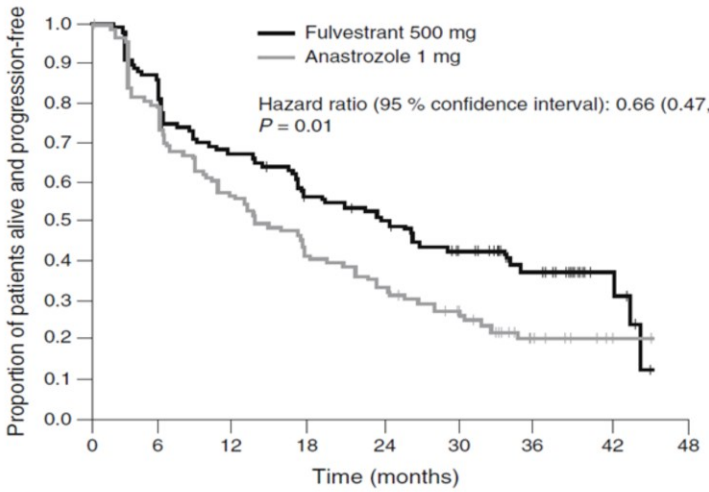
FALCON: PFS, HR 0.797 (0.637, 0.999); **OS** (immature at time of analysis), HR 0.875 (0.629, 1.217) *P Value 0.4277*

The company acknowledge that some of the results for the individual subgroups (covariates) should be interpreted with caution because the sample sizes are very small.

Visceral metastases was a subgroup of interest and identified by clinicians for the scope because people with visceral metastases to the liver and/or lung have a very poor prognosis. The company's submission does not specifically discuss this subgroups but individual analysis of visceral involvement as the only covariate showed fulvestrant was more effective in people without visceral metastases but concluded that more observations were needed (please note: this conclusion is from the published FLACON paper, the CS does not discuss this subgroup).
FIRST: OS, HR 0.68 (0.40 – 1.18); **FALCON** PFS, OR 0.59 (0.42 – 0.84). Results are numerically higher favouring fulvestrant for PFS in FRIST and OS in FALCON

ERG comments on the subgroup analysis (see section 3.1.6 of the ERG report)
The ERG consulted clinical experts who thought the subgroups and covariates included were on the whole, appropriate but some may be irrelevant (not prognostic of the outcome) such as use of use of bisphosphonates and some key covariates may have been omitted, such as performance status.

FIRST: Kaplan–Meier TTP



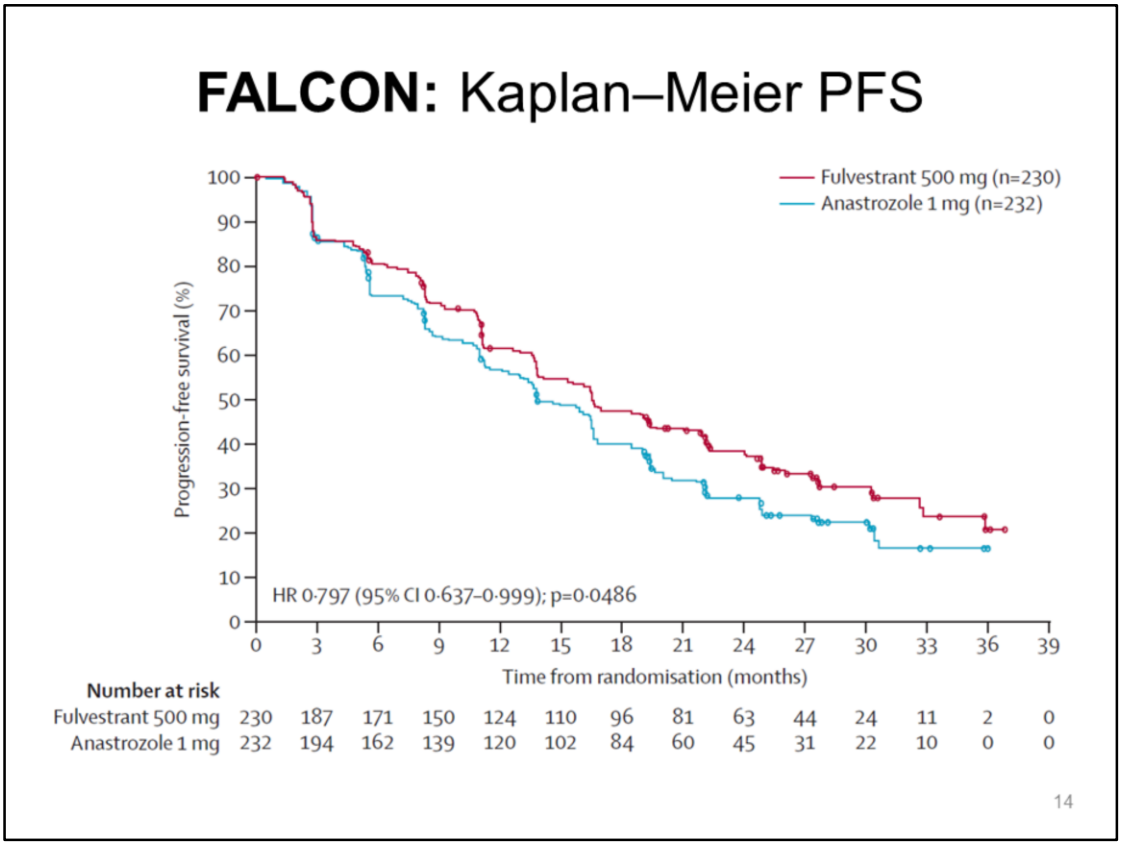
Patients at risk

Fulvestrant 500 mg	102	74	65	52	45	34	20	6	0
Anastrozole 1 mg	103	69	55	39	30	21	8	2	0

After the primary data cut-off, progression was determined by investigator opinion

13

See section 4.7 of the company's submission for full trial results



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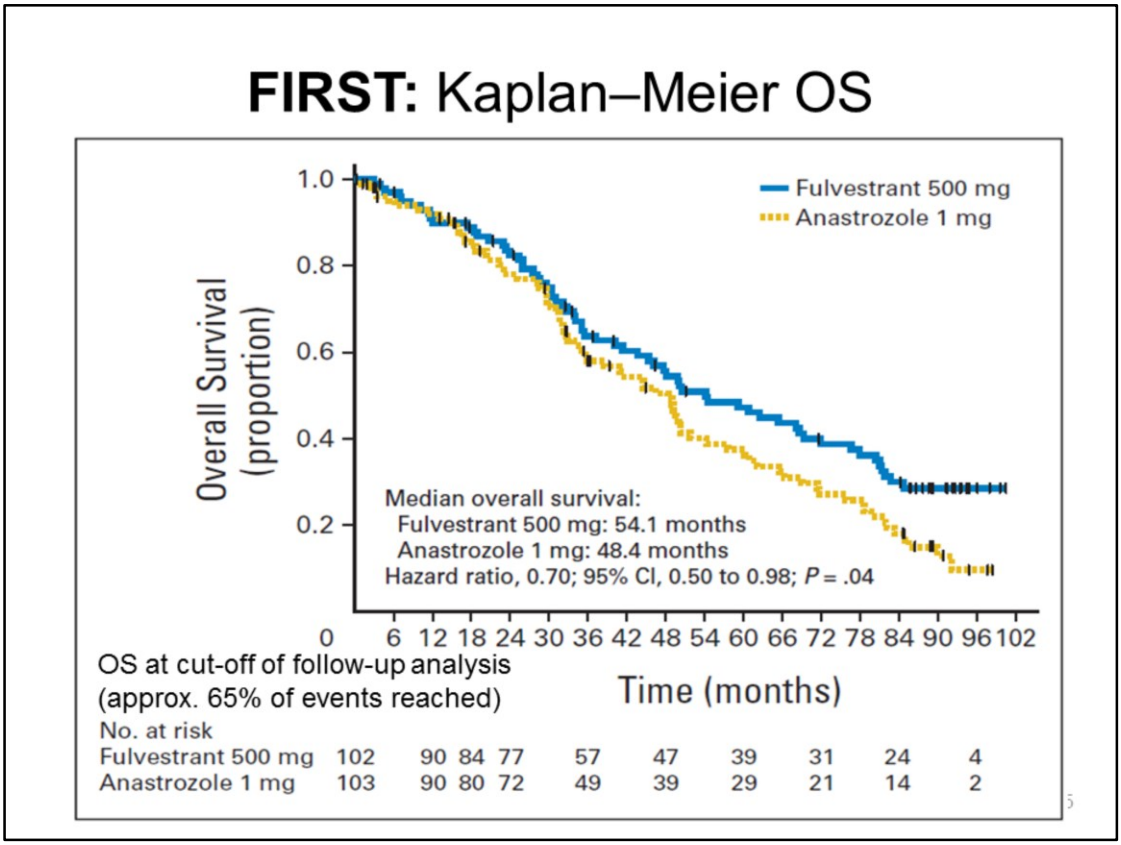

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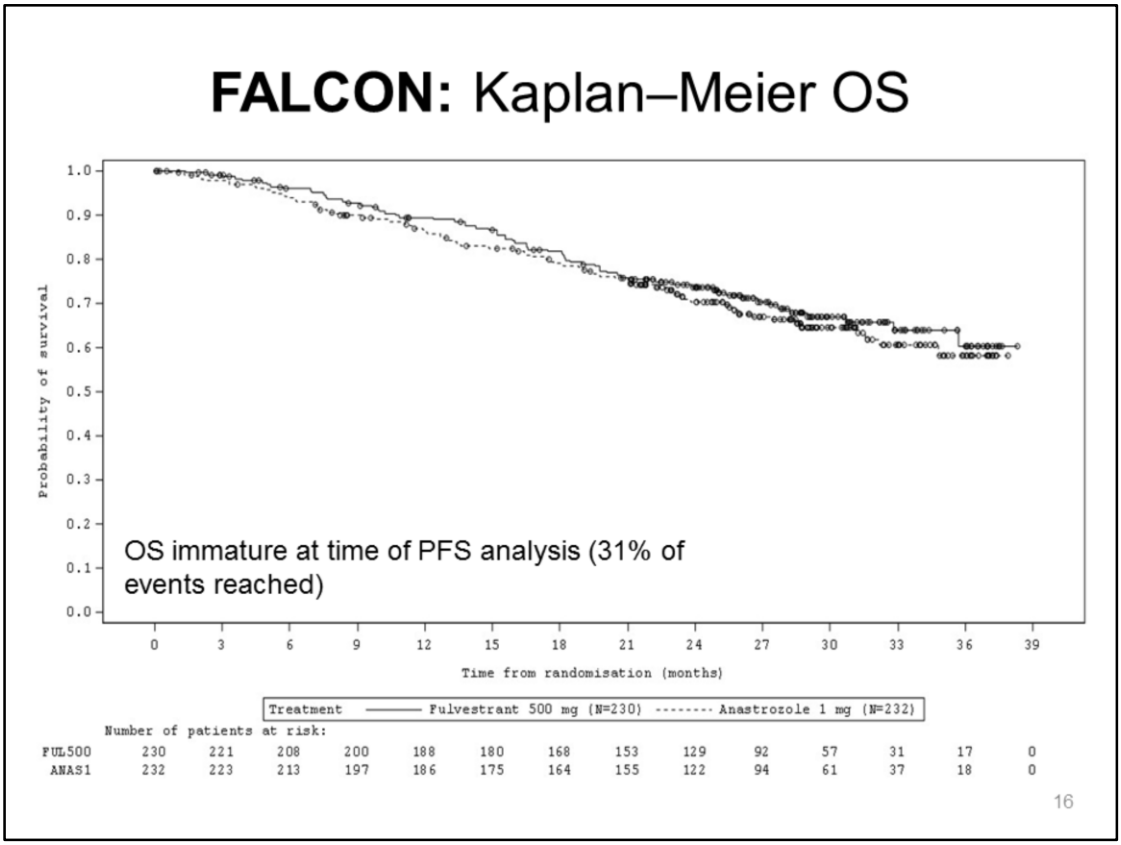
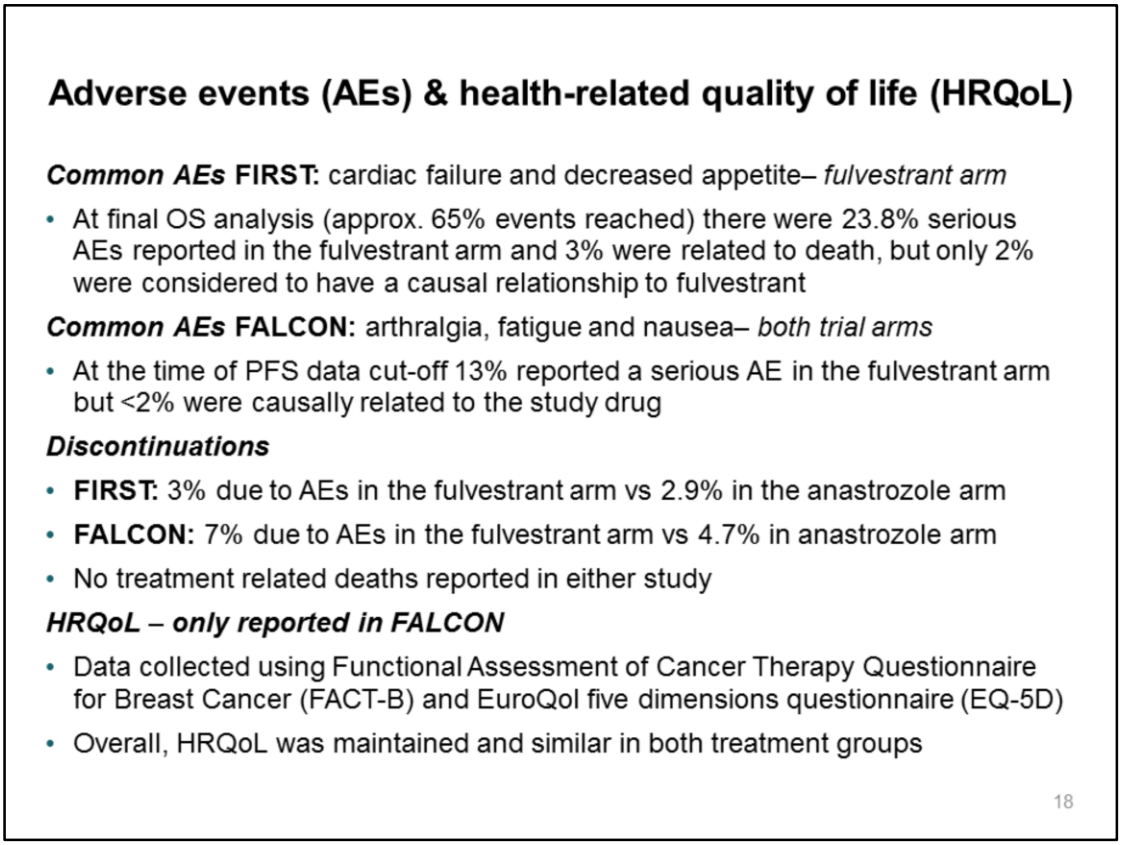


See section 4.7 of the company's submission for full trial results

Comparisons to letrozole and tamoxifen

- Direct evidence was only available for a comparison with anastrozole
- Therefore, the company carried out an indirect treatment comparison (ITC) comparing fulvestrant with letrozole and tamoxifen
- The ITC is presented in the cost effectiveness section

17



See section 4.7.2 and 4.12 of the company's submission for full details on adverse events and HRQoL

HRQoL

'In order to assess the patient-reported outcomes (PROs) and health-related quality of life (HRQoL) associated with fulvestrant 500mg treatment, the FALCON trial utilised the EQ-5D and FACT-B questionnaires. The FACT-B questionnaire comprises the following subscales; physical well-being [PWB], functional well-being [FWB], social well-being [SWB], emotional well-being [EWB], and breast cancer subscale [BCS]; however the main outcome measure from the FACT-B questionnaire was the trial outcome index (TOI), summarising the PWB, FWB, and BCS subscales.'

'The EQ-5D questionnaire collected data on generic health status across three levels (EQ-5D-3L). Results of the EQ-5D-3L questionnaire show that the general health status is maintained over the study period (156 weeks) across both treatment arms. The means per visit of the EQ-5D-3L Index in the fulvestrant 500mg group are consistently greater than in the anastrozole group between week 0 (baseline) and week 156 (end of study) '

ERG comments: clinical effectiveness (1)

- Trials were well conducted and of good quality but there is potential for FIRST to be at high risk of bias due to absence of blinding
- The ERG points out 2 important differences between the baseline characteristics in the trials:
  - More people in FIRST had previous endocrine therapy (99.4% endocrine-naïve in FALCON; 74% in FIRST). Population in FALCON was endocrine-naïve to avoid reducing the efficacy of anastrozole in the control group through exposure to prior adjuvant endocrine therapy
  - 19% of people had HER2+ breast cancer in FIRST but people with HER2+ were excluded from FALCON. HER2+ breast cancer is more aggressive and spreads more quickly so less favourable outcomes would be expected in the FIRST trial

19

See section 3.3 of the ERG report for full interpretation of the company's results

ERG comments: clinical effectiveness (2)

- ERG's clinical experts considered the PFS increase of 2.8 months for fulvestrant vs anastrozole in FALCON not to be clinically meaningful
  - TTP is greater in FIRST (10.3 months) – difference could be due to:
  1. Study design – no blinding in FIRST but a blinded independent review was conducted on the primary endpoint (ERG are unclear whether this was carried out on the other endpoints too)
  2. FALCON study publication suggests that an enhanced effect with fulvestrant may be seen in people with non-visceral disease compared to those with visceral disease – the publication concludes that further observations are needed
- OS data are immature in FALCON but the OS benefit is likely to be lower than in FIRST because the PFS gain was lower than in FIRST
  - ERG note that although OS for FIRST was statistically significant it was not a pre-specified outcome and some people did not contribute data to the outcome (n=35)

20

See section 3.3 of the ERG report for full interpretation of the company's results

Key issues: clinical effectiveness

- What are the current treatment options for people with hormone receptor-positive, human epidermal growth factor receptor-negative, locally advanced or metastatic breast cancer this who have received no prior (including adjuvant) endocrine therapy?
- Who would receive an aromatase inhibitor (AI) in current clinical practice, and who would receive tamoxifen?
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- Direct trial data is only available to compare with anastrozole and the company carried out an indirect comparison with letrozole and tamoxifen; in clinical practice are the AIs usually regarded as having a class effect?

21

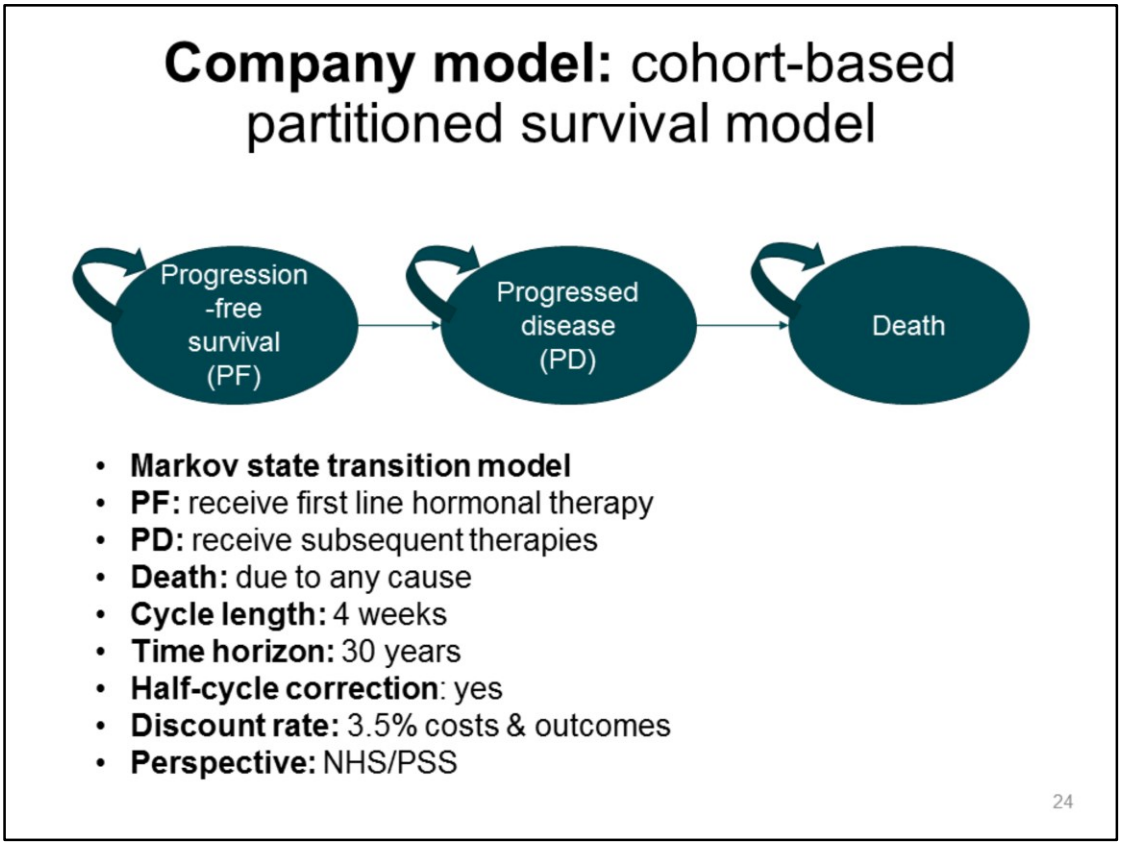
Cost effectiveness evidence

22

Key issues: cost effectiveness

- What is the committee's view on the approach used to estimate treatment effects in the economic model?
  - Is the 'matched' population relevant to the decision problem?
  - Does generating a more homogenous subgroup for the network meta-analysis (NMA) outweigh the potential bias associated with violating trial randomisation?
- What is the committee's view on the robustness of the estimated OS based on the survival extrapolations?
- What is the committee's view on the estimated health utilities?
- What is the committee's view on the cost effectiveness estimates for fulvestrant
  - compared with anastrozole, letrozole and tamoxifen?
- What is the committee's view on the sensitivity of the ICERs to changes in the OS parameter?

23



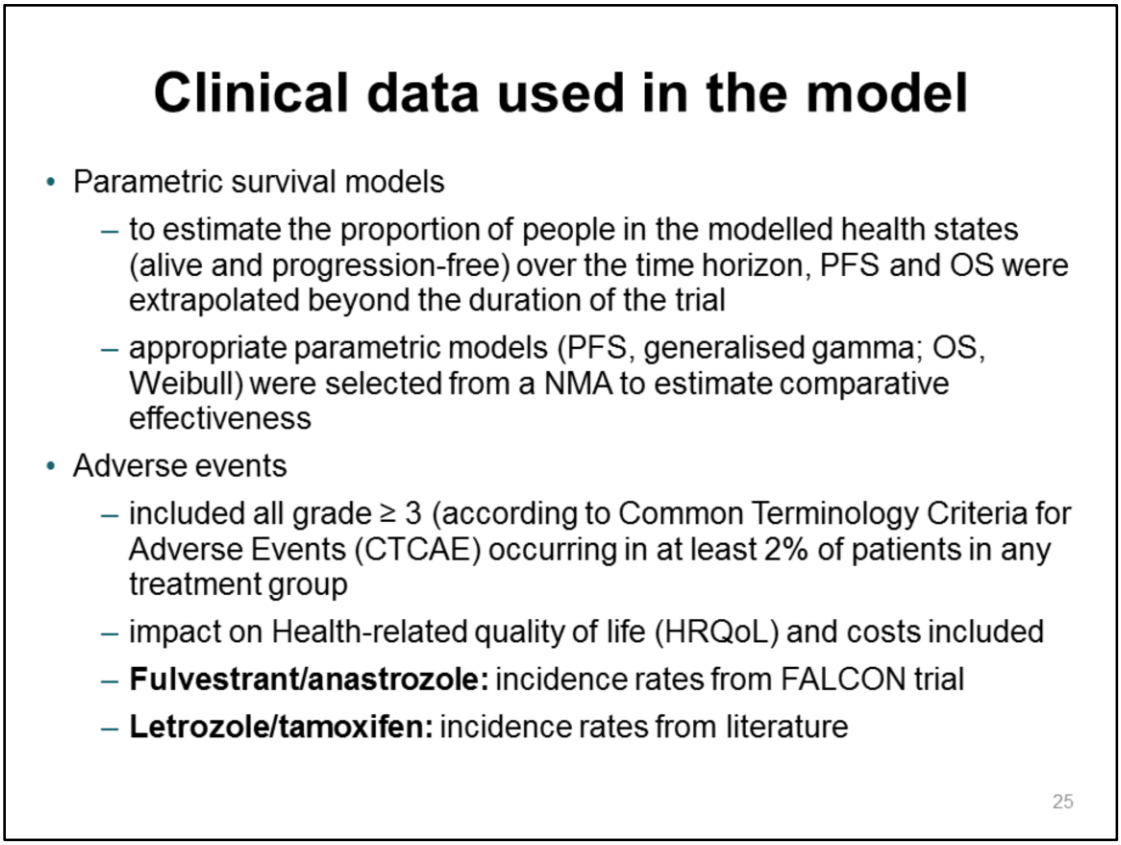
See section 5.2.2 of the company's submission for the full model structure and assumptions

Model structure (section 5.2.2)
'A cohort-based partitioned survival model was developed in Microsoft Excel 2010 to evaluate the cost-effectiveness of fulvestrant 500mg. The model is comprised of three mutually exclusive health states: progression-free survival (PF) [receive first line hormonal therapy], progressed disease (PD) [receive subsequent therapies] and death (due to any cause). This model structure reflects the key clinical events in this disease area; i.e., progression – which usually results in moving the patient onto a new therapy – and death. The health state occupancy of the simulated cohort is estimated by extrapolating the cumulative survival probability of PFS and OS to a lifetime horizon (30 years). The extrapolated survival curves are used directly to estimate the proportion of the cohort who are alive and progression-free, the proportion who are alive and have progressed, and the proportion who have died'

In the context of the partitioned survival model people are assumed to experience events over the course of their treatment, that is, progression of disease, subsequent treatment and death. States are assumed to be progressive, mutually exclusive and irreversible (i.e.

people cannot transition back to PF after moving to PD – this is consistent with the definitions of PFS and OS from the trial and other NICE submissions).

The time-horizon of 30 years was dependant on the OS data and stops when <1% of people remain alive.



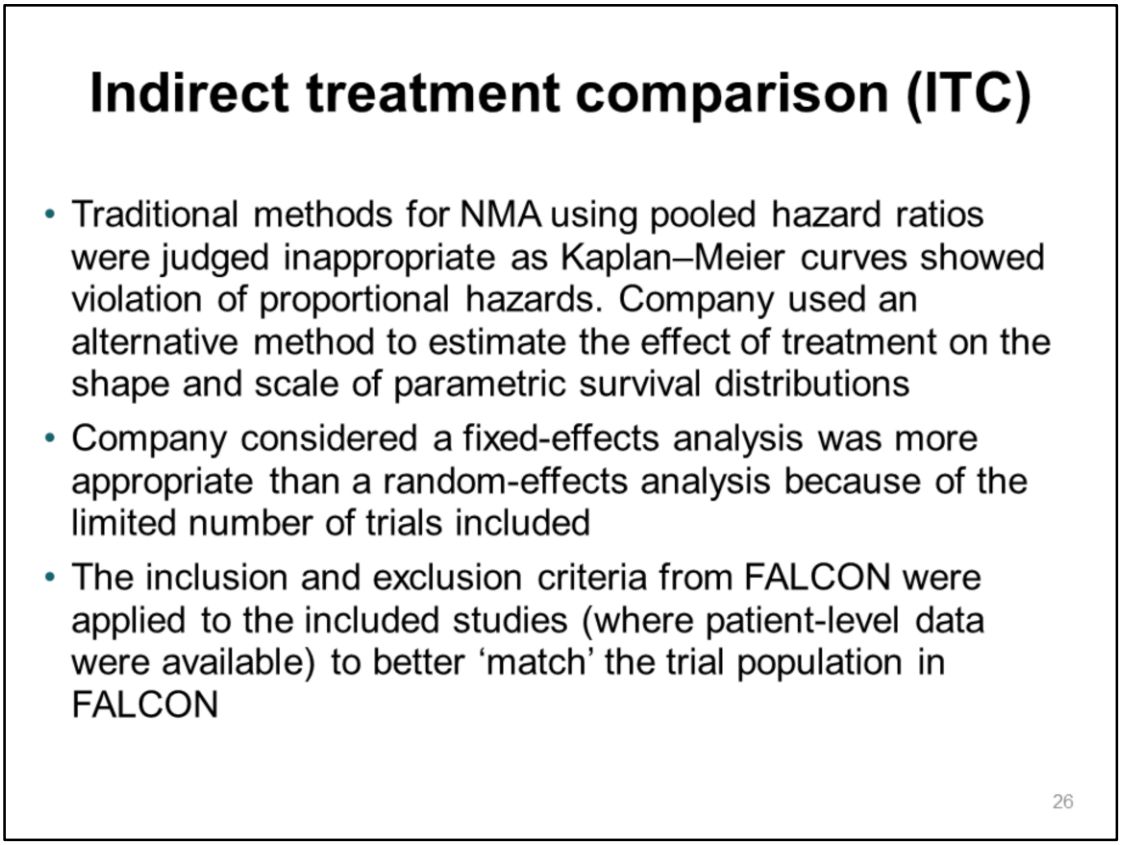
See section 5.3 of the company's submission for full details of the adverse event incidence rates used in the model.

Adverse events

It was not possible to apply an ITC of adverse event data so the difference between treatments may be partially be driven by differences between patient characteristics and follow-up periods in the studies for the intervention and comparators.

The adverse events were applied as 'one-off' events in the first cycle of treatment. The advantage of this is that the time element is already incorporated into this as costs and disutilities are defined are per event and rates are derived from the trial. These should reflect more closely to the observed rates (consistency and validity). The ERG agree this approach is acceptable as adverse events are not expected to last longer than one year.

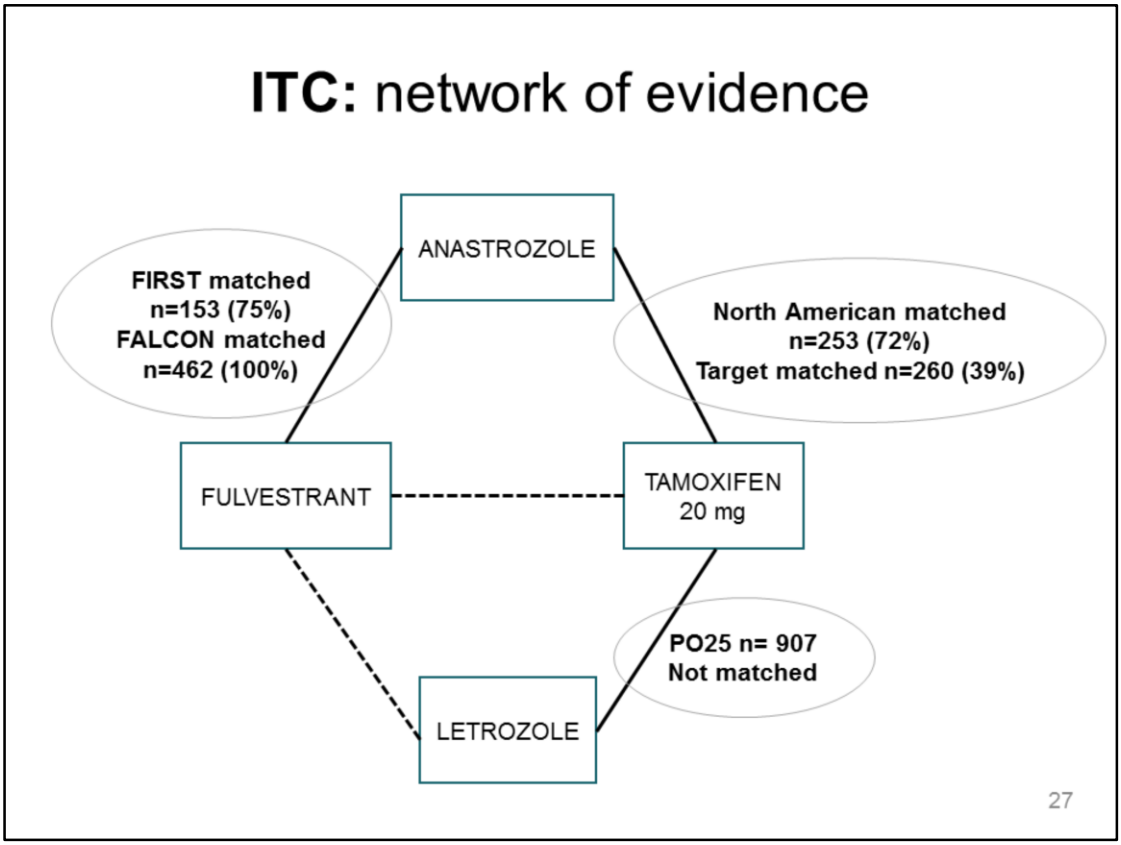
Please note the utility decrements associated with the adverse events were sourced from other sources for fulvestrant and the comparators (i.e. fulvestrant and anastrozole were not sourced from the FALCON trial)



For full NMA methodology and results: see section 4.10 of the company's submission. For full justification for not providing a random effects model, see question A10 of the clarification response.

Summary of methodology

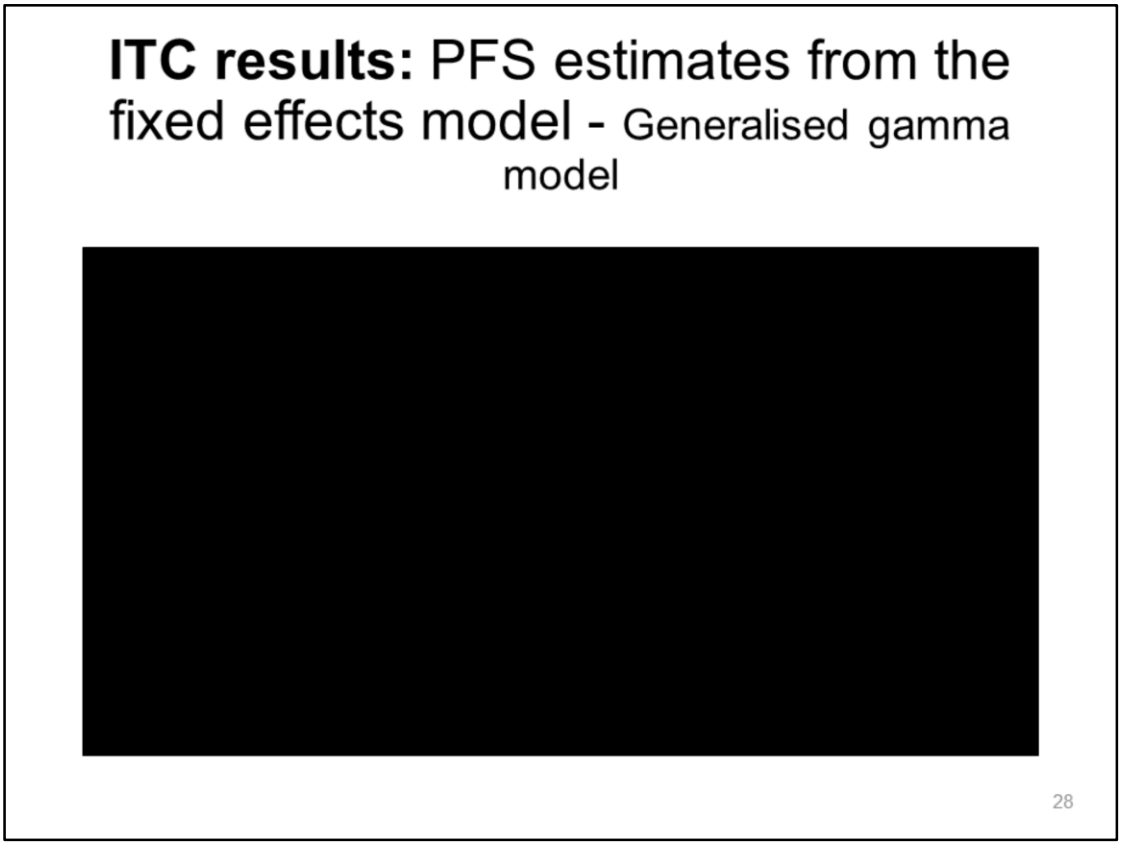
- Patient-level data (PLD) were available from all included trials except for PO25, so the Kaplan-Meier (KM) curves were digitised to produce PLD
- The KM curves for PFS and OS were inspected and showed violation of proportional hazards assumptions, suggesting that traditional methods for NMA using pooled hazard ratios were not appropriate
- Alternative methodology by Ouwens et al allows the use of PLD to estimate the treatment effect on the parameters of the parametric distributions applied in the model (i.e. to estimate the shape and scale parameters of the parametric curve)
- A fixed effects NMA was judged most appropriate due to the limited number of studies. The company acknowledges this has less flexibility than a random effects model (fewer parameters) and may not fit the data to the curve as well.
- Shape and scale parameters (for the chosen distribution; Weibull, Gompertz, log-logistic, lognormal or generalised gamma) were estimated for the baseline comparator (anastrozole; anchor) and used to estimate shape/scale for the other comparators
- Method allows modelling of long-term survival without the assumption of proportional hazards, referred to as the 'all shapes' model. The company also explored the effect of assuming proportional hazards, referred to as the 'no shape arm' model (shape parameter is fixed between the treatment arms – less flexible)
- Based on the log-cumulative hazard plots and visual inspection of the improved curve fits, the 'all shapes' model was chosen to provide the base case survival curves for PFS and OS used in the economic model (i.e. no proportional hazards assumption)



see section 4.10 of the company's submission for full details on the indirect treatment comparison.

For those trials where patient-level data was available (see notes page on previous slide) the inclusion and exclusion criteria from the FALCON trial was applied to each treatment arm in both trials to better match the FALCON trial population. This couldn't be accomplished with the PO25 trial as only reconstructed patient-level data was available.

Outcomes to be compared in the ITC were PFS or TTP and OS. TTP was commonly reported among the studies except for FALCON where PFS was reported but the definitions of both are clinically similar. The ERG agree that the definitions of PFS and TTP are similar and that the Milla-Santos study is not appropriate to include in the NMA.



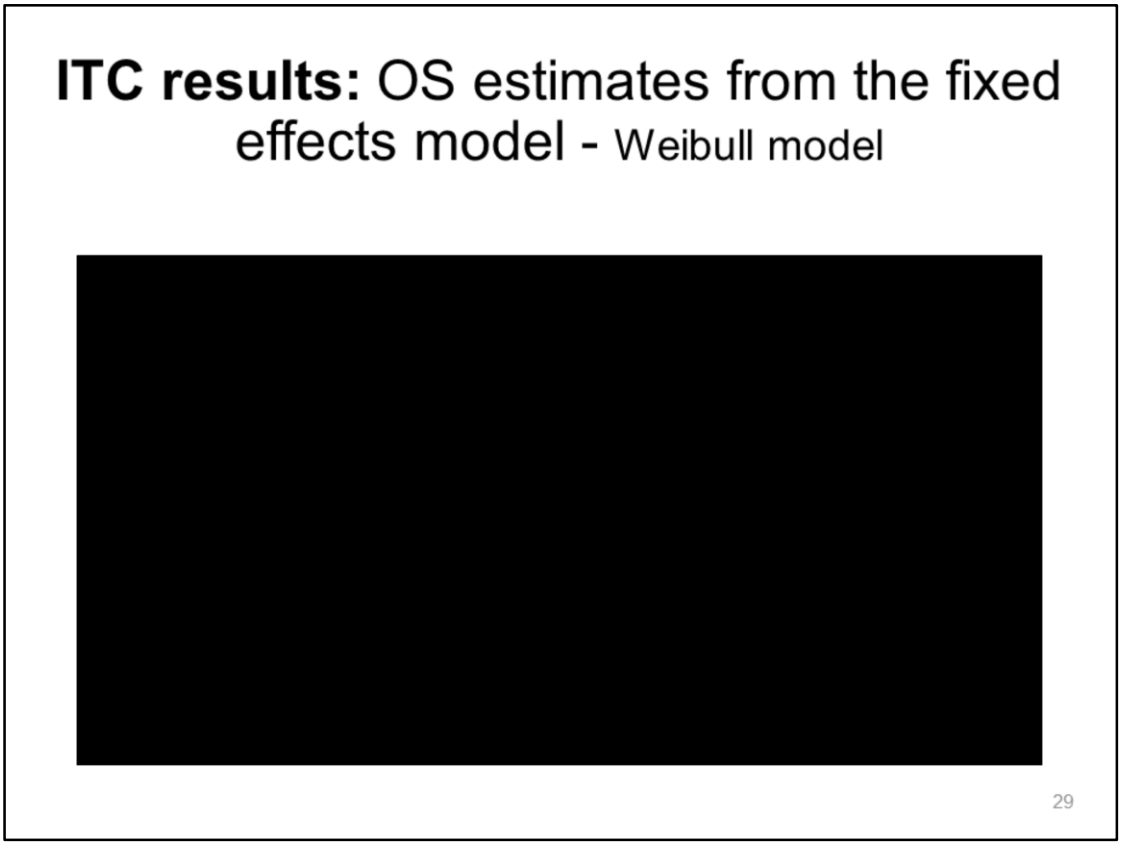
See section 4.10.4 of the company's submission for curve selection details

Parametric curve selection

Expert opinion suggested that generalised gamma, lognormal and log logistic curves provided realistic projections at 5 and 10 years for people treated with anastrozole.

Log-logistics had the best AIC/BIC fit but was rejected because of flattening of the projected curve and the long-tail (over-estimating survival). The Weibull and Gompertz had the highest AIC/BIC score but showed a better projected fit to the Kaplan-Meier PFS on visual inspection but was judged too conservative.

The generalised gamma distribution was chosen as the most appropriate method of extrapolating PFS based on visual inspection; the AIC and BIC values (second best fit – log logistic provided the best fit) and clinical expert opinion for anastrozole. Please note AIC/BIC statistical tests only provide a score of fit to the observed data.
'Guidance from NICE's Decision Support Unit recommends that the same parametric models are applied for all treatment arms per outcome); therefore, the generalised gamma distribution was chosen for all treatment arms. Alternative parametric functions for PFS were explored in sensitivity analysis.'



See section 4.10.5 of the company's submission for full details of curve selection for OS

Parametric survival curve selection

The Weibull had the lowest AIC/BIC, so provided the best fit to the observed data. Visual inspections showed that Weibull and the generalised gamma provided similar fits, with Weibull being slightly more conservative. The lognormal and log logistic curves were rejected because of long tails over-estimating survival. Gompertz was rejected because it was too conservative (no one alive at 10 years) and visually provided a very poor fit to the data.

Expert opinion that only Weibull and generalised gamma provided realistic projections at 10 years.

The Weibull distribution was chosen as the most appropriate method of extrapolating OS based on visual inspection; the AIC and BIC values (best fit) and clinical expert opinion for anastrozole. As guidance from NICE's Decision Support Unit recommends that the same parametric models are applied for all treatment arms per outcome, the Weibull distribution was chosen for all treatment arms. Using alternative parametric functions that provide

plausible OS estimates (generalised gamma) were explored in sensitivity analysis

Clarification response: removal of PO25 from the ITC

- PO25 differs to the other trials in the network
  - No patient level data available
  - Results are compromised by approx 50% cross-over after progression and it is widely accepted that letrozole and anastrozole have equivalent efficacy
- ERG requested an analysis with PO25 removed from the ITC and equal efficacy of letrozole and anastrozole assumed

- Company reported that removing PO25 had a minimal impact on the estimated curve parameters for anastrozole, fulvestrant and tamoxifen and the mean and median survival estimates
- Included as a scenario in the cost effectiveness analysis

30

For full details see question A11 of the company's clarification response

Utility values used in the model

- Utility values were derived from a mixed models with repeated measurements (MMRM) from the FALCON trial
  - used direct EQ-5D-3L data from the trial
  - used to account for repeated measurements of utility during the trial
  - company explored the fit of a covariate-adjusted model but chose the unadjusted model (progression was the only covariate) because it was the best match to the NICE reference case

Health state	Base case: MMRM
Progression-free (PF)	0.7511
Progressed disease (PD)	0.6913

Note; the company acknowledge the PD value used in the base case is higher than those used in past appraisals

31

See section 5.4 of the company's submission for full details of methods for HRQoL used in the model

The EQ-5D-3L questionnaire was given at baseline and every 12 weeks until progression or treatment discontinuation and during survival follow-up for those still on randomised treatment. For those not on treatment at follow-up it was given 3 months after objective disease progression.

The EQ-5D values were similar for both treatment arms in the FALCON trial; no statistically significant difference was observed.

The MMRM model was used to account for repeated measurements of utility during the trial and to estimate an association between the utilities and clinical events (PFS) in the FALCON trial. The model was a regression model and the EQ-5D values were adjusted with covariates, these included:

- Progression
- Metastatic disease
- Prior chemotherapy
- Measurable disease

- Visceral disease (reference=non-visceral disease)
- Stable disease (reference=progressive disease)
- Partial response (reference=progressive disease)
- Complete response (reference=progressive disease)
- Drug discontinuation
- Treatment group (reference=anastrozole)

To note; the statistical goodness-of-fit scores (AIC and BIC) were similar for adjusted and unadjusted models.

Utility decrements due to adverse events

Adverse events and their duration, grade 3 and above, are included in the model as disutilities - *sourced from previous NICE submissions.*

The ERG considers the company's approach to including disutilities for adverse events in the economic model is reasonable and notes that the effect of adverse events on disutilities on the model results is negligible due to the low frequency of serious adverse events.

Utility values used in other technology appraisals

Treatment (submission)	PFS	PD
Trastuzumab emtansine (TA371)	0.78 (TRA) 0.72 (LAP+CAP)	0.5
Everolimus in combination with exemestane (TA295)	0.7644 (EVE+EXE) 0.7571 (PLC+EXE)	0.65
Bevacizumab with capecitabine (TA263)	0.784 (BEV+CAP) 0.774 (CAP)	0.496
Lapatinib plus letrozole (TA257)	0.86	0.62
Trastuzumab plus anastrozole (TA257)	0.73	0.45
Eribulin (TA423)	0.715 (stable) 0.790 (response)	0.443 0.16 (terminal)
Fulvestrant (TA239)	0.72	0.44
Bevacizumab plus weekly paclitaxel (TA214)	0.65 (stable) 0.81 (response)	0.45
Gemcitabine plus paclitaxel (TA116)	0.72 (stable) 0.80 (response)	0.46
Trastuzumab plus paclitaxel (TA34)	NR	NR

BEV, bevacizumab; CAP, capecitabine; EVE, everolimus; EXE, exemestane; LAP, lapatinib; NR, not reported; TA, technology appraisal; TRA, trastuzumab emtansine;.

32

See section 5.4 of the company's submission for full details of methods for HRQoL used in the model

Resource use (1)

- Total drug acquisition per 4-week cycle - based on estimated time-to-treatment discontinuation (assumed to be until disease progression – PFS) and compliance rate (sourced from the FALCON trial; fulvestrant and anastrozole, 0.99; letrozole and tamoxifen assumed to be 1.00 full compliance)
  - **Fulvestrant (1st 4 weeks):** £1,044.82, **(after 1st 4 weeks):** £522.41
  - **anastrozole:** £0.75, **Letrozole:** £1.52, **Tamoxifen:** £1.51
- Disease management costs were based on NICE clinical guideline CG81
- Progression-free health state costs sourced from PSSRU 2015/16
  - Total per 4-week cycle: £183.36
- Progressed disease health state costs sourced from PSSRU 2015/16
  - Total per 4-week cycle: £704.67
- Adverse event costs
  - NHS reference costs sourced from previous NICE submissions

33

See section 5.5 of the company's submission for full details on the resources, costs and assumptions used in the model

Please note tamoxifen is a 30-day pack priced at £1.62 but no wastage is assumed in the base case so the modelled price is lower.

<u>Time to treatment discontinuation (TTD) assumed to be the same as PFS</u>
The company assumes TTD to be until disease progression (when people start the next treatment) because the curves for TTD and PFS are broadly similar. There is a small separation of the curves in TTD for fulvestrant which the company state is most likely due to the different dosing frequency of anastrozole and fulvestrant. Because the most frequent reason for discontinuing treatment was due to disease progression it was assumed reasonable that TTD would be the same as PFS.

Resource use (2)

- Subsequent treatment therapies & cost (2nd and 3rd line)
  - no retreatment with fulvestrant assumed (expert opinion)
  - the estimates for proportion of people going on to the next line of treatment, duration and type of treatment was sourced from literature (Kurosky, 2015; Yardley, 2013)
  - **second line:** endocrine therapy, 54.35%; chemotherapy, 37.57%; targeted therapy, 8.08%; no treatment, 0%
  - **third line:** endocrine therapy, 24.02%; chemotherapy, 30.39%; targeted therapy, 0%; no treatment, 45.59%

34

See section 5.5 of the company's submission for full details on the resources, costs and assumptions used in the model

Summary of key modelling assumptions

- Average treatment dosage assumed to account for dose reductions and treatment gaps
- Subsequent treatment costs are a weighted average
  - this is applied as a one-off when people progress
- Subsequent treatments only impact costs not on survival
  - this is assumed to be captured in the overall survival estimate
- Population characteristics used from the FALCON trial – mean age 63.8 years
- Treatment duration is until objective disease progression
- A mix of subsequent treatments are assumed for all people
  - mix differs for fulvestrant and the comparators because fulvestrant is not included in the treatment mix – i.e. those who receive fulvestrant are not expected to be retreated with fulvestrant subsequently
- Costs and disutilities due to adverse events occur as a one-off in the first cycle of treatment

35

See section 5.6 of the company's submission for full list of variables and assumptions used in the partitioned survival model.

Company's base case results

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER	Pairwise ICER (fulvestrant vs comparator)
Letrozole	£26,221	2.46	--	--	--	£29,991
Anastrozole	£30,572	2.68	£4,351	0.22	£19,702	£34,099
Tamoxifen	£32,328	2.47	£1,756	-0.21	Dominated	£22,498
Fulvestrant	£49,431	3.23	£18,859	0.55	£34,099	--
Probabilistic ICERs fulvestrant; vs anastrozole, **£33,762**; vs letrozole, **£31,264**; vs tamoxifen, £22,815						

36

Please note the company found several calculation errors during clarification and provided an updated model with revised ICERs (shown here). Please see the appendix to the clarification response for these results and the ERG report.

Subgroup analysis

The company did not provide a subgroup cost effectiveness analysis for people with, or without, visceral metastases because the clinical evidence found no statistical or clinically significant difference in the clinical subgroup analysis.

Limitations

The company acknowledge the immaturity of OS data from the FALCON study is a limitation and that inclusion of FIRST in the NMA was most likely the key driver for OS in the model.

It is widely accepted that anastrozole is clinically similar to letrozole in terms of outcomes but the NMA showed a statistical significant difference in the OS extrapolations. This is mostly likely caused by cross-over in PO25 trial which could not be adjusted for because the company had no access to the patient-level data.

ERG comments on the results and validation (see section 4.3.8 to 4.3.10 of the ERG report)

- Face validity – background of third-party experts are not known (clinical or health economics)
- Internal validity – a few calculation errors were found but these did not have a significant impact on the results when corrected
- External validity – comparison of OS data for fulvestrant and anastrozole to the observed data from FIRST was reasonable
- Choice of parameters and ranges in the deterministic sensitivity analysis were reasonable but the ERG would have preferred an exploration of 95% CI for the health state utilities
    - ICERs were most sensitive and shows there is considerable uncertainty in the model results (i.e. long-term effectiveness) to OS parameters
- Scenario analysis yielded broadly similar results to the base case but the ERG explored different OS distributions in its scenario analysis for completeness

Company's base case results: survival outcomes – time spent in health states

Treatment	Time in PFS (months)		Time in PD (months)		Time alive (months)	
	Median	Mean	Median	Mean	Median	Mean
Fulvestrant	16.56	29.58	31.28	30.51	47.84	60.08
Anastrozole	11.96	19.56	27.60	29.38	39.56	48.95
Letrozole	14.72	22.16	23.92	21.26	38.64	43.42
Tamoxifen	9.20	13.16	27.60	31.89	36.80	45.05

37

See section 5.7.2 of the company's submission for full clinical outcomes of the model

Company's deterministic sensitivity analysis: fulvestrant vs anastrozole

Parameter	Base case (ICER)	Lower value (ICER)	Upper value (ICER)
(OS) fulvestrant: Weibull scale parameter	£34,099	£338,729	£23,236
Health state utilities: PF	£34,099	£42,187	£28,613
Discount rate - Outcomes	£34,099	£27,193	£39,387
Treatment acquisition costs per 4 weeks: fulvestrant	£34,099	£28,371	£39,827
Discount rate - Costs	£34,099	£38,592	£31,660
(OS) anastrozole: Weibull scale parameter	£34,099	£36,757	£31,584
(PFS) anastrozole: gamma scale parameter	£34,099	£31,560	£36,791
(OS) fulvestrant: Weibull shape parameter	£34,099	£31,031	£35,450

38

See section 5.8 of the company's submission for a list of all the scenario analyses conducted by the company. For results based on the most recent corrected model, see section 4.3.10 of the ERG report

Deterministic sensitivity analysis

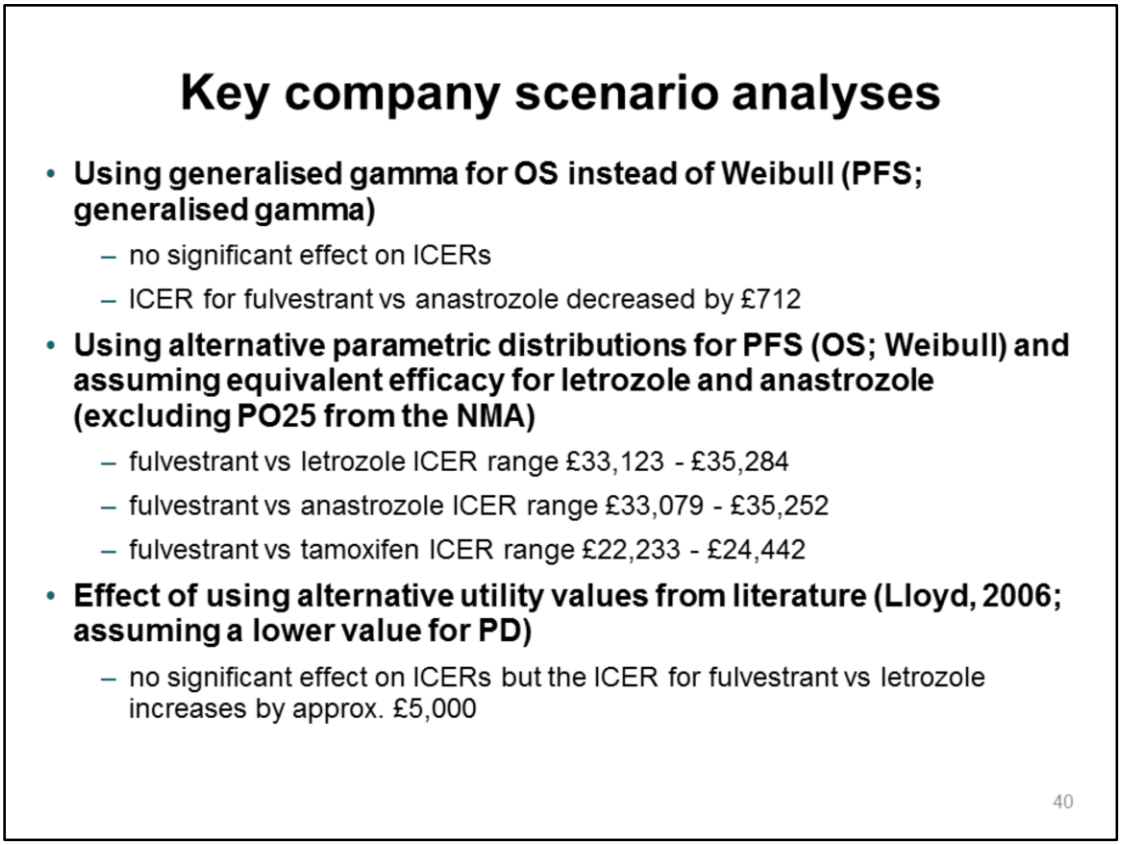
'The deterministic sensitivity analysis showed that the largest drivers across each of the comparisons was the shape and scale parameters (for anastrozole) and differences in shape and scale (for fulvestrant, letrozole and tamoxifen) for PFS and OS. Other key parameters highlighted as being key drivers of changes in costs or QALYs included the health state utility values for progression-free and progressed disease, the discount rate for costs and outcomes, and the treatment acquisition costs for fulvestrant'

Company deterministic sensitivity analysis: fulvestrant vs tamoxifen

Parameter	Base case (ICER)	Lower value (ICER)	Upper value (ICER)
(OS) tamoxifen: Weibull scale parameter	£22,498	£19,408	£40,262
Health state utilities: PF	£22,498	£25,502	£20,495
Treatment acquisition costs per 4 weeks: fulvestrant	£22,498	£18,330	£26,665
Discount rate - Outcomes	£22,498	£17,981	£25,976
Discount rate - Costs	£22,498	£26,239	£20,495
(PFS) tamoxifen: gamma scale parameter	£22,498	£19,975	£25,710
(PFS) tamoxifen: gamma shape parameter	£22,498	£21,151	£24,158
(OS) fulvestrant: Weibull scale parameter	£22,498	£41,586	£18,470

39

See section 5.8 of the company's submission for a list of all the scenario analyses conducted by the company. For results based on the most recent corrected model, see section 4.3.10 of the ERG report



See section 5.8 of the company's submission for a list of all the scenario analyses conducted by the company. For results based on the most recent corrected model, see section 4.3.10 of the ERG report

Scenario analysis of alternative PFS parametric distributions

The scenario analyses showed there was little difference when alternative distributions were used in the base case model but there were large differences in the ICERs when alternative curves were used for an alternative model where proportional hazards were assumed , especially when the log curves are used and in comparison to letrozole.
To note; the company only explored alternative curves for PFS and kept the Weibull model for OS.

Scenario analysis of alternative utility values

The company explored the effect of alternative utility values in the model:
The company acknowledged that the PD values used in the base case may overestimate the true impact of disease progression on HRQoL in first-line metastatic patients so decrement utility values from a model found in literature (Lloyd model) were combined with the MMRM model to estimate a new lower utility value for the PD state (0.491 instead of 0.69). Values from the Lloyd model were tested directly too (similar PF values but lower PD

values)
This had little impact on the ICERs for anastrozole or tamoxifen but increased the ICER vs letrozole by around £5k per QALY gained (approx. £35,000)

ERG comments: ITC

- Agrees there are violations of proportional hazards in the plots for the studies included in the NMA, therefore using the alternative NMA method for the base case is reasonable
- ERG prefers to exclude PO25 - widely accepted that anastrozole and letrozole have similar efficacy and PO25 is the only trial without patient-level data
- ERG accepts that only a fixed-effects model was possible but is concerned that the inability to conduct random-effects analyses means that the potential uncertainty may not be adequately captured
- Re 'matching' the inclusion and exclusion criteria of included studies to FALCON to create a homogenous population:
  - ERG notes that 'matching' reduces the sample size of the comparator studies and breaks randomisation but considers that the advantages of reducing heterogeneity outweigh these disadvantages
  - unclear whether 'matching' excluded people with HER2+ breast cancer from the comparator studies – people with HER2+ breast cancer would be expected to respond less well to treatment thereby putting the comparator studies at a disadvantage

41

See section 3.3 of the ERG report for full interpretation of the company's results

ERG comments: model structure and extrapolations

- The model approach is appropriate and consistent with the clinical pathway for advanced breast cancer
- The generalised gamma provides a good fit to PFS from FALCON and therefore deemed reasonable for modelling PFS
- The ERG note that the OS data from FALCON is immature so much of the data that informs the OS extrapolation is from FIRST – the Weibull provided a good fit to OS from FIRST and therefore deemed reasonable for modelling OS
  - ERG expects the cost effectiveness results to be higher when mature OS data from FALCON become available because the OS benefit may mirror PFS (i.e. be lower than in FIRST)
- The company did not extrapolate time-to-treatment discontinuation (TTD) beyond the trial therefore it cannot be evaluated if PFS is a good proxy for TTD

42

See section 4.3.3 to 4.3.5 of the ERG report for full details

ERG comments: adverse events, HRQoL and resource use

- Errors were found in some adverse event incidence rates and utility decrement values
  - ERG concludes that adverse events have only a minor impact on the results because of the low frequency of serious events in the trial
- The use of EQ-5D data from FALCON for utility data is appropriate and consistent with the NICE reference case
- Disagrees with company's assumption that 32% of people will receive fulvestrant in primary care and basing management costs on NICE clinical guideline CG81
  - primary care assumption removed based on clinical opinion
  - management costs amended (CG81 refers to people receiving chemotherapy not endocrine therapy) to be more consistent with clinical opinion and previous clinical trials for aromatase inhibitors (Karnon et al.)
- Disagrees with subsequent therapy assumptions
  - proportion receiving second line endocrine therapy would be higher (company estimate, 54.35%; ERG estimate, 67 - 80%) than chemotherapy

43

See section 4.3.6 and 4.3.7 of the ERG report for full details

ERG exploratory analyses

- **Scenario 1 - different parametric distributions for OS**
  - no significant effect on ICER, except Gompertz, which provided a poor fit to the data therefore the results should be treated with caution
- **Scenario 2 - effect of changes in the scale parameter for OS**
  - ICERs were most sensitive to OS parameters and shows there is considerable uncertainty in the model results (i.e. long-term effectiveness)
  - ICERs for fulvestrant vs anastrozole vary between £40,761 and £208,231
- **Scenario 3 - resource use for PFS and PD data from Karnon et al.**
  - the ICER for fulvestrant vs anastrozole falls by £2,015
- **Scenario 4 - subsequent therapy based on clinical opinion**
  - the ICER for fulvestrant vs anastrozole decreases by £53
- **Scenario 5 - assume equal efficacy for letrozole to anastrozole**
  - exclusion of PO25 study has almost no impact on base case ICER
- **Scenario 6 - no administration of fulvestrant in primary care**
  - the ICER for fulvestrant vs anastrozole increases by £1,397

44

See section 4.4 of the ERG report for full details

ERG scenario analysis 2: using a range to the upper bound of OS scale parameter

Parameters		Base case ICER (OS: Weibull)	Scenario ICER
Scenario 2: Fulvestrant Incremental scale parameter [redacted]			
Fulvestrant vs	Letrozole	£29,991	**£33,475**
	Anastrozole	£34,099	**£40,761**
	Tamoxifen	£22,498	**£24,432**
Scenario 2: Fulvestrant Incremental scale parameter [redacted]			
Fulvestrant vs	Letrozole	£29,991	**£38,326**
	Anastrozole	£34,099	**£52,405**
	Tamoxifen	£22,498	**£27,146**
Scenario 2: Fulvestrant Incremental scale parameter [redacted]			
Fulvestrant vs	Letrozole	£29,991	**£45,842**
	Anastrozole	£34,099	**£79,337**
	Tamoxifen	£22,498	**£31,404**
Scenario 2: Fulvestrant Incremental scale parameter [redacted]			
Fulvestrant vs	Letrozole	£29,991	**£59,000**
	Anastrozole	£34,099	**£208,231**
	Tamoxifen	£22,498	**£39,027**

Decreasing fulvestrant benefit

45

See section 4.4 of the ERG report for full details

‘The ERG notes that the OS data from the FALCON trial are immature. Therefore OS for fulvestrant vs, anastrozole is largely based upon the FIRST trial. The ERG notes that the gain in PFS for fulvestrant compared to anastrozole was significantly lower in the FALCON trial than in the FIRST trial and therefore suggests that it is likely that the OS benefit will also be lower in the FALCON trial than in the FIRST trial. Given the sensitivity of the model results to changes in OS, the ERG therefore considers there is some uncertainty in the cost-effectiveness estimates and the ICERs are likely to be higher when the full results of the FALCON trial become available.’

ERG exploratory base case results: combines scenarios 3 to 6

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER	Pairwise ICER (Fulvestrant vs comparator)
Letrozole	£11,336	2.68	--	--	**--**	**--**
Anastrozole	£11,356	2.68	--	--	**--**	**£33,455**
Tamoxifen	£11,852	2.47	£496	-0.21	**Dominated**	**£23,687**
Fulvestrant	£29,866	3.23	£18,510	0.54	**£33,455**	**--**
Probabilistic ICERs fulvestrant; vs anastrozole, **£32,956**; vs letrozole, **£32,983**; vs tamoxifen, **£23,999**						

46

See section 4.4 of the ERG report for full details

Innovation & equalities

Innovation

- Fulvestrant has a different mechanism of action because it's the only drug to block the effects of oestrogen
  - this could delay acquired resistance and increase OS
- Fulvestrant has a different and manageable tolerability profile compared to aromatase inhibitors and chemotherapy
- Intramuscular route of administration
  - suited to people unable to swallow (e.g. older people) – increases adherence and length of treatment

Equality

- Intramuscular administration may be suited for people protected by equality legislation

47

See section 2.5 of the company's submission and clinical expert statements for full details

Key issues: cost effectiveness

- What is the committee's view on the approach used to estimate treatment effects in the economic model?
  - Is the 'matched' population relevant to the decision problem?
  - Does generating a more homogenous sub-group for the NMA outweigh the potential bias associated with violating trial randomisation?
- What is the committee's view on the robustness of the estimated OS based on the survival extrapolations?
- What is the committee's view on the estimated health utilities?
- What is the committee's view on the cost effectiveness estimates for fulvestrant
  - compared with anastrozole, letrozole and tamoxifen?
- What is the committee's view on the sensitivity of the ICERs to changes in the OS parameter?

48

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49

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer [ID 951]

AstraZeneca evidence submission

March 2017

File name	Version	Contains confidential information	Date
		Yes	**5 May 2017**

Contents

Tables and figures

1 Executive summary

1.1 Statement of decision problem

The remit from the Department of Health for this appraisal was:

To appraise the clinical and cost effectiveness of fulvestrant within its marketing authorisation for oestrogen-receptor positive (ER+), locally advanced or metastatic breast cancer in postmenopausal women not previously treated with endocrine therapy.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Post-menopausal people with locally advanced or metastatic hormone receptor-positive breast cancer, who have not received endocrine therapy	Same as final scope issued by NICE.	N/A
Intervention	Fulvestrant	Same as final scope issued by NICE.	N/A
Comparator (s)	• Aromatase inhibitors (such as anastrozole and letrozole) If aromatase inhibitors are not tolerated or are contraindicated: • Tamoxifen	Same as final scope issued by NICE.	N/A
Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • response rate • adverse effects of treatment • health-related quality of life.	Same as final scope issued by NICE.	N/A
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	Same as final scope issued by NICE.	N/A

	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.		
Subgroups to be considered	If the evidence allows the following subgroups will be considered: people with visceral disease and people with non-visceral disease. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	Same as final scope issued by NICE.	N/A

1.2 Description of the technology being appraised

Fulvestrant 500mg is an oestrogen receptor (ER) antagonist that binds to the ER in a competitive manner, with an affinity comparable to that of oestradiol, and downregulates the ER protein in human breast cancer cells. Fulvestrant 500mg targets and degrades the ER by exerting selective ER downregulation, antiproliferative activity and induction of apoptosis in a dose-dependent manner (1). It binds competitively to ERs, with an affinity 100 times that of tamoxifen, to completely inhibit oestrogen signalling (1, 2). ER function is blocked by inhibition of ER dimerisation, reduced nuclear uptake of the drug-receptor complex and prevention of ER binding to oestrogen-responsive genes (3). In addition, the turnover of ER is increased, the half-life of the protein is reduced, and the receptor is rapidly degraded, resulting in downregulation of the ER protein in breast carcinoma cells, making the receptor unavailable or unresponsive to oestrogen or oestrogen agonists (1, 3, 4).

Table 2: Technology being appraised

UK approved name and brand name	Fulvestrant (Faslodex®)
Marketing authorisation/CE mark status	Fulvestrant is being considered for a change in the marketing authorisation. CHMP opinion is expected in late June 2017, with full marketing authorisation expected in late August 2017.
Indications and any restriction(s) as described in the summary of product characteristics	According to the existing marketing authorisation, fulvestrant is indicated for the treatment of postmenopausal women with oestrogen receptor positive (ER+), locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-oestrogen (AO) therapy, or disease progression on therapy with an AO. The proposed change in marketing authorisation would amend this to: *Faslodex is indicated for the treatment of oestrogen-receptor positive, locally advanced or metastatic breast cancer in postmenopausal women:*

	• *not previously treated with* prior anti-oestrogen or aromatase inhibitor therapy' or • *with disease relapse on or after adjuvant anti-oestrogen therapy, or disease progression on anti-oestrogen therapy*
Method of administration and dosage	The recommended dose is 500mg to be administered intramuscularly (IM) into the buttocks (gluteal area) slowly (1-2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29 and once monthly thereafter.

1.3 Summary of the clinical effectiveness analysis

Evidence for the clinical efficacy and safety of fulvestrant 500mg in postmenopausal women with oestrogen-receptor positive, locally advanced or metastatic breast cancer who have not previously been treated with endocrine therapy comes from 2 RCTs: FIRST and FALCON. FIRST was a Phase II, randomised, open-label non-inferiority study of fulvestrant 500mg versus anastrozole 1 mg in postmenopausal women with advanced disease previously untreated with endocrine therapy (or at least a year after completing adjuvant endocrine therapy) (5). The results of the FIRST study showed an efficacy benefit for fulvestrant 500mg compared with anastrozole as first line endocrine therapy for patients with ER+ ABC, and supported further investigation of fulvestrant 500mg in this clinical setting.

FIRST

Fulvestrant 500mg demonstrated a significant increase in time to progression (TTP) compared with anastrozole (HR: 0.66; 95% CI: 0.47-0.92; p=0.01) Robertson 2012). The median TTP for fulvestrant 500mg was 10.3 months longer than for anastrozole (23.4 months vs. 13.1 months, respectively). Furthermore, a follow-up analysis when approximately 65% of deaths had occurred demonstrated that fulvestrant 500mg significantly improved OS when compared with anastrozole (HR: 0.70; 95% CI: 0.50-0.98; median 54.1 months vs. 48.4 months, respectively; p=0.041) (6). Indeed, in an

exploratory subgroup analysis of OS in patients who had not received prior endocrine therapy the benefit was even greater (HR: 0.63; 95% CI: 0.42 – 0.93) (6).

FALCON

Following on from FIRST, the Phase III, randomised, double-blind, parallel-group, multicentre, FALCON study (7) was conducted to confirm the superior efficacy and acceptable tolerability of fulvestrant 500mg versus anastrozole (the SoC). The proposed patient population of endocrine therapy-naïve postmenopausal women with ABC reflected the population of patients who had experienced a clinical benefit in the FIRST study (5) and those most likely to benefit from the study treatment.

This primary objective was met, with a statistically significant improvement in Progression Free Status (PFS, directly analogous to the TTP metric used in FIRST) observed in the fulvestrant 500mg arm compared with the anastrozole arm (p=0.0486) (8). Median PFS was 2.8 months longer in the fulvestrant 500mg arm (16.6 months; 95% CI: 13.83-20.99) than in the anastrozole arm (13.8 months; 95% CI: 11.99-16.59). The hazard ratio (HR) was 0.797 (95% CI: 0.637-0.999). The OS data were immature at the time of interim analysis (only 31% of events had been reached), to the extent that median OS could not be calculated. There was no statistically significant difference in OS between treatment with fulvestrant 500mg or anastrozole (HR: 0.875; 95% CI: 0.629-1.217; p=0.4277).

Table 3: Summary outcome data for studies using fulvestrant in untreated advanced BC patients

	FIRST ITT (6, 9) (N=205)	**FIRST endocrine naïve (6, 9) (N=153)**	**FALCON ITT (7) (N=462)**
Median PFS/TTP	FUL: 23.4 months ANA: 13.1 months	N/A	FUL: 16.6 months ANA: 13.8 months
HR (95% CI)	0.66 (0.47-0.92)	0.52 (0.35 – 0.77)	0.797 (0.637-0.999)
Progression Events	FUL: 62% ANA: 77%	N/A	FUL: 62% ANA: 72%
Median OS	FUL: 54.1 months ANA: 48.4 months	N/A	Not reached
HR (95% CI)	0.70 (0.50-0.98)	0.63 (0.42 – 0.93)	0.88 (0.63-1.22)
Deaths	FUL: 62% ANA: 72%	FUL: 60% ANA: 74%	FUL: 29% ANA: 32%

Overall, HRQoL (FACT-B TOI score and EQ-5D) was maintained and similar in both treatment groups. Indeed, as well as providing support for the use of fulvestrant 500mg in mBC patients who are endocrine-naïve, both FALCON and FIRST are the latest in a number of studies to demonstrate clinical benefits in BC patients at later stages of the treatment pathway (i.e. CONFIRM).

INDIRECT TREATMENT COMPARISON

A comprehensive network of evidence was available to potentially compare fulvestrant 500mg with all the comparators of interest in the final scope; anastrozole (via FALCON (7) and FIRST (5)), tamoxifen (via comparison with anastrozole in North America (10) and TARGET (11) studies) and letrozole (via comparison with tamoxifen in PO25 trial (12)). It is worth noting that the inclusion of PO25 is somewhat controversial given that subjects recruited to that study had a lower proportion of hormone-receptor (HR) +ve disease and the OS results are compromised by approximately 50% cross-over of therapies after progression (12). Nevertheless, in order to make a comparison against letrozole, PO25 remains the only source of evidence in this setting. Visual inspection of the Kaplan-Meier survival plots indicated ‘crossing of survival curves’ and suggested that traditional methods for network meta-analysis (NMA) using pooled hazard ratios (HR) are not appropriate. An alternative method of NMA which is not reliant on an assumption of proportional hazards was used to estimate the effect of treatment on the shape and scale of parametric survival distributions derived from all the available RCT evidence (13).

The generalised gamma distribution was chosen as the most appropriate method of extrapolating PFS based on visual inspection; the AIC and BIC values (second best fit) and clinical expert opinion for outcomes for patients treated with standard of care (anastrozole). Similarly, the Weibull distribution was chosen as the most appropriate method of extrapolating OS based on visual inspection; the AIC and BIC values (best fit) and clinical expert opinion. The predicted mean and median time to progression, time in progressed disease and time alive for each arm of the simulation are summarized in Table 4.

Table 4: Survival outcomes; time (mean and median) spent in health states, undiscounted

Treatment	Time in PFS (months)		Time in PD (months)		Time alive (months)	
	Median	Mean	Median	Mean	Median	Mean
Fulvestrant	16.56	29.58	31.28	30.51	47.84	60.08
Anastrozole	11.96	19.56	27.60	29.38	39.56	48.95
Letrozole	14.72	22.16	23.92	21.26	38.64	43.42
Tamoxifen	9.20	13.16	27.60	31.89	36.80	45.05

Abbreviation: PD, progressed disease; PFS, progression-free survival.

These predictions are similar to those calculated for letrozole in a recent appraisal by NICE (ID915), providing reassurance that the methods used are robust (Table 5).

Table 5: Comparison of PFS and OS predictions for AIs in NICE appraisals

Outcome	Anastrozole (NMA)	Letrozole (NMA)	Letrozole (ID915)
Median PFS (months)	12.0	14.7	15.7
Patients progression-free at 30 months	19%	23%	21%
Median OS (months)	39.6	38.6	35.1
Patients alive at 48 months	41%	37%	30%
Mean OS (months)	48.9	43.4	38.9

1.4 Summary of the cost-effectiveness analysis

A cohort-based partitioned survival model was developed to evaluate the cost-effectiveness of fulvestrant 500mg. The model is comprised of three mutually exclusive health states: progression-free survival (PFS) [receive first line hormonal therapy], progressed disease (PD) [receive subsequent therapies] and death (due to any cause). The model adopts an NHS/PSS perspective and includes the resource use and costs associated with disease management, treatment acquisition, administration, adverse events and terminal care. Utilities for both time spent in PFS and PD health states were calculated from EQ-5D responses collected from patients enrolled in the FALCON study (7).

The model considers a lifetime horizon (<30 years), and the cycle length is 4 weeks. Costs and health-state utility values are allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle by taking the average between the number of patients present at the beginning of the cycle

and the number of patients at the end of the cycle (half cycle correction). An annual discount rate of 3.5% is applied to costs and outcomes.

In the base case analysis, the efficacy of the treatment options (fulvestrant, anastrozole, letrozole or tamoxifen) were derived from the results of the NMA described previously. An incremental analysis of fulvestrant versus the aromatase inhibitors demonstrated that letrozole was associated with the lowest overall cost (£25,928), followed by anastrozole (£30,261) and fulvestrant (£49,165). This resulted in an ICER for anastrozole versus letrozole of £19,621 per QALY, and for fulvestrant versus anastrozole of £34,179 per QALY. A comparison of fulvestrant versus tamoxifen produced an ICER of £22,655 per QALY for those patients in whom aromatase inhibitors are not tolerated or contraindicated (Table 6). These results varied by no more than approximately 5% in a probabilistic sensitivity analysis demonstrating the stability of the model outcomes.

In one-way deterministic sensitivity analyses, model outcomes were most sensitive to the health state utility values employed and the parametric functions used to extrapolate overall survival. The impact of 5 parametric functions were explored for PFS and OS. OS was found to be accurately modelled by only 2 parametric functions with the Weibull function chosen as the base case and the generalized gamma function used as a sensitivity analysis. Other functions tested resulted in implausible estimates for OS and were not explored further.

The ICERs for fulvestrant versus anastrozole, letrozole and tamoxifen when OS is modeled by the generalized gamma distribution (the only other distribution that provided a clinically plausible extrapolation) were £28,665, £33,387 and £22,183, respectively. Scenario analyses were also conducted using alternative parametric distributions for extrapolating PFS (Weibull, generalized gamma, Gompertz, lognormal and loglogistic) when OS was modelled using Weibull models. Differences in costs and outcomes relative to the base case were associated with different times spent in pre- and post-progression health states. The ICERs for fulvestrant versus each comparator in these scenarios ranged from £22,402 to £35,340 demonstrating the stability of the cost-effectiveness estimates from this model.

Table 6: Incremental cost-effectiveness results

Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	Incremental analysis
Letrozole	£25,928	3.399	2.455	-	-	-	-
Anastrozole	£30,261	3.736	2.676	£4,333	0.337	0.221	£19,621
Fulvestrant	£49,165	4.475	3.229	£18,904	0.739	0.553	£34,179
Tamoxifen	£31,941	3.479	2.469	-	-	-	-
Fulvestrant	£49,165	4.475	3.229	£17,223	0.996	0.760	£22,655
QALYs, quality-adjusted life years							

2 The technology

2.1 Description of the technology

Brand name: Faslodex 500mg

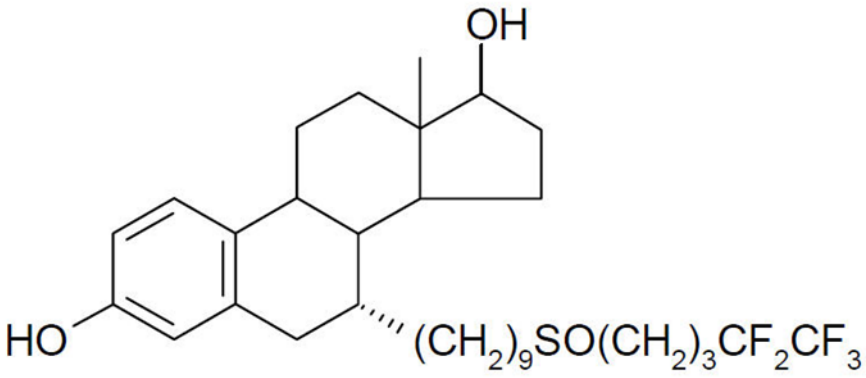
Approved name: Fulvestrant

Therapeutic class: Fulvestrant 500mg is an oestrogen receptor (ER) antagonist that binds to the ER in a competitive manner with affinity comparable to that of oestradiol and downregulates the ER protein in human breast cancer cells. Fulvestrant 500mg can therefore be described as a Selective Oestrogen Receptor Degrader (SERD).

Chemistry

Fulvestrant is an ER antagonist. The chemical name is 7-alpha-[9-(4,4,5,5,5-penta fluoropentylsulphinyl)nonyl]estra-1,3,5-(10)-triene-3,17-beta-diol. The molecular formula is $C_{32}H_{47}F_5O_3S$ and its structural formula is presented in Figure 1.

Figure 1: Structural formula of fulvestrant (14)



Mechanism of action

Fulvestrant is an ER antagonist that binds to the ER in a competitive manner with affinity comparable to that of oestradiol and downregulates the ER protein in human breast cancer cells (14).

In vitro studies have demonstrated that fulvestrant is a reversible inhibitor of the growth of tamoxifen-resistant, as well as oestrogen-sensitive, human breast cancer

cell lines. In postmenopausal women, the absence of changes in plasma concentrations of follicle-stimulating hormone (FSH) and luteinising hormone (LH) in response to fulvestrant treatment (250 mg monthly) suggests no peripheral steroidal effects (14).

Selective oestrogen receptor degraders (SERDs)

SERDs are a therapeutic strategy for ABC directed against the ER (1, 2). Fulvestrant 500mg targets and degrades the ER by exerting selective ER downregulation, antiproliferative activity and induction of apoptosis in a dose-dependent manner (1). It binds competitively to ERs, with an affinity 100 times that of tamoxifen, to completely inhibit oestrogen signalling (1, 2). The complete abrogation of transcription of ER-regulated genes and oestrogen signalling is due to the ability of fulvestrant 500mg to block both the AF1 and AF2 functions of the ER (3).

Due to its steroidal structure and long side-chain, binding of fulvestrant 500mg to the ER induces a conformational change within the receptor that triggers a series of changes in ER function (3, 4). These include inhibition of ER dimerisation, reduced nuclear uptake of the drug-receptor complex and prevention of ER binding to oestrogen-responsive genes (3). In addition, the turnover of ER is increased, the half-life of the protein is reduced, and the receptor is rapidly degraded, resulting in downregulation of the ER protein in breast carcinoma cells, making the receptor unavailable or unresponsive to oestrogen or oestrogen agonists (1, 3, 4). Fulvestrant 500mg also consistently reduces PgR levels in the tumour, making it first in a new class of endocrine therapies and SERDs without agonist activity (1, 15).

Activity of fulvestrant 500mg has been confirmed in women previously treated with a SERM, such as tamoxifen, or with a nonsteroidal AI, such as anastrozole (1). Additionally, it does not show cross-resistance with tamoxifen, or the ER agonist activity associated with tamoxifen (1, 3).

2.2 Marketing authorisation/CE marking and health technology assessment

Fulvestrant has a marketing authorisation in the UK (at the time of writing) for the treatment of the treatment of postmenopausal women with oestrogen receptor positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-oestrogen therapy, or disease progression on therapy with an anti-oestrogen. The current marketing authorisation for the 500mg dose was received from the European Medicines Agency (EMA) on 16th March 2010 and was launched in the UK on 3rd June 2010. Prior to this the EMA approved the marketing authorisation for the now superseded 250 mg dose, on 10 March 2004, which was launched on 1st June 2004.

A submission (a Type II variation for a new indication) based on the FALCON study (7) was submitted to the EMA for a procedure start on 24 November 2016. The proposed target indication is as follows:

> *Faslodex is indicated for the treatment of oestrogen-receptor positive, locally advanced or metastatic breast cancer in postmenopausal women:*
>
> - *not previously treated with* prior anti-oestrogen or aromatase inhibitor therapy' or
> - *with disease relapse on or after adjuvant anti-oestrogen therapy, or disease progression on anti-oestrogen therapy*

Approval is anticipated in late August 2017 (with CHMP opinion expected in late June 2017).

Anticipated restrictions or contraindications

Contraindications in the current marketing authorization are:

- Hypersensitivity to the active substance, or to any of the other excipients
- Severe hepatic impairment
- Pregnancy and lactation

Main issues discussed by EMA

There were no major issues with the evidence submitted identified by the Rapporteurs which are expected to have any material impact on the current appraisal.

Regulatory approval outside EU

Fulvestrant is currently being assessed by the Federal Drug Agency (FDA) in this indication and a final decision is expected in [redacted]. It is also being assessed by Japan's Pharmaceutical and Medical Devices Agency (PMDA) in this indication and a final decision is expected in [redacted].

Health Technology Assessments

Fulvestrant in this indication is not currently being assessed by any HTA bodies.

Submissions to Scotland's Scottish Medicine's Consortium (SMC) and Canada's pan-Canadian Oncology Drug Review (pCODR) are expected in [redacted] 2017.

2.3 Administration and costs of the technology

Table 7: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	The solution for injection is a clear, colourless to yellow, viscous liquid	(16)
Acquisition cost (excluding VAT) *	The current list price per pack of 2 × 5-mL (250-mg) prefilled syringes is £522.41.	(17)
Method of administration	Fulvestrant should be administered intramuscularly (IM) into the buttocks (gluteal area) slowly (1-2 minutes per injection) as two 5 mL injections, one in each buttock.	(16)
Doses	The recommended dose of fulvestrant is 500mg.	
Dosing frequency	Fulvestrant 500mg should be administered on days 1, 15, 29 and once monthly thereafter	
Average length of a course of treatment	Treatment is recommended to continue until disease progression. In the pivotal study, the average exposure to fulvestrant was 29.6 months.	Section 5.7
Average cost of a course of treatment	Total expected acquisition cost is £15,841 with administration and monitoring costs of £2,458.	Section 5.7
Anticipated average interval between courses of treatments	N/A	N/A
Anticipated number of repeat courses of treatments	N/A	N/A
Dose adjustments	No dose adjustments are necessary.	(16)
Anticipated care setting	Secondary care and outpatient services	N/A
* Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.		

2.4 Changes in service provision and management

Fulvestrant 500mg is administered via IM injection once per month, compared with current comparators taken as oral tablets once daily. It is therefore anticipated that additional staff time in secondary care or outpatient services will be required to treat eligible patients with fulvestrant 500mg.

2.5 Innovation

Fulvestrant has a differentiated mechanism of action, whereby it is the only endocrine therapy that blocks oestrogen, by targeting and degrading the ER. This unique mechanism of action could potentially delay acquired resistance and increase overall survival. The Phase III FALCON trial demonstrated the clinical superiority of fulvestrant 500mg versus anastrozole 1mg in terms of PFS and fulvestrant 500mg also showed significant improvements in PFS and OS in the Phase II FIRST study. Fulvestrant also has a different and manageable tolerability profile versus aromatase inhibitors (AIs) and chemotherapy (5, 7).

In addition, the IM administration has the potential to improve compliance and is suitable for patients who have difficulty with oral therapies or when compliance may be limited, for example in the elderly or those with psychiatric illness. Some metastatic patients are no longer able to swallow, have poor compliance to daily tablets, or are frail and unsuitable for chemotherapy (due to poor tolerability and associated risks). The different route of administration for fulvestrant (intramuscular injection) will enable these patients to remain on endocrine therapy for longer. Other patients may simply wish to avoid the undesirable effects of chemotherapy.

3 Health condition and position of the technology in the treatment pathway

3.1 Overview of advanced breast cancer

Breast cancer is a disease in which malignant (cancer) cells form in the tissues of the breast. Breast cancer can be described as in-situ (non-invasive), which is confined to the ducts/lobules of the breast, or invasive. The most common type of breast cancer is invasive ductal carcinoma, which begins in the cells of the ducts. Lobular carcinoma begins in the lobes or lobules and is more often found in both breasts than other types of breast cancer (18).

After a diagnosis of breast cancer, immunohistochemistry testing is carried out in order to identify a patient's molecular (oestrogen [ER], progesterone [PgR], and human epidermal growth factor [HER2]) receptor status, which helps inform treatment decisions (18). In addition to molecular categories, prognosis and therapy choice may be influenced by the menopausal status of the patient (18). Menopausal status has a substantial effect on a patient's endocrine profile and some endocrine therapies are specific to a woman's menopausal status.

3.1.1 Endocrine receptor positive breast cancer

Endocrine receptor positive breast cancer is the most prevalent form of the disease, with 81% of breast cancers expressing endocrine receptors at diagnosis (19). The focus of this submission is on the oestrogen receptor positive (ER+) subset of endocrine receptor positive breast cancer, which accounts for 96% of all endocrine receptor positive breast cancers; the remainder being progesterone receptor positive (PgR+) (19). Of note, PgR expression is generally considered a surrogate of ER positivity as PgR expression requires a functioning ER (20). In ER+ breast cancer, oestrogen binds to the ER triggering a series of processes which result in the stimulation of cell growth and proliferation (21). As ERs play a key role in cell proliferation, the expression of these receptors is the primary indicator of the potential response to endocrine therapy (22). While ER+ disease is the predominant breast cancer in all age groups, the relative incidence of ER positivity increases with

age, such that breast cancers in postmenopausal women are mostly ER+ at diagnosis (20).

Based upon expression of endocrine receptors and HER2 molecular receptors, breast cancers fall into four subcategories:

- HER2+ (ER-, PR-, HER2+)
- Luminal A, and Luminal B (ER+, PR±, HER2±)
    - Both are ER+ and can be PR+ or PR- (23). The difference lies in the presence or absence of HER2 (24)
        - Luminal A (ER+ and/or PR+, HER2− and CK8/18+);
        - Luminal B (ER+ and/or PR+, HER2+ and CK8/18+)
- Triple negative breast cancer (TNBC)/Basal-like breast cancer (ER-, PR-, and HER2-) (24).

These categorisations are both prognostic for disease progression (ER+ having the most favourable prognosis and TNBC the worst) and predictive of response to endocrine and HER2 targeted therapies(18).

Metastatic breast cancer is where the cancer has spread from the breast to other tissues, most often bones, the lungs, or the liver (25). Visceral metastasis (i.e., metastasis to internal organs including the liver, lungs and body cavities like the pleura and peritoneum) confers a worse prognosis than bone metastasis alone (26, 27). Brain metastases are observed in 15% to 30% of women with advanced breast cancer (ABC) and have a poor prognosis, with a median survival from the time of development of brain metastases of 3 to 6 months in women with breast cancer (28, 29).

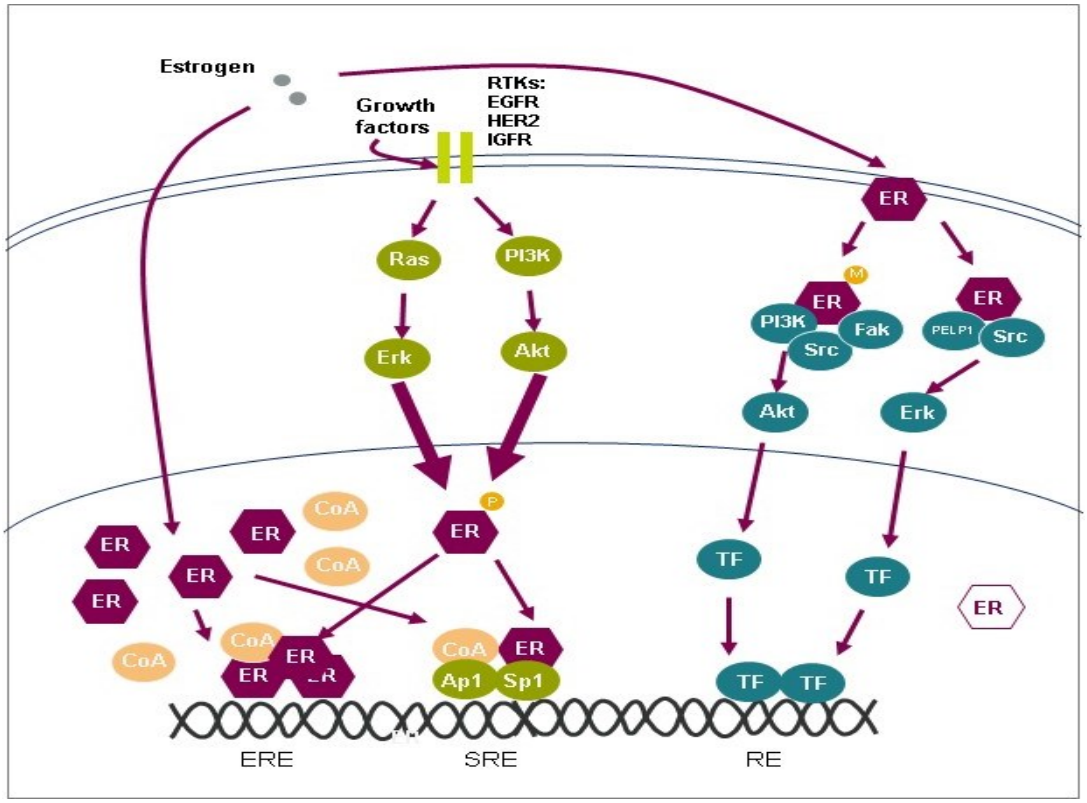
3.1.2 Pathophysioloogy of endocrine receptor positive breast cancer

Under normal conditions oestrogen and progesterone are important regulators of breast growth and development however; they also play important roles in the pathogenesis of breast cancer (30). In ER+ breast cancer, genetic dysfunction and increased cellular levels of ERs drive cancer cell proliferation and metastasis (21).

In women with ER+ breast cancer, oestrogen, through binding to the ER, can contribute to the growth and proliferation of normal and cancerous breast tissue cells (31). The ER is a member of the nuclear receptor superfamily that acts as a ligand-dependent transcription factor (32). The biological effects of oestrogen are mediated by its binding to one of the structurally and functionally distinct ERs (ER*α* and ER*β*). ER*α* is the major ER subtype in the mammary epithelium and plays a critical role in mammary gland biology as well as in breast cancer progression. Binding of oestrogen to ER*α,* to form the oestrogen-ER complex, induces receptor dimerisation allowing the ligand-activated ER*α* to translocate to the nucleus, bind to the responsive element in the target gene promoter, and stimulate gene transcription and the expression of proliferation factors (genomic/nuclear signalling; Figure 2) (15, 21, 31). In addition, ER outside of the nucleus can indirectly regulate gene activation through non-genomic "cross-talk" with other cell-signalling pathways (15).

PgRs play a similar role to that of ERs in breast cancer biology. They function not only as critical regulators of transcription, but also to activate signal transduction pathways, many of which are involved in pro-proliferative signalling in the breast (33).

Figure 2: The role of the ER in breast cancer



Source: Adapted from (34)

Ap1: Activation protein 1; CoA: Co-activators; EGFR: Epidermal growth factor receptor; ER: Oestrogen receptor; ERE: Oestrogen response element; Erk: Extracellular signal-related kinase; Fak: Focal adhesion kinase; HER2: Human epidermal growth factor receptor 2; IGFR: Insulin-like growth factor; M: Methylation; PELP1: Proline, glutamate and leucine-rich protein 1; PI3K: Phosphoinositide 3-kinase; RE: Response element; RTKs: Receptor tyrosine kinases; Sp1: Specificity protein 1; Src: Sarcoma genes; SRE: Serum response element; TF: Transcription factor

3.2 The effects of advanced breast cancer on patients, carers and society

Mortality

Breast cancer is a leading cause of cancer death amongst women worldwide with around 522,000 deaths from breast cancer in 2012 (35). Breast cancer is also the leading cause of cancer death in Europe for women and the third most common cause of cancer death overall, with more than 131,000 deaths from all forms of breast cancer in 2012 (36).

ER+ HER2- ABC is largely incurable and fatal; 44% of women with ABC die within 5 years of diagnosis, rising to over 70% in patients with Stage IV disease (37-39). The 5-year relative survival of women with Stage IV breast cancer was reported as 25.3% in the US (2008-2012) and 14.7% in the UK (2002-2006) (40, 41).

Disease progression

Approximately 6% of women with incident breast cancer have advanced disease at initial presentation, termed “de novo metastatic disease” (42). Of these patients, a panel of UK Breast cancer Oncologists estimated that 40% have visceral disease (defined as metastasis to internal organs of the body, including liver, lungs or brain) while 60% have non-visceral metastasis only (including bone, soft tissue and lymph nodes). An additional 20% to 40% of women with breast cancer develop advanced disease at some point following diagnosis (42).

The majority of women with advanced disease develop bone metastases, which have been observed in 73% of women with ABC (27). Although bone metastases can have severe and debilitating consequences for patients including fractures,

hyperkalaemia, and bone pain, they are not usually life-threatening, unlike other common sites of metastases such as the lung, pleura, liver, and brain (25). Visceral metastasis confers a worse prognosis than bone metastases (26, 27).

Burden of disease

ABC is a largely incurable disease, which has a severe impact on a patient's quality of life (QoL). This detrimental impact on QoL has been demonstrated in several studies. Firstly, women with breast cancer experience a significant decrease in their global QoL over 18 months from diagnosis, as measured by the EORTC QLQ-BR23 questionnaire (43). Secondly, a bibliographic literature review of health-related QoL (HRQoL) in breast cancer publications between 1974 and 2007 found that women receiving treatment experience several side-effects and symptoms that negatively affect their QoL, including pain, fatigue, and postmenopausal symptoms (44). Finally, in terms of ABC, treatment for brain metastases negatively impacts QoL further. Women who developed brain metastases have reported future uncertainty and fatigue as the most prominent symptoms that impact their QoL (45).

In addition to the humanistic burden on patients, ABC also poses a burden on caregivers; 69% of caregivers of women with ABC report some kind of adverse impact on their work (46). In addition to the impact on their day-to-day lives, caregivers report increases in depression and perceived burden as the patients' functional status declines. At the start of the terminal period of the patients' disease, 30% of caregivers reported being depressed (46).

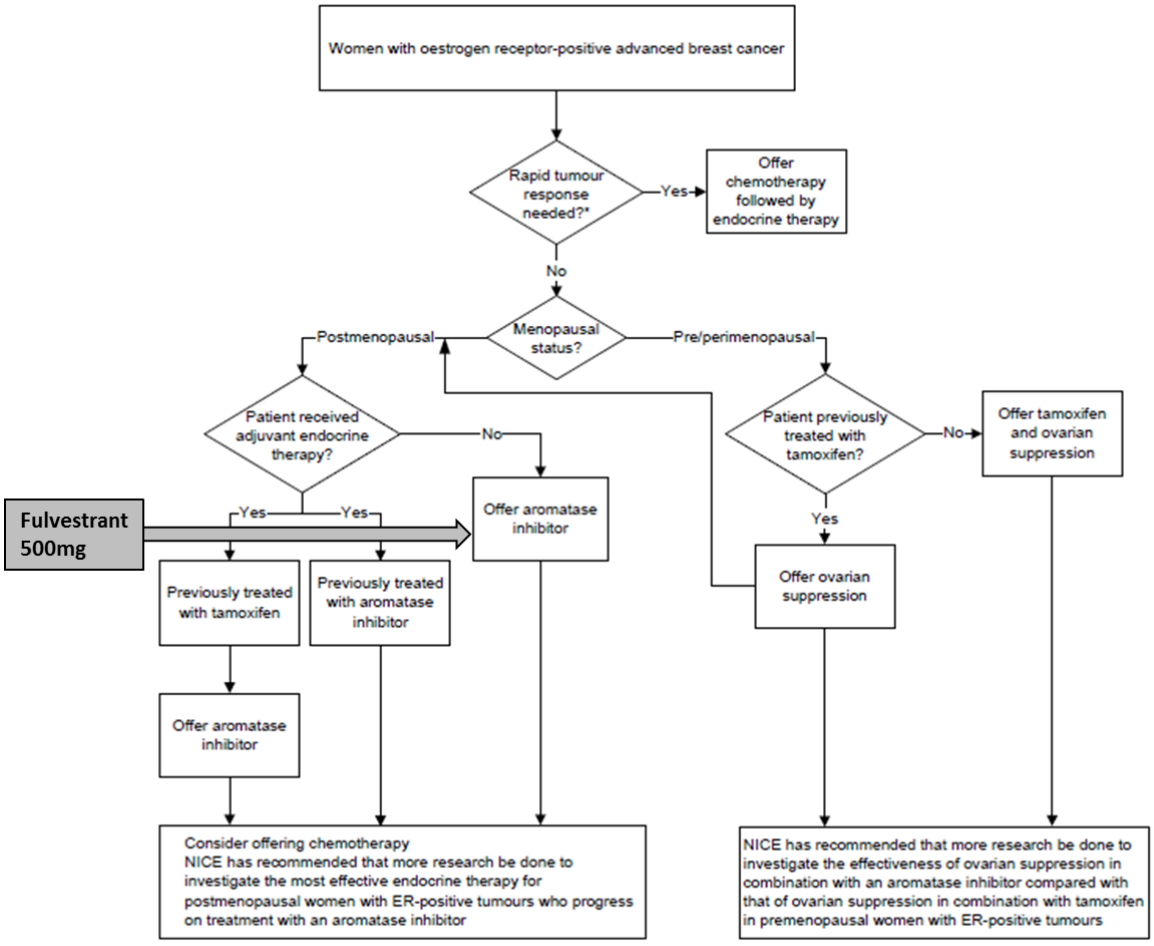
3.3 The existing clinical pathway

Patients presenting with ER+ ABC who do not have imminently life-threatening disease should preferably be treated with endocrine therapy (Figure 3) (47-50). This is the target population in the present technology appraisal and a study of more than 17,000 patients with ER+/HER2- metastatic breast cancer in the UK found that 72% were treated initially with hormone therapy (51). Patients who relapse on adjuvant therapy or who suffer recurrence soon after completing adjuvant therapy are not within the scope of the present appraisal. For ABC with imminently life-threatening disease or symptoms (due, for example, to significant visceral organ involvement), first line chemotherapy is recommended. If these are ineffective or contraindicated,

then sequential systemic monotherapy involving taxanes (paclitaxel and docetaxel), capecitabine, or vinorelbine is recommended.

Some women suffer recurrence or progression after a first line of AI therapy and may be switched to a second line AI such as exemestane (potentially in combination with everolimus). The use of everolimus in combination with exemestane for treating advanced HER2-ve HR+ breast cancer after endocrine therapy in the Cancer Drugs Fund (CDF) has recently been recommended by NICE (52). Market research also suggests that although fulvestrant is not recommended in England or Wales for this indication, some NHS trusts may offer it to women who have suffered recurrence or progression following treatment with aromatase inhibitors (53).

Figure 3: The NICE treatment pathway for ABC showing the likely positioning for fulvestrant 500mg (adapted from (50))



Detailed data are lacking on how many lines of different endocrine therapies are typically administered in the UK, but a panel of UK Breast Cancer Oncologists have estimated that the mean number of lines of endocrine therapy received would be approximately 2.5 (54).

3.4 Current life expectancy

Prognosis of patients with ABC is poor compared with that of patients with early-stage breast cancer, and survival rates fall as the disease advances: 5-year OS is 99% for women in the UK with stage I breast cancer, 90% for stage II, 60% for stage III, and 15% for stage IV (metastatic) (55). Studies from European countries and the US consistently report average OS for patients with HR+/HER2- ABC as <5 years (10, 56-58). Median OS of women receiving their first post-adjuvant systemic therapy can range from 32 to 48 months(12, 59, 60).

The duration of survival in postmenopausal women with endocrine sensitive, de novo metastatic disease has been estimated to be 20-30% at 5 years by a panel of UK Breast cancer Oncologists (54).

3.5 Relevant NICE guidance

NICE recommends endocrine therapy as first line treatment for the majority of women with ER+ HER2- ABC (NICE 2015). AIs (either nonsteroidal or steroidal) are offered to postmenopausal women with ER+ HER2- breast cancer, with no prior history of endocrine therapy, or those previously treated with tamoxifen (Figure 3). On disease progression chemotherapy may be selected as the most appropriate next sequential therapy (NICE 2015).

Chemotherapy is offered as first line treatment for women with ER+ HER2- ABC whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, providing they understand and are prepared to accept the associated toxicity (NICE 2015). For patients with ER+ ABC who have been treated with chemotherapy as their first line treatment, endocrine therapy is recommended following the completion of chemotherapy.

Combination chemotherapy can be considered for patients with ABC for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity (NICE 2015).

3.6 Other clinical guidelines

Although, most guidelines agree on the use of endocrine therapies as the standard of care for ER+ HER2- ABC, at present, no definitive recommendations exist for the optimal sequence of these therapies as single drugs or in combination with other endocrine therapies, and as such, treatment must be individualised (31). Treatment guidelines have also not deemed any particular chemotherapeutic regimen superior for second line or further therapy, and no third line or later standard of care has been established for treatment of ABC (61).

American Society of Clinical Oncology (ASCO) Guidelines 2016

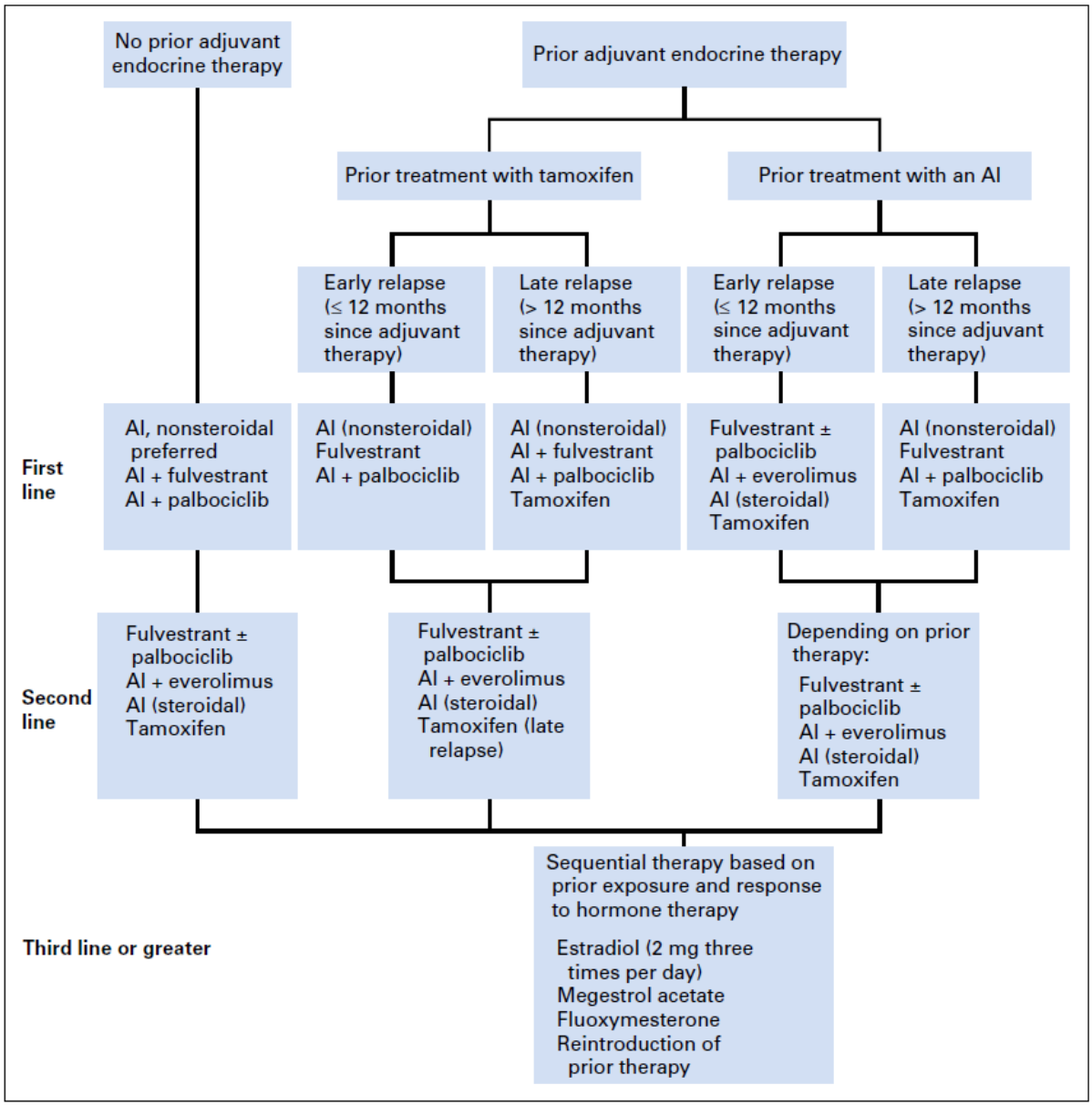
The most recent guidelines (47) recommend that postmenopausal women with HR-positive MBC should be offered AIs as first-line endocrine therapy (Recommendation 1.1) (Figure 4).

In postmenopausal women, AIs are considered to provide potentially better disease control compared with tamoxifen in the first-line setting, without a benefit in OS. According to the Expert Panel, available data suggest that either nonsteroidal (i.e. anastrozole or letrozole) or steroidal (i.e. exemestane) AIs can be used without differential efficacy in patients without prior exposure to AIs (or those experiencing relapse >12 months after completing adjuvant AI therapy). Treatment is recommended to be administered until disease progression is documented by imaging, examination, or symptoms (47).

The Expert Panel acknowledged that there are situations in which chemotherapy is appropriate as initial therapy for HR-positive MBC, including in patients with immediately life-threatening disease or where tumour biology (eg, extremely low levels of ER) makes endocrine treatment less likely to be effective. There was also an recognition that although there is some limited evidence to suggest that combinations of hormone therapy should be considered only in specific situations,

ongoing trials evaluating additional settings and drug doses are expected to provide further clarity in this area.

Figure 4: ASCO Guidelines for hormone therapy for post-menopausal women with HR+ve mBC by line of therapy and adjuvant treatment (47)



National Comprehensive Cancer Network (NCCN) Guidelines 2016

For women with ER+ HER2- ABC without visceral symptoms, three consecutive lines of endocrine therapy are recommended before the initiation of chemotherapy (38, 62). AIs, SERMs, and SERDs were the recommended first line agents in ER+ postmenopausal women, with modest evidence indicating a preference of AIs (62).

Palbociclib in combination with letrozole may be considered as a treatment option for first line therapy for postmenopausal women with ER+, HER2- ABC.

European Society for Medical Oncology (ESMO) 3rd International Consensus Guidelines on Advanced Breast Cancer (ABC3) 2016

Similar to most other guidelines, endocrine therapy is the preferred option for HR+ disease, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance (63). The preferred first line endocrine therapy for postmenopausal women depends on the type and duration of adjuvant endocrine therapy as well as time is an AI or tamoxifen, depending on the type, duration of and time elapsed since adjuvant endocrine therapy and can be an AI, tamoxifen or fulvestrant.

In contrast with the ASCO guidelines (47), the ABC3 panel did not support the first line combination of endocrine therapies due to lack of evidence, but recognised this was an area of ongoing research.

3.7 Variations in established practice

Consistent with the range of biological subtypes of breast cancer and the diversity of patient clinical characteristics, treatment histories and therapeutic responses, the treatment of ABC is complex and strongly dependent on numerous patient-specific factors (discussed in section 3.3). Patient characteristics and treatment history should therefore be considered carefully when assessing the safety and efficacy of ABC treatments in clinical trials, and when prescribing treatments in the clinic. However, given the broad consensus of main clinical guidelines and the lack of novel treatments in this setting in recent years, there is very little variation in UK practice outside of NICE clinical guidelines outlined above (Section 3.5).

3.8 Equality issues

It is not expected that this appraisal will exclude or lead to a recommendation that would have a different impact for people protected by equality legislation and/or have a particular disability or disabilities to that of the wider of the population.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

Search strategy

The objective of the systematic literature review (SLR) was to assess the clinical efficacy, safety, and tolerability associated with pharmacological interventions as first-line treatment for post-menopausal women with hormone receptor-positive, locally advanced or metastatic breast cancer who had no prior hormonal treatment.

Comprehensive searches were run in the electronic databases and conference proceedings listed below to identify studies which were potentially relevant to the review. The complete search strategy is provided in Appendix A, but is summarised in Table 8.

Table 8: Summary of the protocol for the systematic literature review

Parameter	Inclusion/exclusion criteria in current review	
Study designs	Randomized controlled trials (irrespective of blinding status)	
Population	Age: Adults (≥18 years) Gender: Female patients (in particular post-menopausal) Race: Any Disease: HR+, HER2 negative locally advanced or metastatic breast cancer	
Interventions	Fulvestrant Anastrozole Letrozole Tamoxifen Toremifene Exemestane Abiraterone acetate Megestrol acetate Atamestane Z-endoxifen Palbociclib Ribociclib Lapatinib	Everolimus Bevacizumab Docetaxel Paclitaxel Abemaciclib Temsirolimus Entinostat Alpelisib Taselisib Pictilisib Buparlisib
Comparators	Any included intervention Any pharmacological intervention Placebo/best supportive care/observation	
Language	English language only	
Publication timeframe	Database inception to 10 Jan 2017	

- HR+: Hormone receptor positive; HER: Human Epidermal Receptor

Only randomized controlled trials (RCTs) published in the English language were eligible for inclusion.

The following literature databases were searched from database inception to 10 January 2017:

- Embase®
- MEDLINE®
- MEDLINE® In-Process
- Cochrane Central Register of Controlled Trials

The following conference proceedings were hand searched for last three years (2013 to 2015):

- American Society of Clinical Oncology
- European Society of Medical Oncology
- San Antonio Breast Cancer symposium

Bibliography of systematic reviews and meta-analysis identified through database searches were utilized for the identification of key studies. This ensured that comprehensive evidence is included in the review. In addition, references of the included studies were checked to identify any additional studies.

Study selection

Abstracts of citations found through the search strategy provided in Appendix A were initially reviewed for inclusion based on title and abstract. Full-text copies were ordered for studies that potentially met the inclusion criteria or where it was not possible to determine whether the study could meet the inclusion criteria based on abstract alone. Following the receipt of full-texts, eligibility criteria were applied to the full-text publications. During the course of both full-text and abstract review, screening was conducted by two independent reviewers, and any discrepancies between them were reconciled by a third independent reviewer.

Patient population

The patient population of interest to the review comprised adult females of any race (Table 9).

Table 9: Population of interest to the review

Parameter	Inclusion	Notes
Age	Adults	Adult patients ≥18 years of age
Gender	Females	Female patients (in particular post-menopausal) are of interest to the review
Race	Any	The objective of the review does not restrict it to any particular race

Studies focusing on children or adolescents were excluded. Also, studies focusing on pre-menopausal females were excluded. Studies which assessed a population comprising both pre- and post-menopausal females were included only if sub-group data for post-menopausal population was reported.

Disease

Patients with HR positive (expressing ER and/or PR), HER2 negative locally advanced or metastatic breast cancer are of interest to the review. Studies which enrol a mixed population of breast cancer and other diseases were only included if there was subgroup data for breast cancer patient population.

The disease stage of interest is locally advanced or metastatic breast cancer, therefore studies which reported the disease stage of interest were included. Studies recruiting a mixed population of early and advanced disease stage were only included if subgroup data for the disease stage of interest was reported separately.

HER2 receptor testing was not usually carried out in regular clinical practice until mid-2000s, therefore, it is suggested not to restrict the eligibility criteria to HER2 negative population as it would result in exclusion of some important comparators (64).

- If subgroup ER/PR+ was not reported separately, as long as 70% of the population met inclusion criteria they could be included

- If ER/PR+ status was unknown, a decision was made to consider study inclusion

- If subgroup HER2 was not reported separately, as long as 70% of the population met inclusion criteria they could be included

- If HER2 status was not clear or not reported, a decision was made to consider inclusion (as HER2 testing became standard) after many of the pivotal studies were conducted

Further, the Cochrane handbook does not recommend exclusion of studies based on diagnostic tests that were recently developed and that might not be used in earlier studies (65).

Line of therapy

The SLR focuses on studies evaluating first-line treatment i.e. studies assessing the effect of interventions on patients with endocrine naïve HR+ (expressing ER and/or PR) locally advanced or metastatic breast cancer. Studies enrolling patients who were previously treated with hormonal therapy in the adjuvant setting were excluded from the review. Also, patients who were receiving hormonal replacement therapy (HRT) were not of interest to the review.

In-line with the Phase III FALCON trial (7), studies considering patients with EITHER:

- locally advanced disease not amenable to surgery or radiotherapy of curative intent (patients may have had 1 line of cytotoxic chemotherapy, following which they must remain unsuitable for therapy of curative intent)

  OR

- metastatic disease (patients may have had 1 line of cytotoxic chemotherapy as previous treatment of breast cancer but must show progressive disease prior to enrolment

were included in the review. Studies containing >70% patients who were endocrine naïve were also included.

Interventions

The SLR included both licensed and investigational pharmacological treatments for HR+ (expressing ER and/or PR) locally advanced or metastatic breast cancer. Table 10 provides the list of interventions to be included in the review.

- Studies investigating the role of radiotherapy, chemo-radiotherapy, or surgery were not included
- Adjuvant or neo-adjuvant therapy were not included
- Studies comparing different doses of the same intervention (i.e. dose-ranging studies), two formulations of the same intervention, and intervention with two different routes of administration were not included

The list of interventions is based on recommendations of clinical guidelines, searching of clinicaltrials.gov, and by expert inputs.

Table 10: Included intervention list

Interventions list		
Hormonal therapy	**Chemo or biologic therapy**	
Fulvestrant	Palbociclib	Entinostat
Anastrozole	Ribociclib	Alpelisib
Letrozole	Lapatinib	Taselisib
Tamoxifen	Everolimus	Pictilisib
Toremifene	Bevacizumab	Buparlisib
Exemestane	Docetaxel	
Abiraterone acetate	Paclitaxel	
Megestrol acetate	Abemaciclib	
Atamestane	Temsirolimus	
Z-endoxifen	Trastuzumab	

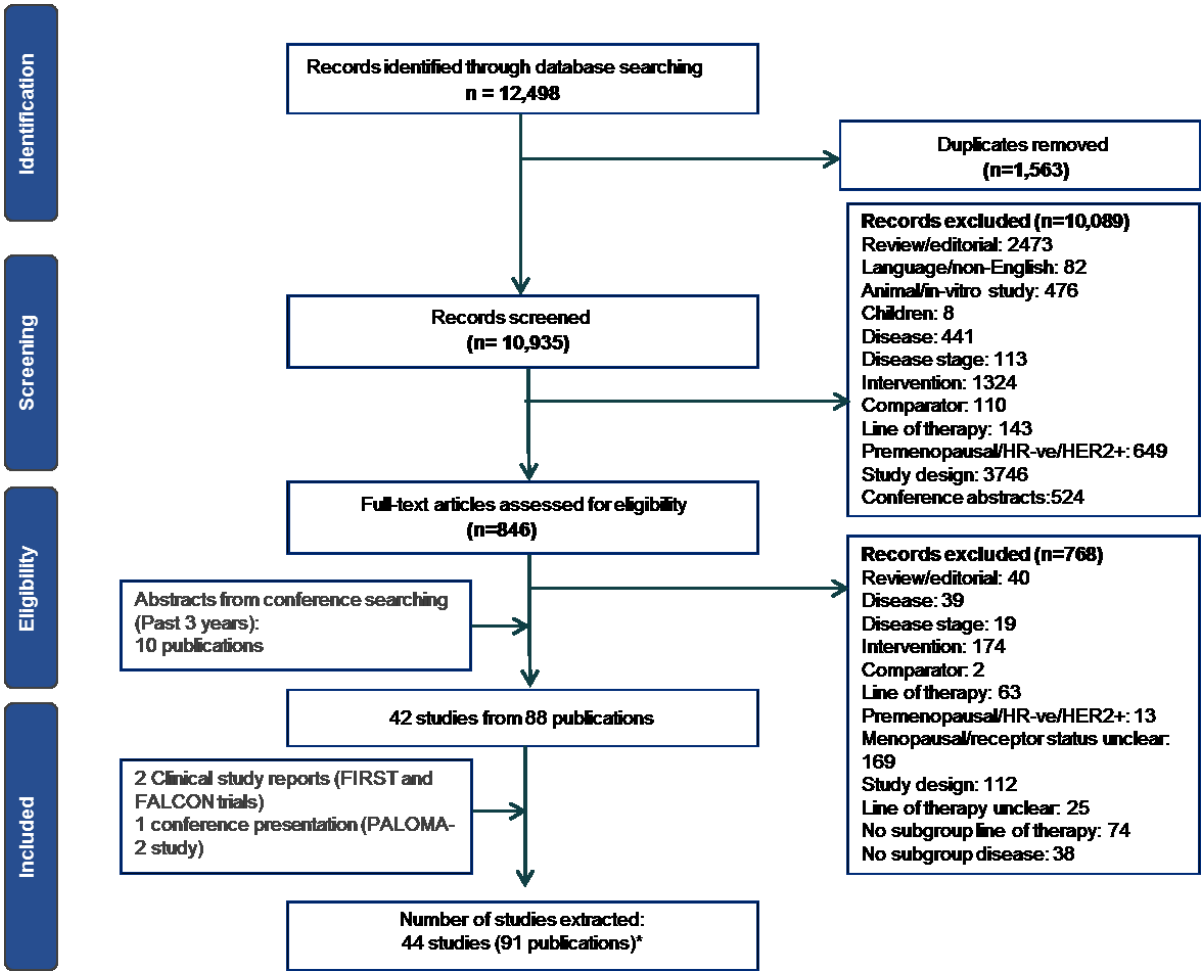
Any of the above listed intervention administered either as monotherapy or combination therapy with other interventions from the list (or any other pharmacological intervention, placebo/best supportive care) were included.

Extraction of included studies was carried out in parallel by two independent reviewers, and any discrepancy was reconciled by a third reviewer. Studies with multiple publications were extracted into a single entry with multiple publications of the same trial linked to one another. The included RCTs were critically appraised using a comprehensive critical appraisal tool based on National Institute for Health and Care Excellence checklist.

Trial flow

Figure 5 shows the flow of studies through the systematic review process. The search of electronic literature databases identified 12,498 separate references. Following the removal of duplicate references, 10,935 citations were screened for inclusion based on the eligibility criteria of the review. Following the first-stage screening, 10,089 references were excluded, resulting in the full-text screening of 846 potentially relevant publications. Detailed examination of these citations resulted in inclusion of 42 references from 88 publications. Additionally, two clinical study reports; FIRST study and FALCON trial as well as one conference presentation of PALOMA-2 study were also included in this clinical review; thereby, resulting in the inclusion of 44 studies from 91 publications. List of included and excluded studies have been presented in Appendix B.

Figure 5: Flow of studies through the systematic review process



n: number of studies; HR-: Hormone Receptor negative; HER: Human Epidermal Receptor

Of the 44 studies included in this master evidence network, a number of studies were further excluded for other reasons (e.g. termination of clinical trial program or evaluation of a clinically non-relevant comparator – for a complete list of reasons, please see Appendix B) to derive a relevant evidence network that would form the basis of detailed comparability and heterogeneity assessment (Figure 6). The final list of 6 studies relevant to this appraisal is provided in Table 11 and a critical appraisal of each study using the NICE checklist is provided in Table 12.

Of the 6 studies included in the final network, 2 compared fulvestrant 500mg against another treatment (anastrozole 1mg): FIRST (5) and FALCON (7).

Figure 6: Flow of studies from SLR to produce a relevant evidence network

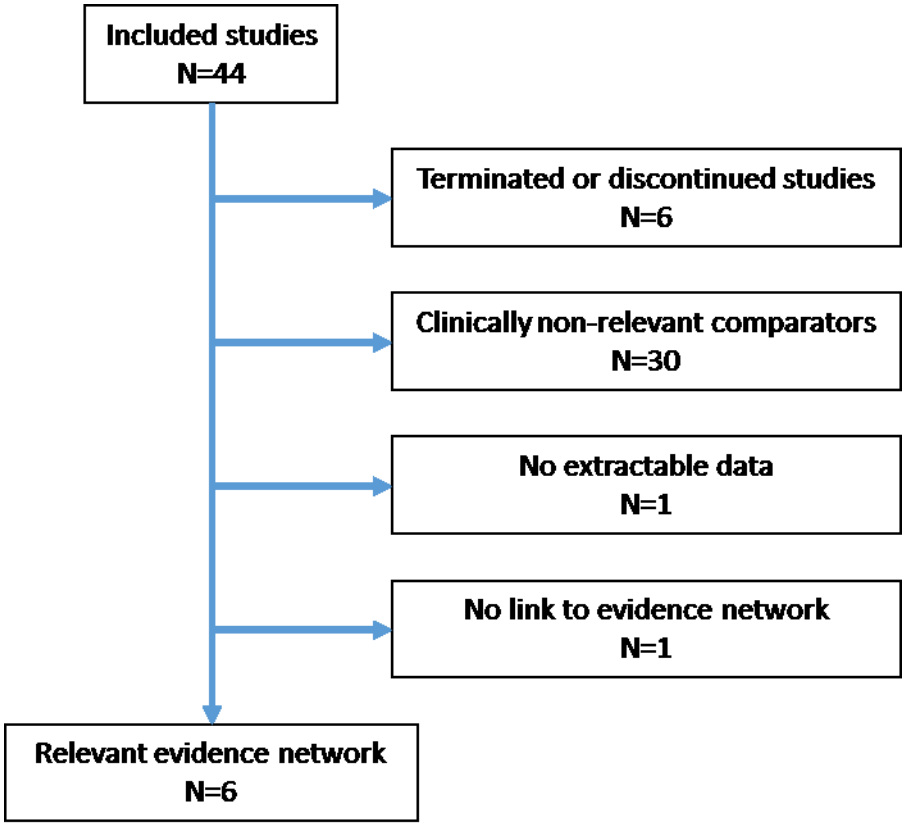


Table 11: List of included studies in the relevant network

Study Name	Publication type	Sample size	Treatment
FALCON trial (7)	Journal article	462	Fulvestrant 500mg
			Anastrozole 1mg
FIRST study (5)	Journal article	205	Fulvestrant 500mg
			Anastrozole 1mg
Milla-Santos 2003 (66)	Journal article	238	Anastrozole 1mg
			Tamoxifen 40mg
North American trial (10)	Journal article	353	Anastrozole 1mg
			Tamoxifen 20mg
TARGET trial (11)	Journal article	668 (298)*	Anastrozole 1mg
			Tamoxifen 20mg
PO25 trial (12)	Journal article	916	Letrozole 2.5mg
			Tamoxifen 20mg

- *Data in brackets represents sample size of subgroup of interest.
- CSR: Clinical Study Report

Table 12: NICE critical appraisal checklist

Study name	Jadad score	Allocation concealment grade	Randomization and allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcomes selection and reporting	Statistical analysis
FALCON trial (7)	5	A	**Low risk**; Patients were randomized through IVRS/IWRS	**Low risk**; Baseline demographic characteristics were generally well balanced between the treatment arms	**Low risk**; This was a double-blind study. Double dummy technique was used to maintain blinding	**Low risk**; The withdrawals, and the specific reasons for withdrawal were reported	**Low risk;** Author has measured all the outcomes that have been reported in published protocol and in clinical trial registry (NCT01602380)	**Low risk**; The safety and efficacy analysis was done using ITT population
FIRST study (5)	2	B	**Low risk**; Central randomization	**Low risk**; Baseline demographic characteristics were generally well balanced between the treatment arms	**High risk**; This was an open label study	**Low risk;** The withdrawals, and the specific reasons for withdrawal were reported	**Low risk;** Author has measured all the outcomes that have been reported in published protocol and in clinical trial registry (NCT01602380).	**Low risk;** The safety and efficacy analysis was done using mITT and ITT population
Milla-Santos 2003 (66)	2	B	**Not clear**; This was a randomized trial but the method of randomization was not reported	**Low risk**; Baseline demographic characteristics were generally well balanced between the treatment arms	**Not clear**; Details regarding blinding were not reported	**Low risk**; All the patients completed the study	**Not clear**; There was no evidence to conclude whether all outcomes assessed were reported or not	**Low risk**; The safety and efficacy analysis was done using ITT population
North American trial (10)	4	A	**Low risk**; Central randomization	**Low risk**; Baseline demographic	**Low risk**; This was a double-	**Not clear;** Withdrawals and reasons	**Not clear**; There was no evidence to conclude	**Low risk;** The safety and efficacy

				characteristics were generally well balanced between the treatment arms	blind study, double dummy technique was used	for withdrawals were not reported	whether all outcomes assessed were reported or not	analysis was done using ITT population
P025 trial	4	A	**Low risk**; Randomization was done by computer generated randomization method	**Low risk**; Baseline demographic characteristics were generally well balanced between the treatment arms	**Low risk**; This was a double-blind study, double dummy technique was used	**Not clear**; Withdrawals and reasons for withdrawals were not reported	**Not clear**; There was no evidence to conclude whether all outcomes assessed were reported or not	**Low risk**; The safety and efficacy analysis was done using mITT population
TARGET trial (11)	4	A	**Low risk**; Central randomization	**Low risk;** Baseline demographic characteristics were generally well balanced between the treatment arms	**Low risk**; This was a double-blind study, double dummy technique was used	**Not clear;** Withdrawals and reasons for withdrawals were not reported	**Not clear**; There was no evidence to conclude whether all outcomes assessed were reported or not	**Low risk**; The safety and efficacy analysis was done using mITT and ITT population

- ITT: Intent-To-Treat; IVRS: Interactive Voice Response System; mITT: Modified Intent-to-Treat; PS: Performance Status

4.2 List of relevant randomised controlled trials

Direct evidence of the efficacy of fulvestrant 500mg compared to AIs in endocrine-naïve postmenopausal women with advanced HR+ disease comes from two studies: FIRST and FALCON (5, 7).

Evidence that fulvestrant 500mg may provide a clinical advantage over AIs in the first line setting was initially provided by the FIRST study. This was a Phase II, randomised, non-inferiority open-label study of fulvestrant 500mg versus anastrozole 1 mg in postmenopausal women with advanced HR+ disease previously untreated with endocrine therapy (or at least a year after completing adjuvant endocrine therapy) (5).

The results of the FIRST study showed an efficacy benefit for fulvestrant 500mg compared with anastrozole as first line endocrine therapy for patients with HR+ ABC, and supported further investigation of fulvestrant 500mg in this clinical setting. Exploratory subgroup analyses from the FIRST study suggested that the efficacy benefit for fulvestrant 500mg observed was likely to be driven by its superior efficacy in patients who were truly endocrine-naïve (75% of the patients enrolled) **(6, 9)**.

Consequently, the Phase III, randomised, double-blind, parallel-group, multicentre, FALCON study was conducted to confirm the superior efficacy and acceptable tolerability of fulvestrant 500mg versus anastrozole (the SoC) (7). The proposed patient population of endocrine therapy-naïve postmenopausal women with HR+ ABC reflects the population of patients who had experienced a clinical benefit in the FIRST study and those most likely to benefit from the study treatment.

Table 13: List of relevant RCTs

Trial number (acronym)	Study phase	Population	Intervention	Comparator	Primary study reference
FIRST (NCT00274469)	Phase II	Postmenopausal women presenting with HR+ advanced disease who had either, never received endocrine therapy for advanced disease or had received previous adjuvant endocrine therapy for ABC completed at least 12 months prior to randomisation into the study.	fulvestrant 500mg	anastrozole 1 mg	(5, 6, 8)
FALCON (NCT01602380)	Phase III	Postmenopausal women with ER+ and/or PgR+ ABC not previously treated with any endocrine therapy	fulvestrant 500mg	anastrozole 1 mg	(7)

4.3 Summary of methodology of the relevant randomised controlled trials

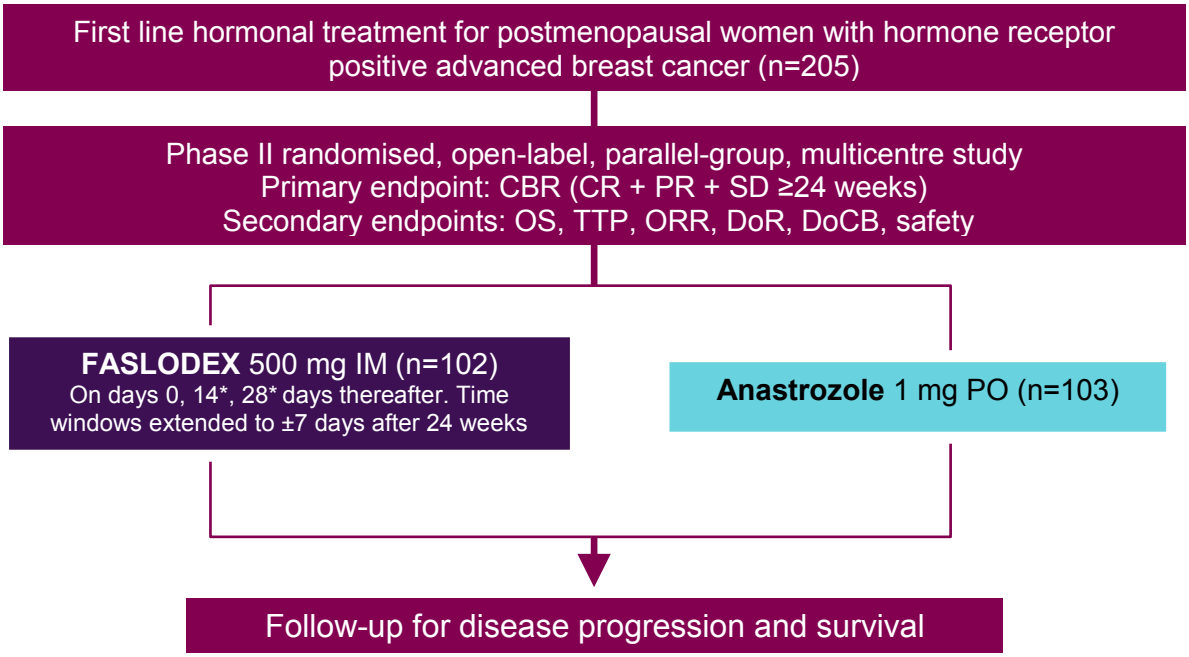
4.3.1 FIRST

FIRST (Fulvestrant First-Line Study Comparing Endocrine Treatments) is a Phase II, randomised, open-label, parallel-group, multi-centre non-inferiority study that compared the efficacy and tolerability of fulvestrant 500mg with anastrozole 1 mg as first line endocrine therapy for postmenopausal women with ER+ ABC (5). The primary objective of the study was to compare the clinical benefit rate (CBR) in patients treated with fulvestrant 500mg with the CBR in patients treated with anastrozole. The key secondary objectives included ORR, time to progression (TTP), DoR, OS, and safety (5). Both TTP (8) and OS (6) were included as secondary endpoints after primary analysis of CBR (5) was complete.

Study design

The target population was postmenopausal women presenting with advanced hormone receptor positive disease who had either, never received endocrine therapy for advanced disease or had received previous endocrine therapy for ABC completed at least 12 months prior to randomisation into the study. The study was open to patients with measurable disease, as per RECIST (Response Evaluations Criteria in Solid Tumours) or patients with non-measurable disease, in the presence of bone metastases with a lytic component (67). Figure 7 presents a schematic of the design of the study and the sequence of treatment periods (67).

Figure 7: FIRST trial design and treatment schedule



Source: (67)

ABC: Advanced breast cancer; CR: Complete response; DoCB: Duration of clinical benefit; DoR: Duration of response; ER: Oestrogen receptor; IM: Intramuscularly; OS: Overall survival; PgR: Progesterone receptor; PO: orally; PR: Partial response; SD: Stable disease; TTP: Time to progression

Selection of study population

Before entering the study, patients were assessed to ensure that they met the eligibility criteria, which were defined in line with key characteristics of the target population, including:

Inclusion criteria:

- Documented ER+ and/or PgR+ status
- Patients with ABC not amenable to therapy with curative intent
- Women defined as postmenopausal

Exclusion criteria:

- Previous systemic therapy for ABC
- The presence of life-threatening metastatic visceral disease.

Treatment regimens

Fulvestrant 500mg was provided as 250 mg in 5 mL as a pre-filled syringe formulation. Each dose of fulvestrant 500mg was administered, via two 5 mL IM injections, one in each buttock. Following administration, the injection sites were assessed by the investigator for any local reaction. Anastrozole 1 mg was administered as one tablet daily (5).

4.3.1 FALCON

A Phase III, randomised, double-blind, double-dummy, parallel-group, multicentre, study that compared the efficacy and tolerability of fulvestrant 500mg with anastrozole as endocrine therapy for endocrine-therapy-naïve postmenopausal women with ER+ and/or PgR+ ABC from 113 academic hospitals and community centres in 20 countries in Asia, Europe, North America, South America, and South Africa(7).

The primary objective of this study was to demonstrate the superior PFS of patients treated with fulvestrant 500mg versus patients treated with anastrozole. Patients were assessed for eligibility for the study based on local laboratory results for endocrine receptor status. The key secondary objectives were to compare OS, objective response rate (ORR: defined as best overall response of CR or PR), clinical benefit rate (CBR: defined as best overall response of CR, PR or SD [≥24 weeks]), duration of response (DoR), quality of life (QoL), safety and tolerability (7).

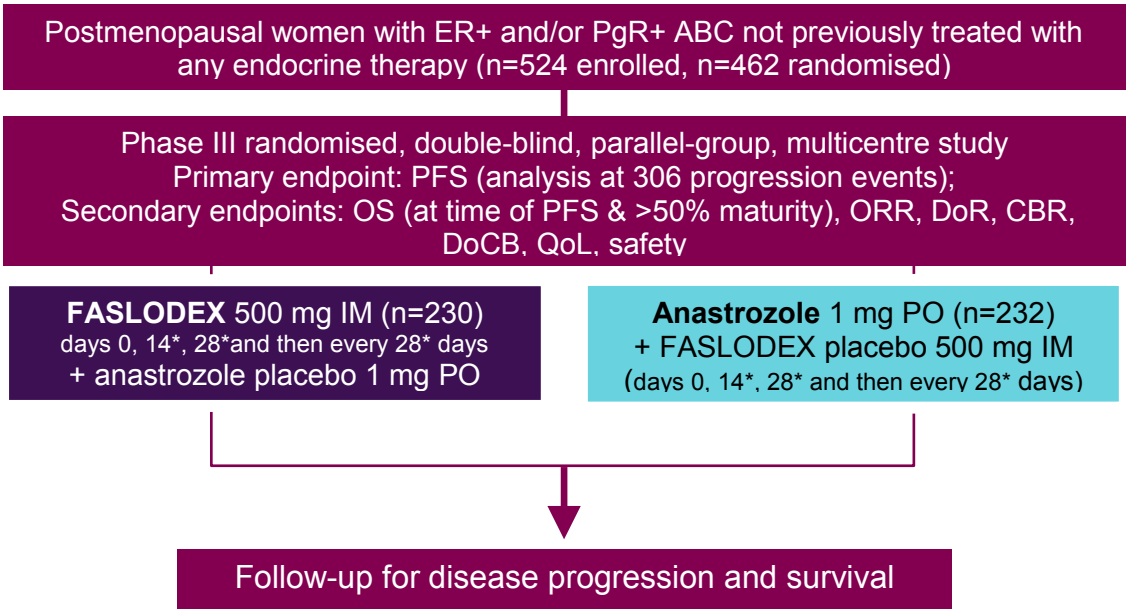
Study Design

A total of 462 women were randomised and included in the intention–to-treat (ITT) population (fulvestrant 500mg: n=230; anastrozole: n=232; Figure 8). Patients were stratified at randomisation based on whether:

- they had locally advanced or metastatic breast cancer,
- they had received prior chemotherapy for locally advanced or metastatic breast cancer or not and,
- they had measurable or non-measurable disease.

To maintain blinding, patients randomised to fulvestrant 500mg also received placebo tablets to match anastrozole and patients randomised to anastrozole also received placebo injections to match fulvestrant 500mg (7).

Figure 8: FALCON trial design and treatment schedule



SOURCE: (7)

*±3 day window

ABC: Advanced breast cancer; CBR: Clinical benefit rate; DoCB: Duration of clinical benefit; DoR: Duration of response; ER: Oestrogen receptor; IM: Intramuscularly; ORR: Objective response rate; OS: Overall survival; PgR: Progesterone receptor; PFS: Progression-free survival; PO: Orally; QoL: Quality of life

Selection of study population

Before entering the study, patients were assessed to ensure that they met the eligibility criteria, which were defined in line with key characteristics of the target population. The key eligibility criteria for the FALCON trial were defined as outlined below(7):

Inclusion criteria:

- Documented ER+ and/or PgR+ status
- Locally advanced disease not amenable to surgery or radiotherapy (RT) of curative intent OR metastatic disease

- Patients could have received one line of cytotoxic chemotherapy for breast cancer but had to show progressive disease prior to enrolment
- Postmenopausal woman
- WHO performance status of 0 to 2
- One or more measurable or non-measurable lesions

Exclusion criteria:

- Prior endocrine therapy for breast cancer
- Presence of life-threatening metastatic visceral disease
- Prior systemic therapy for breast cancer other than one line of cytotoxic chemotherapy, where the last dose of chemotherapy must have been received more than 28 days prior to randomisation
- RT if not completed within 28 days prior to randomisation (unless for bone pain control)
- Herceptin-eligible
- HER overexpression or gene amplification
- Concomitant anti-cancer treatment
- Systemic oestrogen-containing endocrine-replacement therapy use within 6 months prior to randomisation

Treatment regimens

In order to support the double-blind, double-dummy design of this trial, each patient received two study treatments, one being placebo (7):

- Patients randomised to receive fulvestrant 500mg also received placebo to match the anastrozole schedule (tablets, once daily)
- Patients randomised to receive anastrozole also received placebo to match the fulvestrant 500mg schedule (injections on Days 0, 14 [±3], 28 [±3], and every 28 [±3] days thereafter.

Fulvestrant 500mg (or matching placebo) was administered as two 5 mL intramuscular injections, one in each buttock, at each visit on Days 0, 14 [±3], 28 [±3], and every 28 [±3] days thereafter until the patient permanently discontinued the treatment. Anastrozole (or matching placebo) was taken orally as a single daily tablet

at a dose of 1 mg/day from randomisation on Day 0 until the patient permanently discontinued the treatment (7, 68).

Treatment continued unless any of the criteria for treatment discontinuation were met first. Criteria for treatment discontinuation included (68):

- Patient decision
- Adverse events (AEs)
- Severe non-compliance to study protocol
- Incorrect enrolment and randomisation
- Objective disease progression
- Patient lost to follow-up

Primary outcome subgroup analysis

Analysis of the following subgroups was performed, as defined by covariates, for the ITT analysis set (7, 68):

- ER+ and PgR+ at baseline
- Breast cancer type (locally advanced or metastatic)
- Use of bisphosphonates/denosumab as concomitant medication at baseline
- Measurable or non-measurable disease at baseline
- Prior chemotherapy for ABC
- Geographic region (US and Canada/ Japan/ China/ Asia)
- Prior systemic oestrogen containing hormone replacement therapy
- Visceral disease.

The subgroup analyses were performed on the primary endpoint PFS using an unstratified log-rank test including randomised treatment as the only factor (68).

4.3.3 Comparison of the study design in the FALCON and FIRST studies

The FALCON and FIRST studies both compared fulvestrant and anastrozole in a first line setting in HR+ ABC patients. However, there are some differences between the designs of these trials (Table 14). These include that patients in the FALCON study could have received one prior line of chemotherapy (7), whereas patients in

the FIRST study were chemotherapy-naïve in the metastatic/advanced setting (adjuvant chemotherapy for early breast cancer was permitted)(5). Further, patients in the FALCON study were endocrine therapy-naïve (7), whereas in FIRST, patients could have received prior adjuvant endocrine therapy if completed at least 12 months prior to randomisation into the study (5). Finally, while subjects in FALCON could not have been HER2+ve (7), this was not an exclusion criteria in FIRST (5).

Table 14: Study design of the FALCON and the FIRST trials

	FALCON (7)	FIRST (5)
Location	Asia, Europe, North & South America & South Africa	Europe, North & South America
Design	Randomised	
	Double-blind	Open-label
	Parallel-group	Parallel-group
	Phase III study	Phase II study
Key eligibility criteria	Postmenopausal women	
	ER+ and/or PgR+ ABC	
	No prior endocrine therapy	No prior endocrine therapy for advanced disease Adjuvant endocrine therapy allowed if completed 12 months prior to randomisation into the study
	HER2- only	HER2- or HER2+
	Prior chemotherapy for ABC allowed (1 line only)	No prior chemotherapy for ABC
Setting	Academic hospitals and community centres	
Trial drugs	Fulvestrant 500mg Anastrozole 1mg	
Primary outcome	PFS	CBR
Secondary outcomes	OS ORR, DoR, and EDoR CBR, DoCB, and eDoCB QoL Safety and tolerability	TTP - (OS included in protocol amendment) ORR, DoR DoCB - Safety and tolerability

	FALCON (7)	FIRST (5)
Pre-planned subgroups	ER+ and PgR+ at baseline Breast cancer type (locally advanced or metastatic) Use of bisphosphonates/ denosumab as concomitant medication at baseline Measurable or non-measurable disease at baseline Prior chemotherapy for ABC Geographic region Prior systemic oestrogen containing HRT Visceral/Non-visceral disease.	N/A – subgroup analysis was post-hoc • Age (<65 years or >=65 years) • Receptor status (ER+ and PgR+ or not ER+ and PgR+) • Visceral involvement • Prior chemotherapy • Measurable disease • Prior endocrine therapy

SOURCE: (5-8)

*The last dose of chemotherapy must have been received more than 28 days prior to randomisation

CBR: Clinical benefit rate; CR: Complete response; DoCB: Duration of clinical benefit; DoR: Duration of response; EBC: Early breast cancer; EDoCB: Expected duration of clinical benefit; EDoR: Expected duration of response; ER+: Oestrogen receptor positive; HRQoL: Health-related quality of life; HRT: Hormone replacement therapy; mPFS: Median progression-free survival; ORR: Objective response rate; OS: Overall survival; PD: Progressive disease; PgR+: Progesterone receptor positive; PR: Partial response; RECIST: Response Evaluation Criteria in Solid Tumours; RT: Radiotherapy; SD: Stable disease; TTP: Time to progression

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

4.4.1 FIRST

In order to provide assurances that the open-label design did not bias the results of the tumour assessments in this study, a blinded independent review was carried out by a radiologist at BioImaging Technologies.

Statistical analyses were performed using SAS software version 8.2 (SAS Institute, Cary, NC). Sample size calculations for this noninferiority trial estimated that 100 randomly assigned patients per treatment group would be required to give 80% power to rule out an absolute deficiency of 20% in CBR for fulvestrant 500mg with a two-sided 95% CI. The primary analysis was stipulated in the protocol to occur 6 months after the last patient had been randomly assigned.

The primary end point (CBR) was compared in the two groups using a logistic regression model where the absolute differences, odds ratios, and associated 95% CIs and P values were reported. The same methods were used for the secondary end point of ORR. Kaplan-Meier plots were produced for TTP, DoR, and DoCB, and a log-rank test was used to generate the hazard ratios, 95% CIs, and P values for TTP. Treatment differences in the incidence of prespecified AEs were evaluated using a two-sided Fisher's exact test.

Patients could be discontinued from study treatment and assessments at any time, at the discretion of the investigator(s).

The nominal significance level of 0.05 was used in the analysis of all end-points. For the primary endpoint CBR, the treatment comparison was performed using a logistic regression model with treatment as the only factor. The results are expressed in terms of the odds ratio together with corresponding 95% confidence interval and p-value. The estimate of the difference in CBR (fulvestrant – anastrozole) and the corresponding 2-sided 95% confidence interval is also presented.

The same methods are used in the analysis of ORR, a secondary endpoint.

For the further secondary endpoints of TTP, DoR and DoCB summaries are presented using the Kaplan-Meier method. For TTP, a log-rank test is used to assess the treatment effect.

4.4.2 FALCON

For the primary outcome, progression-free survival was assessed at a single timepoint when approximately 306 progression events had occurred. Randomisation of approximately 450 patients was planned to achieve 306 progression events. The HR of 0·69 was considered to be a reasonable estimate of the true HR in the FALCON population based on results from the FIRST phase 2 study (5, 8). If 0·69 was the true progression-free survival HR for the comparison of fulvestrant with anastrozole, then 306 events was calculated to provide 90% power for statistical significance at the 5% two-sided level. A progression-free survival HR of 0·80 would deliver a statistically significant difference for the primary outcome.

The primary analysis for this study was done in the intent-to-treat population comprising all randomly assigned patients. All safety outcomes were assessed in all patients who received at least one dose of randomized treatment (including placebo) according to the actual treatment initially received.

Comparison of PFS for fulvestrant versus anastrozole was done using a stratified log-rank test at the two-sided 5% significance level in the intention-to-treat population. Strata included were previous chemotherapy for locally advanced or metastatic disease and measurable disease; locally advanced versus metastatic disease was not included because only a small number of patients had locally advanced disease. Results are presented as an estimate of the HR, associated 95% CI, and p value. An interim analysis of overall survival was done at the time of progression-free survival analysis, and overall survival was analysed in the same way as progression-free survival.

Overall survival and objective response rate were tested with a multiple testing procedure with an α-exhaustive recycling strategy to control type I error at the overall α level (69). Clinical benefit rate was analysed with a logistic regression model including the same stratification factors as for progression-free survival and examination of the OR of the two treatment groups. Objective response rate was

analysed in the same way as clinical benefit rate; however, measurable disease was not included in the model.

Using the α=2% arm of the MTP (assuming that ORR is not statistically significant), the following was the case for the OS interim analysis:

- It was predicted that 159 death events (out of the total study estimated size of 450 patients) had occurred
- The final OS analysis is planned for when it is estimated that at least 50% of the death events will have occurred
- Therefore, at the time of the interim OS analysis, it was estimated that 0.7 of the full death information was available (ie, 159/225 deaths)

If this were the case, the 1-sided significance level to be applied for the OS interim analysis would be 0.0054.

- If the interim OS was statistically significant, all 2% of alpha would be recycled to ORR (as ORR was to be analysed at 1 time point only)
- If the interim OS was not statistically significant, none of the 2% of alpha would be recycled to ORR (as ORR was to be analysed at 1 time point only).

Hence, if the interim OS (conducted at the time of the PFS analysis) was statistically significant, then ORR would be assessed using α=0.025 (ie, the full 2% of alpha used in the OS analysis would be recycled to ORR). If the interim OS was not statistically significant, then ORR would be assessed using α=0.005.

Kaplan-Meier plots were produced for duration of clinical benefit and duration of response. Expected duration of clinical benefit and expected duration of response are designed to provide an unbiased treatment comparison of duration of clinical benefit and duration of response by including all randomly assigned patients (rather than only responding patients) and were calculated using the method described by Ellis and colleagues (6). Expected duration of response and expected duration of clinical benefit allow a statistical comparison to be made on the duration of response and clinical benefit between the two treatment groups. An analysis of time to

deterioration of Trial Outcome Index and FACT-B total score was done as described for progression-free survival.

A subgroup analysis was done on progression-free survival data in the intention-to-treat population, HRs and 95% CI were calculated, and a Kaplan-Meier was generated for each subgroup. A global interaction test was done with a Cox-proportional hazard model to assess whether the treatment effect was consistent across the covariates. A post-hoc interaction test to assess for consistency of the treatment effects across the visceral and non-visceral subgroups was also done. Adverse events were summarised descriptively using the Medical Dictionary for Regulatory Activities preferred terms. SAS versions 9.2 and 9.4 were used for statistical analyses.

Proportional hazards were tested firstly by examining plots of complementary log-log (event times) vs. log (time) and, if these raised concerns, by fitting a time dependent covariate to assess the extent to which this represented random variation. If a lack of proportionality was evident, the variation in treatment effect was described by presenting piecewise HR calculated over distinct time periods. In such circumstances, the HR could still be meaningfully interpreted as an average HR over time unless there was extensive crossing of the survival curves. If lack of proportionality was found, this could have been a result of treatment-by-covariate interactions, which was investigated.

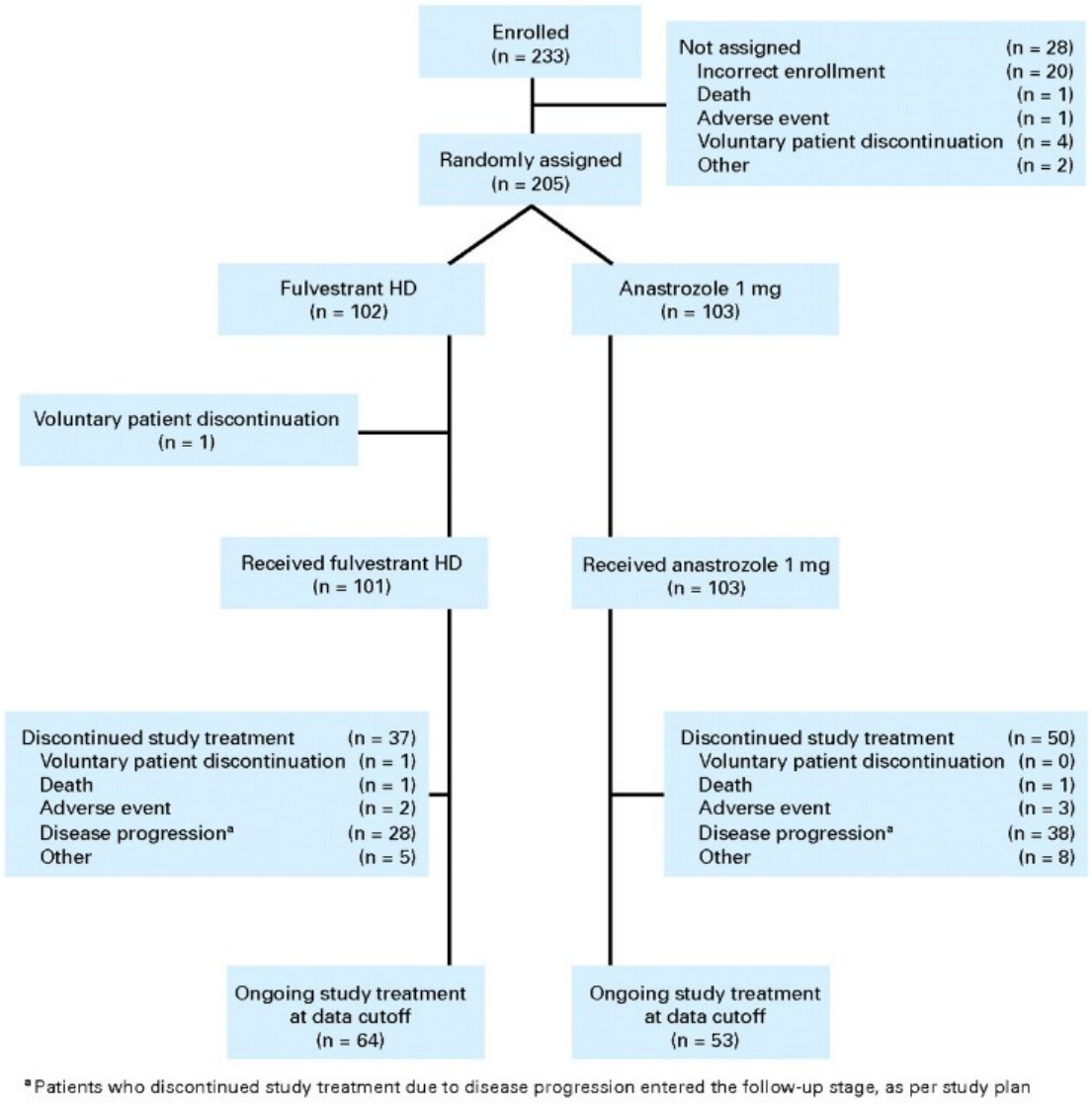
4.5 Participant flow in the relevant randomised controlled trials

4.5.1 FIRST

A total of 233 women were enrolled onto the study, 205 of whom were randomised to receive either fulvestrant 500mg (n=102) or anastrozole (n=103) in the FIRST clinical trial. All 205 randomised patients were included in the full analysis set, however one patient did not receive treatment (5).

Patients were recruited from 62 centres in nine countries (Brazil, Bulgaria, Czech Republic, France, Italy, Poland, Spain, United Kingdom, and the United States).

Figure 9: Patient disposition. (*) Patients who discontinued study treatment due to disease progression entered the follow-up stage, as per the study plan. HD, high dose.



Patients within the two treatment arms were of a similar mean age, and had a similar distribution of age groups, and race (Table 15). Patients had a mean age of 67.1 years (range: 40-89). All patients (100%) enrolled in the trial had ER positive disease. All but one of the patients were considered to be first line with respect to endocrine therapy, in that they had either never had endocrine therapy, or had completed endocrine therapy more than 12 months prior to randomisation. Of the enrolled patients, over a quarter of patients in the fulvestrant arm had received prior endocrine therapy, with 72% being truly endocrine therapy-naïve (6).

Table 15: Characteristics and demographics of patients enrolled in the FIRST trial

Demographic characteristic	Fulvestrant 500mg (n=102)	Anastrozole 1 mg (n=103)
Sex, %		
Male	0	0
Female	100	100
Age (years)		
Mean (SD)	67 (9)	68 (9)
Median	66	68
Range	40–89	48–87
Race, n (%)		
Caucasian	97 (95.1)	102 (99)
Black	3 (2.9)	0
Other	2 (2.0)	1 (1)
Disease stage, %		
Locally advanced only	19 (18.6)	18 (17.5)
Metastatic	83 (81.4)	85 (82.5)
Previous treatment modalities[a], %		
Prior endocrine therapy		
None	73 (71.6)	80 (77.7)
Completed ≤12 months prior to randomisation	1 (1.0)	0
Completed >12 months prior to randomisation	28 (27.5)	23 (22.3)
Prior chemotherapy		
None	73 (71.6)	78 (75.7)
Received adjuvant chemotherapy	29 (28.4)	25 (24.3)

SOURCE: (5, 6, 8)

[a]Previous study treatment, as deemed by the sponsor to be relevant to the interpretation of the results

SD: Standard deviation

Analysis sets

Patient populations were defined as follows (Table 16):

- The Full analysis set includes all randomized patients. Comparison of treatment groups was on the basis of randomized treatment regardless of the treatment actually received.

- The Per Protocol population (PP analysis set) includes all treated patients who did not have any major protocol deviations. A PP analysis was carried out on CBR in addition to the primary analysis of CBR in the full analysis set.

- The Evaluable for Response analysis set includes all randomized patients (regardless of whether any study treatment was received) for whom OR could be assessed. The Evaluable for Response analysis set is a subset of the full analysis set.

- The Safety analysis set comprises all patients who received at least one dose of fulvestrant or anastrozole.

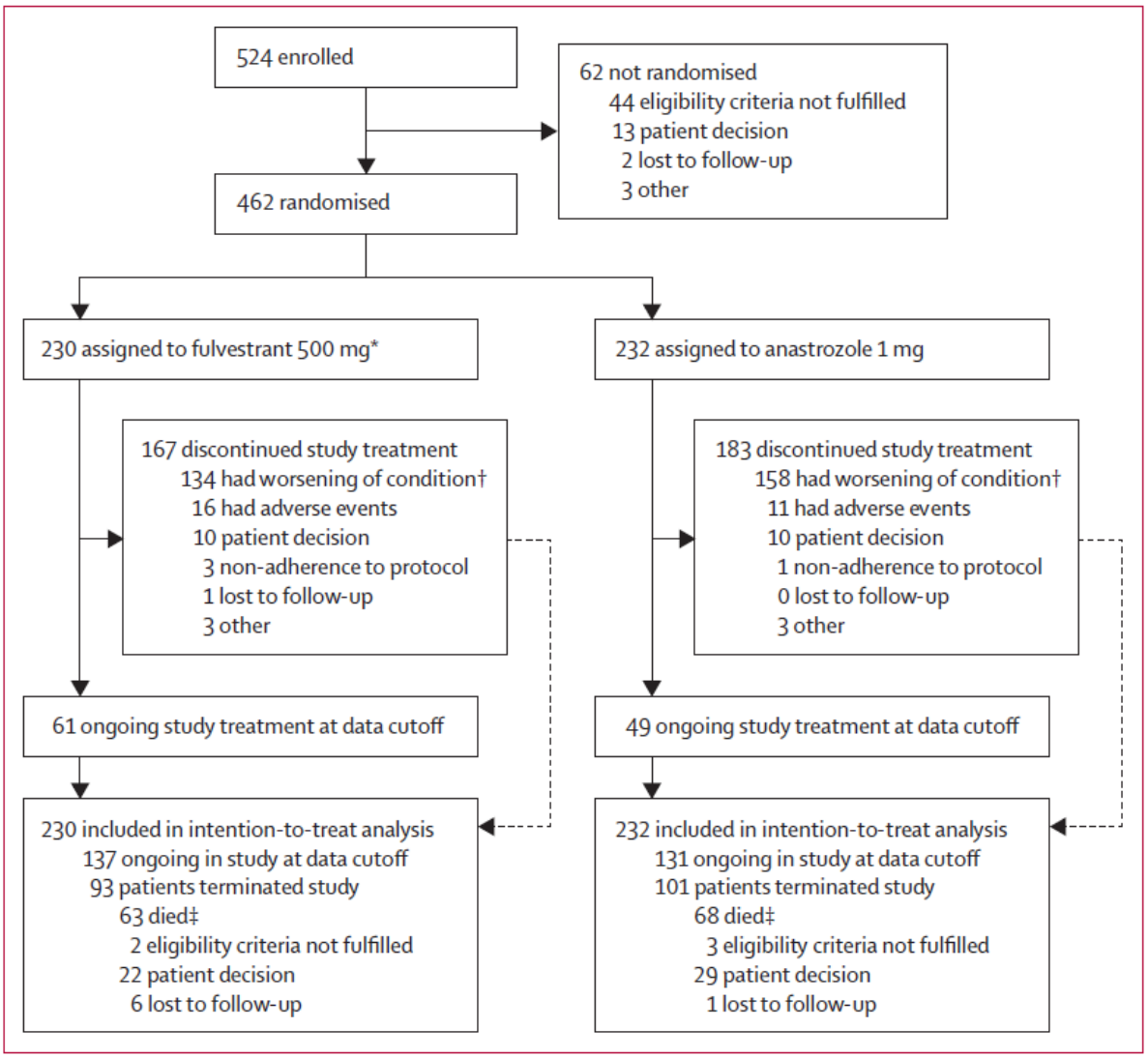
Table 16: Summary of patient disposition and analysis sets

	Number of patients		
	Fulvestrant 500mg	**Anastrozole 1mg**	**Total**
Disposition			
Patients enrolled			233
Patients randomised	102	103	205
Patients who received treatment	101	103	204
Patients ongoing any study treatment at data cut-off	64	53	117
Analysis sets			
Full analysis set	102	103	205
Per protocol analysis set	99	99	198
Safety analysis set	101	103	204
Evaluable for Response analysis set	89	93	182

4.5.2 FALCON

A total of 524 patients were enrolled in this study, 462 of whom were randomised to study treatment at 113 centres across 20 countries (7). Patient decision and failure of eligibility criteria to be fulfilled were the main reasons for 62 patients not being randomised. Similar numbers of patients were randomised to receive fulvestrant 500mg (n=230) or anastrozole (n=232) within the ITT population (Figure 10 and Table 17) (7).

Figure 10: Trial profile (7).



*Two patients in the fulvestrant 500mg group did not receive treatment (patient decision). †Includes patients with disease progression. ‡Deaths exclude patients who terminated the study for other reasons (four patients in the fulvestrant group and seven patients in the anastrozole group) but were subsequently found to have died.

All patients enrolled in this study were female. There were no major differences between treatment arms in terms of patient disease characteristics at baseline, where the majority of patients presented with metastatic disease (Table 17) (7). The median age of patients in the fulvestrant 500mg arm was slightly older than in the anastrozole arm (64.0 years vs. 62.0 years, respectively) (7). In general, previous disease-related treatment modalities were similar across the two treatment arms. A slightly larger proportion of patients in the fulvestrant 500mg arm had received prior

adjuvant chemotherapy compared with the anastrozole arm (15% vs. 12%, respectively) (7).

Table 17: Characteristics and demographics of patients enrolled in the FALCON trial (7)

Demographic characteristic	fulvestrant 500mg (n=230)	Anastrozole 1 mg (n=232)
Sex, %		
Male	0	0
Female	100	100
Age (years)		
Mean (SD)	63.8 (9.86)	63.3 (10.38)
Median	64.0	62.0
Range	38-87	36-90
Race, %		
White	76	75
Asian	16	15
Black or Other	8	10
Disease stage, %		
Locally advanced	12	14
Metastatic	88	86
Measurable disease,%	84	84
Previous treatment modalities[a], %		
Prior endocrine therapy	1	<1
Any chemotherapy	34	35
Advanced disease[b]	16	19
Adjuvant	15	12
Neo-adjuvant	5	7
Any radiotherapy	23	22

SOURCE: (7)

[a]Therapies prior to enrolment

[b]Includes 1L, 2L, 3L, metastatic and palliative chemotherapies

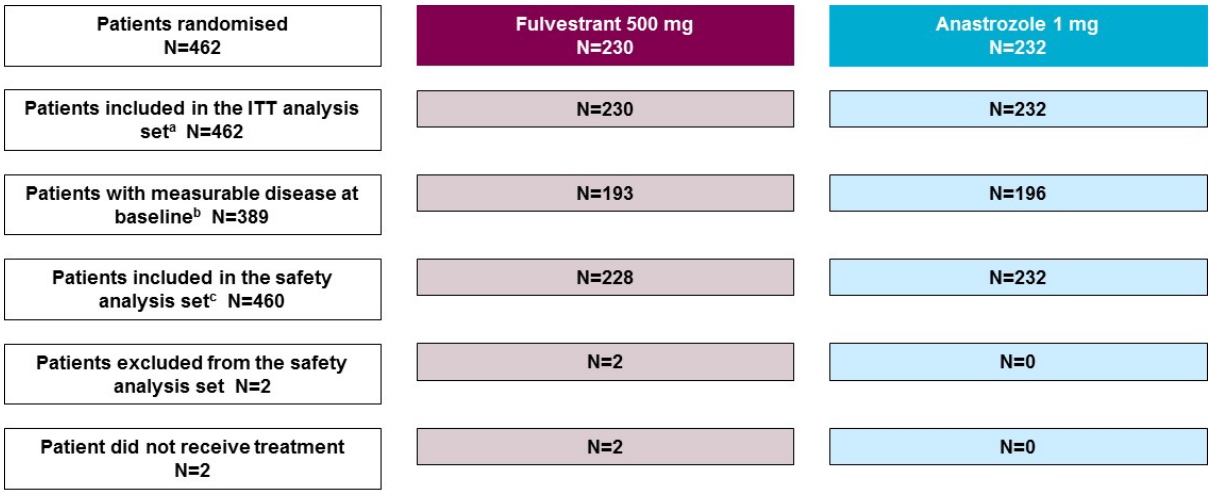
SD: Standard deviation

Analysis sets

In total, 462 patients were randomised and were also included in the ITT analysis set (230 and 232 patients in the fulvestrant and anastrozole arms, respectively). A total of 460 patients were included in the safety analysis set (228 and 232 patients in the fulvestrant and anastrozole arms, respectively). Two (0.9%) patients randomised to the fulvestrant arm did not receive study medication and were excluded from the

safety analysis set. One patient randomised to anastrozole did not receive active anastrozole and only received 1 dose of placebo fulvestrant, was included in the safety analysis set. Similar numbers of patients in each treatment arm were included in each of the analysis sets (Figure 11).

Figure 11: Analysis sets for FALCON (7)



4.6 Quality assessment of the relevant randomised controlled trials

A critical appraisal of FIRST and FALCON using the NICE checklist is provided in Table 12. The FIRST study was judged to have a Jadad score of 2 with an allocation concealment grade of B, while FALCON had a score of 5A.

4.7 Clinical effectiveness results of the relevant randomised controlled trials

4.7.1 FIRST

Primary efficacy outcome - CBR

The primary outcome variable of this study was CBR. The CBR numerically favoured treatment with FASLDOEX 500mg (73%) over anastrozole treatment (67%), with an absolute difference (fulvestrant 500mg minus anastrozole) of 6% (95% CI: -7.8-15.8) (Table 18). Comparison of the CBRs of the two treatment arms gave an odds ratio of 1.302 (95% CI: 0.72-2.4; p=0.386), numerically favouring treatment with fulvestrant 500mg (5). This numerical difference was not statistically significant (p-

value=0.386), and this is consistent with the fact this study was not powered to detect a statistically significant difference for CBR but rather was designed to detect non-inferiority only.

The independent reviewers' evaluation was used to corroborate the local investigator read analysis of the primary endpoint (CBR), which was based on the onsite investigator tumour measurements. The concordance rates between the local investigator read and the blinded independent review were high in both treatment arms and were similar between the two treatment arms (88.4% [84/95] in the fulvestrant arm compared to 86.3% [82/95] in the anastrozole arm).

Table 18: Summary of clinical benefit: Full analysis set

		Fulvestrant 500mg (N=102)	**Anastrozole 1mg (N=103)**	
CB	Complete response	0	1(0)	
	Partial response	32 (31.4)	32 (31.1)	
	Stable disease >=24 weeks	42 (41.02)	36 (35.0)	
	Total with CB	74 (72.5)	69 (67.0)	
No CB	Stable disease <=24 weeks	15 (14.7)	12 (11.7)	
	Progression	10 (0.8)	2 (1.9)	
	Not evaluable	3 (2.9)	2 (1.9)	
	Total with no CB	28 (27.5)	34 (33.0)	
Odds ratio (95% CI)				1.30[a] (0.72-2.4)
P value				0.386
Absolute difference (95% CI)				6%[b] (-7.8-15.8)

SOURCE: (5)

*Clinical benefit is defined as CR, PR, or SD ≥24 weeks

[a]An OR >1 favours fulvestrant 500mg

[b]Conditioned on the anastrozole treatment arm

CBR: Clinical benefit rate; CI: Confidence interval; CR: Complete response; OR: Odds ratio; PR: Partial response; SD: Stable disease

The CBRs for the two treatment arms were similar when calculated using the blinded independent review data (69.5% [66/95] in the fulvestrant arm compared to 66.3% [63/95] in the anastrozole arm). There was no evidence of bias between the groups

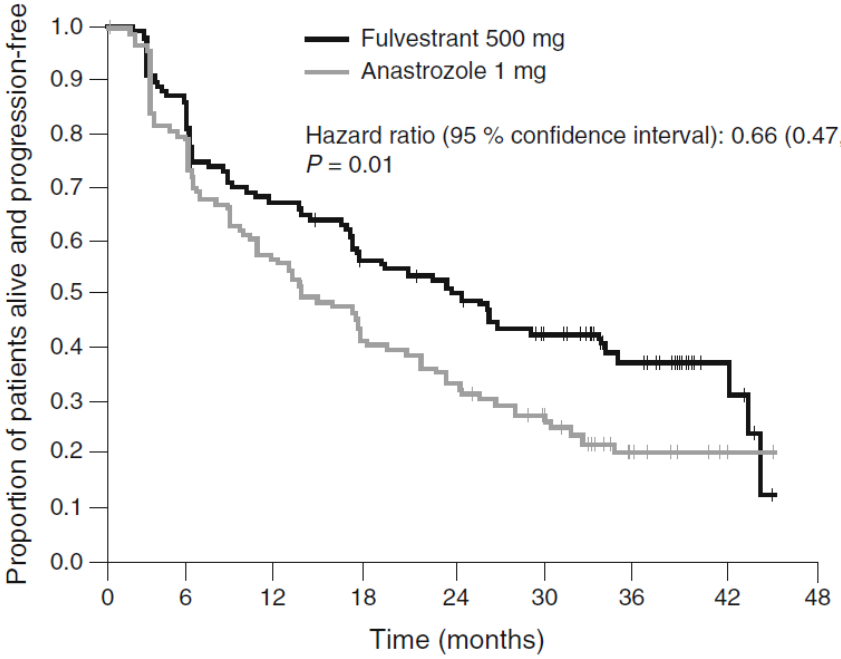
in the assessment of CBR. The independent review corroborates the findings of the primary analysis.

Secondary efficacy outcomes

Time to progression (TTP)

The primary analysis of FIRST led to a protocol amendment, to allow a new analysis when progression data was more mature (69.3% patients had progressed; 61.8% in the fulvestrant 500mg group and 76.7% in the anastrozole group.). Fulvestrant 500mg demonstrated a significant increase in time to progression compared with anastrozole (HR: 0.66; 95% CI: 0.47-0.92; p=0.01) (8). The median TTP for fulvestrant 500mg was 10.3 months longer than for anastrozole (23.4 months vs. 13.1 months, respectively). Separation in the KM curves between each treatment arm is observed from 5 months, and is maintained for the remainder of the study period, favouring fulvestrant 500mg (Figure 12) (8).

Figure 12: Kaplan-Meier plot of TTP in the overall FIRST population (8)



Patients at risk

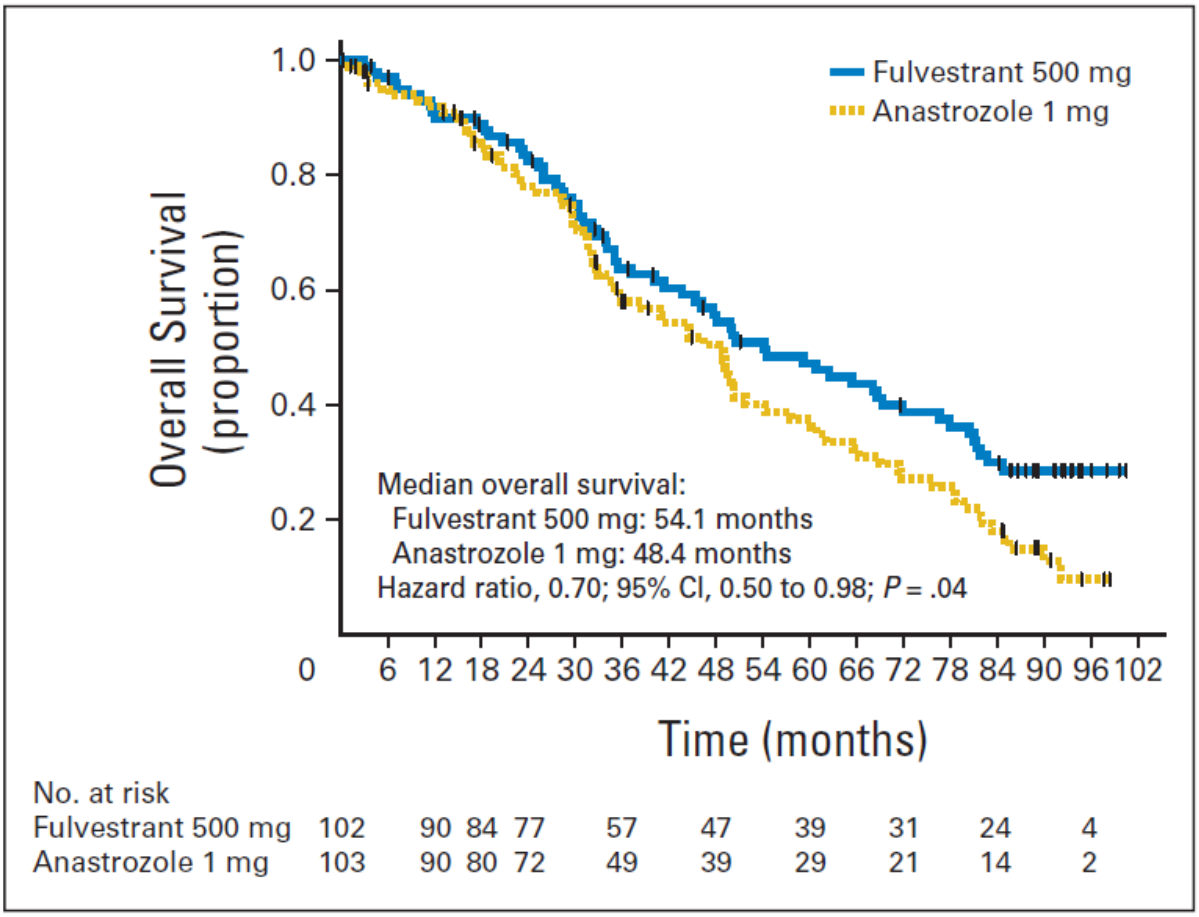
Fulvestrant 500 mg	102	74	65	52	45	34	20	6	0
Anastrozole 1 mg	103	69	55	39	30	21	8	2	0

After the primary data cut-off, progression was determined by investigator opinion

Overall survival (OS)

A further addendum of the FIRST clinical study report (CSR) presented data from a follow-up analysis of the trial, performed when approximately 65% of deaths had occurred (6). At the time of data cut-off of the follow-up analysis, 66.8% of patients had died; 62% in the fulvestrant 500mg group and 72% in the anastrozole group. fulvestrant 500mg significantly improved OS when compared with anastrozole (HR: 0.70; 95% CI: 0.50-0.98; median 54.1 months vs. 48.4 months, respectively; p=0.041) (Figure 13).

Figure 13: Kaplan-Meier plot of OS in the overall FIRST population (6)



OS: Overall survival

Additional secondary objectives

The outcomes of additional secondary outcomes (ORR, mDoR, and mDoCB) are presented in Table 19 and were similar for both treatment arms. As the median DoR

value for fulvestrant 500mg had not been reached at the time of analysis (the K-M estimate of DoR had not dropped below 50%), results suggest that fulvestrant 500mg is associated with numerically more durable and prolonged treatment responses than anastrozole (5, 8).

Table 19: Summary of additional secondary outcomes in FIRST

Secondary outcome	fulvestrant 500mg (n=193)	Anastrozole 1 mg (n=196)	OR (95% CI)
ORR, %	36	36	1.021 (0.556-1.687) p=0.95
CR, %	0	1	-
PR, %	36.0	34	-
SD, %	51	44	-
PD, %	10	19	-
mDoR, months	NC	12.0*	-
mDoCB, months	NC	NC	-

SOURCE: (5, 8)

*DoR defined as time from response through to progression

CI: Confidence interval; CR: Complete response; DoCB: Duration of clinical benefit; DoR: Duration of response; NC: Not calculable; OR: Odds ratio; PD: Progressive disease; PR: Partial response; SD: Stable disease

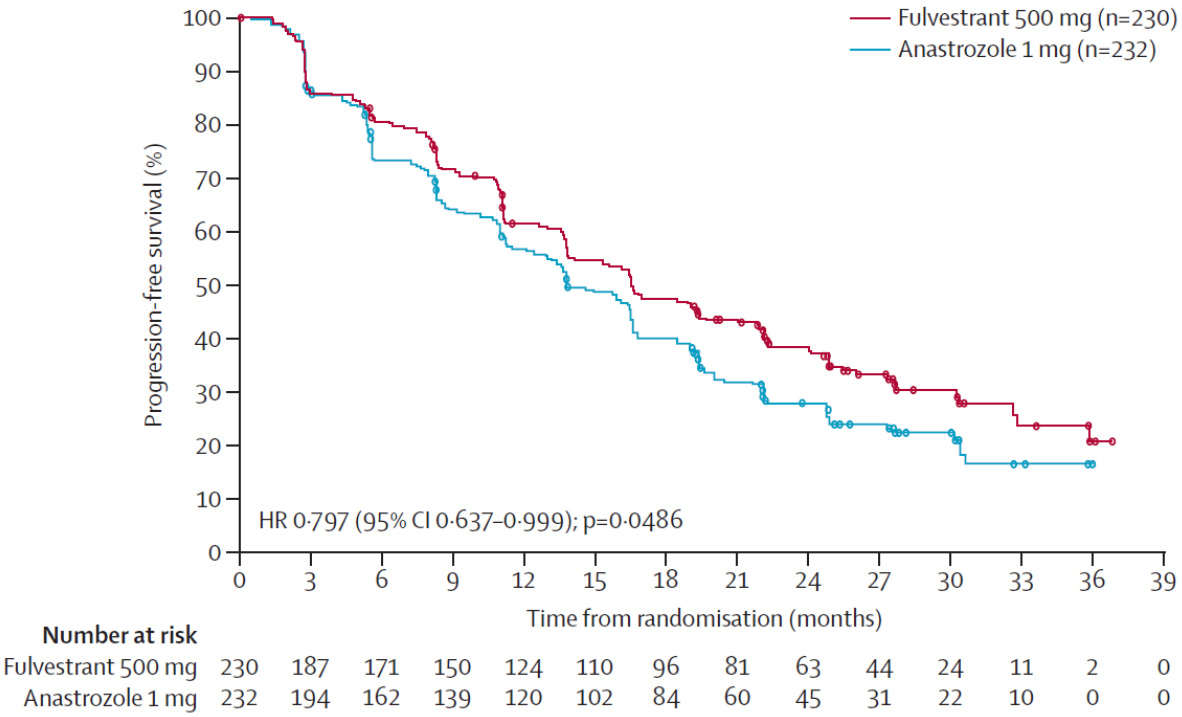
4.7.2 FALCON

Primary efficacy outcome - PFS

The primary objective of this study was to demonstrate the superior efficacy of fulvestrant 500mg versus anastrozole in postmenopausal women with ER+ ABC by assessment of PFS (7). This primary objective was met, with a statistically significant improvement in PFS observed in the fulvestrant 500mg arm compared with the anastrozole arm (p=0.0486). Median PFS was 2.8 months longer in the fulvestrant 500mg arm (16.6 months; 95% CI: 13.83-20.99) than in the anastrozole arm (13.8 months; 95% CI: 11.99-16.59). The hazard ratio (HR) was 0.797 (95% CI: 0.637-0.999), indicating an approximate 20% reduction in the risk of disease progression in the fulvestrant 500mg arm compared with the anastrozole arm over the study period (7).

The Kaplan-Meier (K-M) analysis shows a clear difference between treatment arms. Separation in the curves for each treatment arm is observed from around 6 months, and is maintained for the remainder of the study period (Figure 14). This analysis indicates that disease progression occurred at a slower rate with fulvestrant 500mg treatment relative to treatment with anastrozole (7).

Figure 14: Kaplan-Meier plot of PFS in the FALCON trial (7)

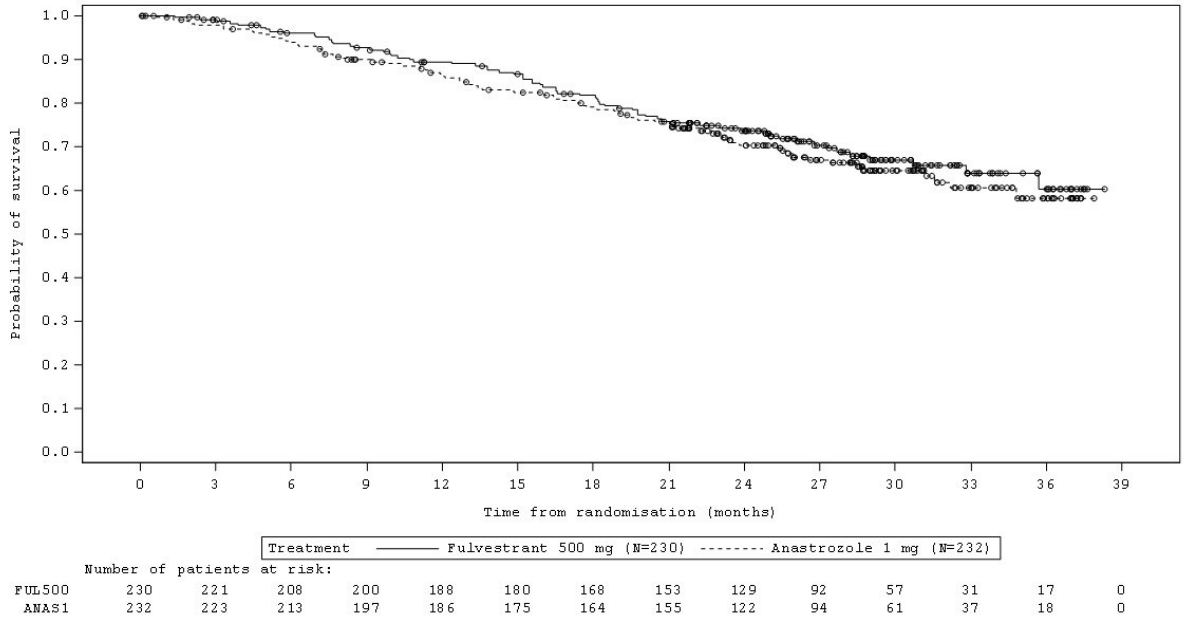


SOURCE: (7)
Note: A circle represents a censored observation
ANAS1: Anastrozole 1 mg; FUL500: fulvestrant 500mg; PFS: Progression-free survival

Secondary efficacy outcome - OS

The OS data were immature at the time of interim analysis (only 31% of events had been reached), to the extent that median OS could not be calculated (7). A K-M plot of OS at the time of the primary efficacy analysis is presented in Figure 15. There was no statistically significant difference in OS between treatment with fulvestrant 500mg or anastrozole (HR: 0.875; 95% CI: 0.629-1.217; p=0.4277)(7, 68).

Figure 15: Kaplan-Meier plot of OS at the time of the PFS analysis (68)



SOURCE: (68)

Note: A circle represents a censored observation

ANAS1: Anastrozole 1 mg; FUL500: fulvestrant 500mg; OS: Overall survival; PFS: Progression-free survival

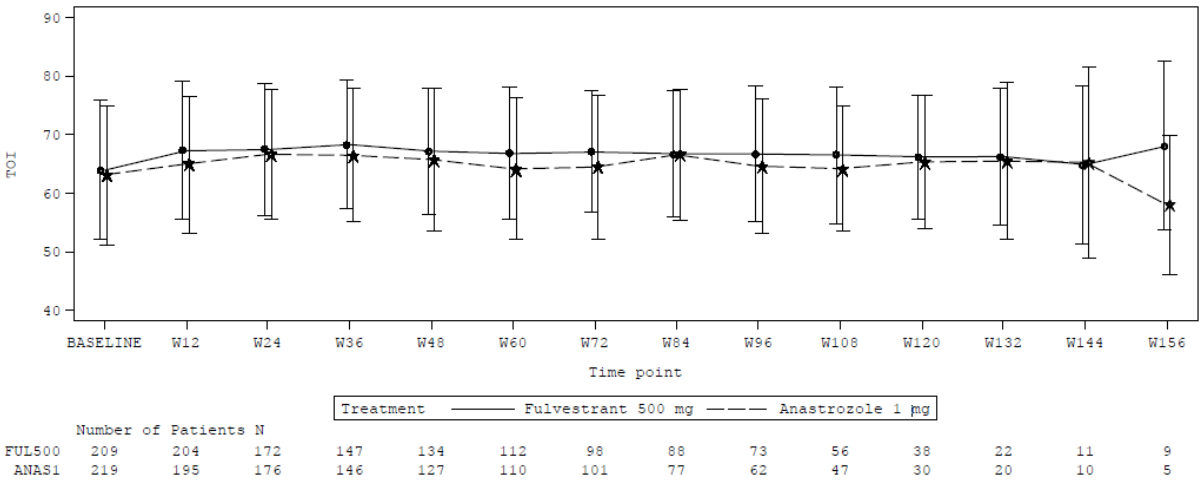
Health related quality of life (HRQoL)

In order to assess the patient-reported outcomes (PROs) and health-related quality of life (HRQoL) associated with fulvestrant 500mg treatment, the FALCON trial utilised the EQ-5D and FACT-B questionnaires (7). The FACT-B questionnaire comprises the following subscales; physical well-being [PWB], functional well-being [FWB], social well-being [SWB], emotional well-being [EWB], and breast cancer subscale [BCS]; however the main outcome measure from the FACT-B questionnaire was the trial outcome index (TOI), summarising the PWB, FWB, and BCS subscales(68).

Mean baseline values for TOI scores were high and comparable between the fulvestrant 500mg and anastrozole treatment arms (63.9 [SD: 11.86] and 63.2 [SD:11.89], respectively, Figure 16). Mean TOI scores over time were similar in both treatment arms and remained high during the duration of treatment. The mean

change from baseline was minimal while on treatment (approximately ±3 points over time) and was comparable between treatment arms (70).

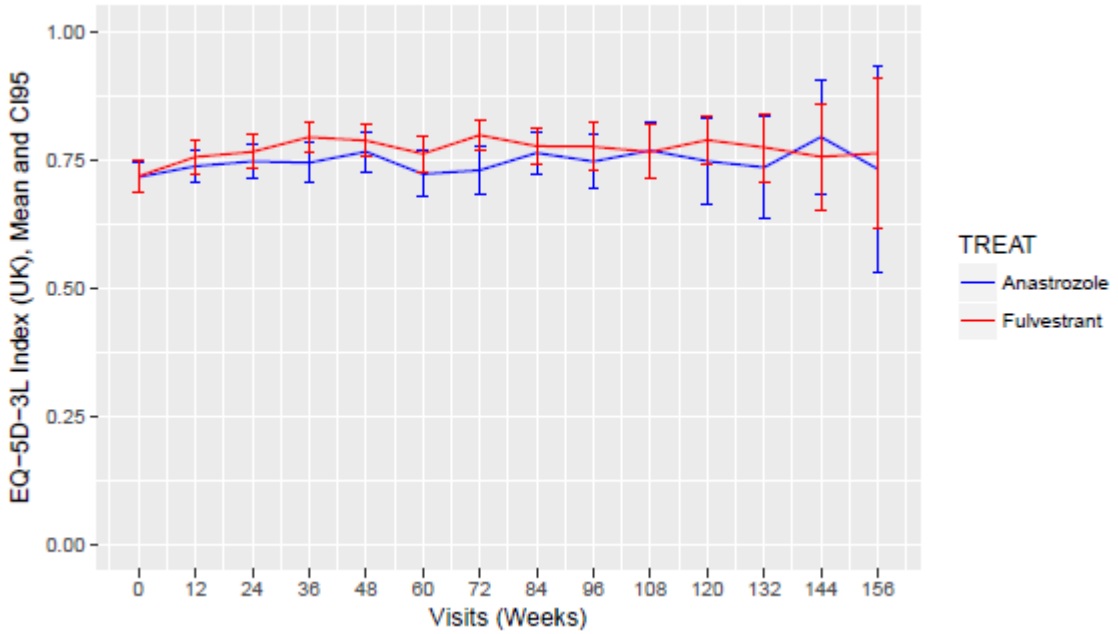
Figure 16: Mean TOI score across timepoints, by treatment group



SOURCE: (AstraZeneca 2015a)
ANAS1: Anastrozole 1 mg; FUL500: fulvestrant 500mg; TOI: Trial outcome index

The EQ-5D questionnaire collected data on generic health status across three levels (EQ-5D-3L). Results of the EQ-5D-3L questionnaire show that the general health status is maintained over the study period (156 weeks) across both treatment arms. The means per visit of the EQ-5D-3L Index in the fulvestrant 500mg group are consistently greater than in the anastrozole group between week 0 (baseline) and week 156 (end of study) (Figure 17).

Figure 17: EQ-5D-3L Index (UK) per treatment and visit



SOURCE: (70)
CI95: Confidence interval (95%); EQ-5D-3L: EuroQoL-5 dimensions-3 levels; UK: United Kingdom

Overall, HRQoL (FACT-B TOI score and EQ-5D) was maintained and similar in both treatment groups (7).

Additional secondary efficacy objectives

The outcomes of additional secondary outcomes (ORR, mDoR, EDoR, CBR, DoCB, and EDCoB) are presented in Table 20. Similar ORRs and CBRs were observed in both treatment arms, with results slightly favouring fulvestrant 500mg. However, fulvestrant 500mg treatment numerically increased the durability of these benefits compared with anastrozole, with a 6.8 month higher median duration of response and 3.0 months higher duration of clinical benefit (7).

Table 20: Summary of other secondary outcomes in FALCON

Secondary outcome	fulvestrant 500mg	anastrozole 1mg	Statistics
Measurable disease*	**n=193**	**n=196**	
ORR, %	46	45	OR: 1.07 (95% CI: 0.72-1.61) p=0.7290
Median DoR, months	20.0	13.2	-
median time to onset of response, months	8.1	5.6	-
EDoR, months	11.4	7.5	EDoR ratio: 1.52 (95% CI: 1.03-2.26) p=0.0367
Median DoCB, months	22.1	19.1	-
ITT population	**n=230**	**n=232**	
CBR (CR, PR, or SD ≥24 weeks), %	78	74	OR: 1.25 (95% CI: 0.82-1.93) p=0.3045
CR, %	3	3	-
PR, %	37	35	-
SD ≥24 weeks, %	38	35	-
PD, %	13	14	-
EDoCB, months	21.9	17.5	EDoCB ratio: 1.26 (95% CI: 0.99-1.59) p=0.0561

SOURCE: (7)
*Patients with measurable disease at baseline
CBR: Clinical benefit rate; CI: Confidence interval; CR: Complete response; DoCB: Duration of clinical benefit; DoR: Duration of response; EDoCB: Expected duration of clinical benefit; EDoR: Expected duration of response; OR: Odds ratio; ORR: Objective response rate; PD: Progressive disease; PR: Partial response; SD: Stable disease

4.8 Subgroup analysis

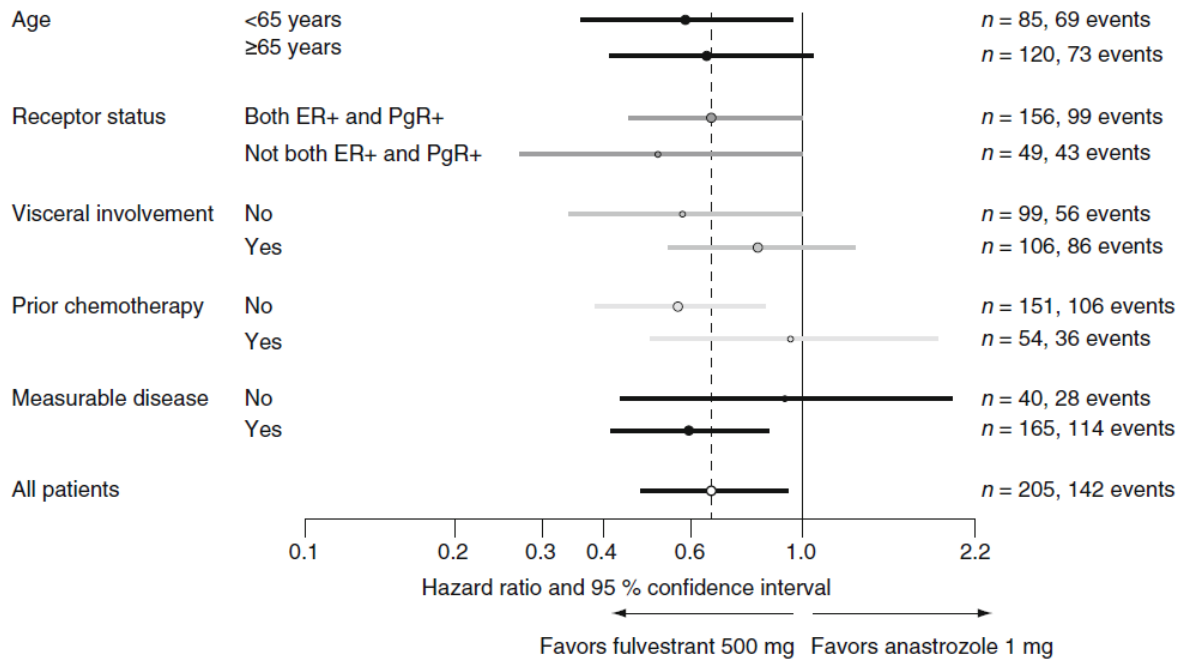
4.8.1 FIRST

Subgroup analysis of outcomes in the FIRST trial was not planned in the original trial design (5), but was incorporated into 2 subsequent follow-up analyses of TTP (8) and OS (6).

Secondary efficacy outcome – TTP

The difference in TTP observed in the full population (Figure 12) was also statistically significant when adjusted for pre-defined covariates (HR 0.64; 95 % CI: 0.46, 0.90; P = 0.01). The global interaction test was not significant (P = 0.34) (8). A forest plot representing TTP according to the pre-defined covariates is shown in Figure 18, demonstrating that the treatment effect is consistent across all subgroups.

Figure 18: Time to progression by pre-defined covariates (8)



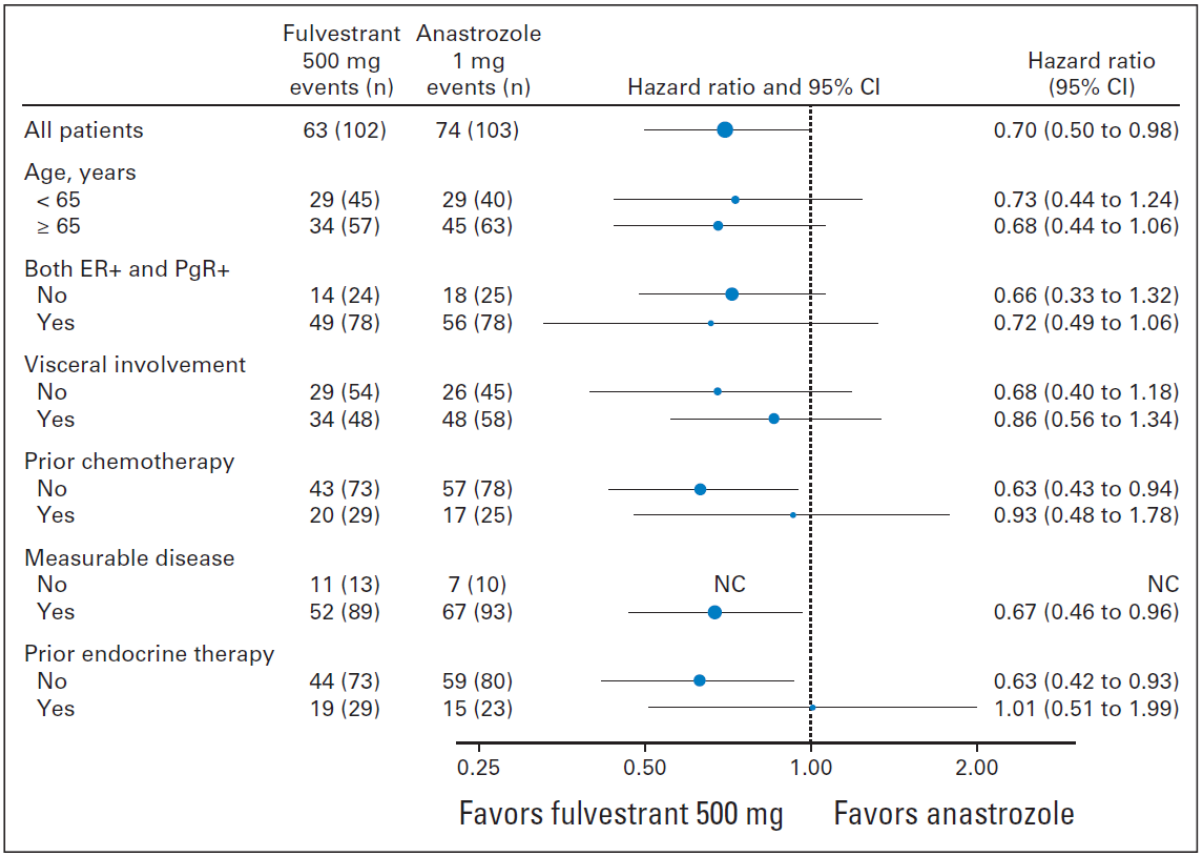
ER estrogen receptor, *PgR* progesterone receptor

Secondary efficacy outcome – OS

The HR for fulvestrant 500mg versus anastrozole was found to be generally consistent across all subgroup analyses (6). In patients who were endocrine-therapy

naïve the HR was 0.63 (0.43 to 0.94), although it should be noted that this is based on a very small sample size (100 events in 151 patients).

Figure 19: OS subgroup analysis of FIRST (6)

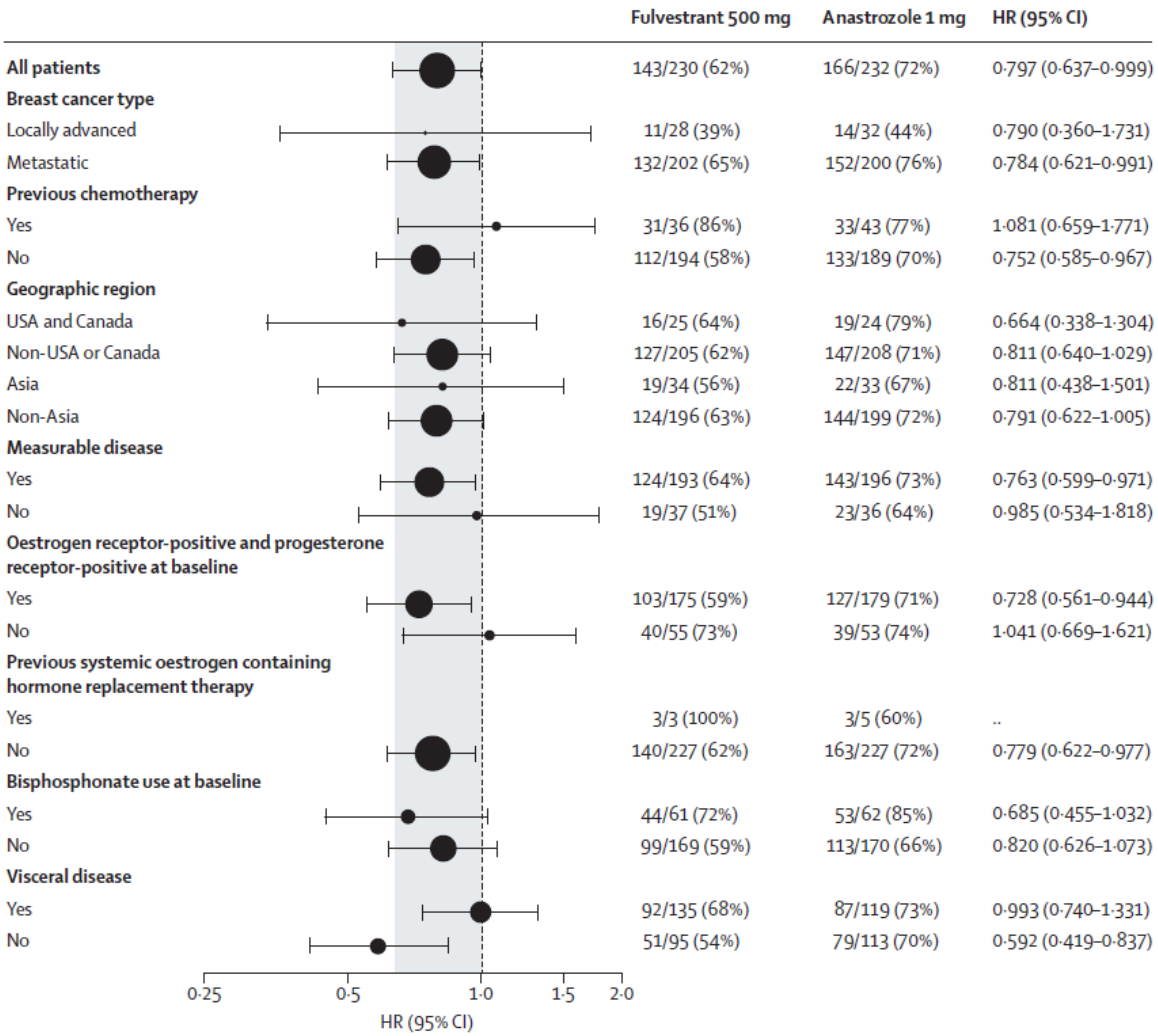


4.8.2 FALCON

Primary efficacy outcome - PFS

As discussed previously in XXX, pre-specified analyses were performed for multiple treatment subgroups in the FALCON trial (Figure 20). Treatment effects were largely consistent with the primary analysis across prespecified patient subgroups (global interaction test p=0·1061), i.e. improvement in PFS numerically favoured fulvestrant 500mg (Figure 20)(7).

Figure 20: Forest plot of PFS by subgroup (ITT analysis, (7))



SOURCE: (7)
[a] Prior chemotherapy for locally advanced or metastatic disease
[b] ER +ve and PgR +ve at baseline equal to "No" means that subject is ER –ve or PgR –ve at baseline.
Note: Results are presented on the log scale, x-axis labels are on the linear scale. Hazard ratio (fulvestrant 500mg: anastrozole) and 95% CI. A hazard ratio of <1 favours fulvestrant. The analysis was performed using a stratified log-rank test (with IVRS-derived stratification factors). The subgroup analysis was performed using a log-rank test.
CI: Confidence interval; ER: Oestrogen receptor; HRT: Hormone replacement therapy; IVRS: Interactive voice response system; PgR: Progesterone receptor

Secondary variables

The key secondary endpoints ORR and OS are part of an MTP to strongly control type-I error. Secondary endpoints were only to be tested for statistical significance if the primary endpoint (PFS) was significant. As the analysis of PFS met the criteria for statistical significance (1-sided p=0.0243, ie, p≤0.025), statistical testing of secondary endpoints was appropriate.

Overall survival

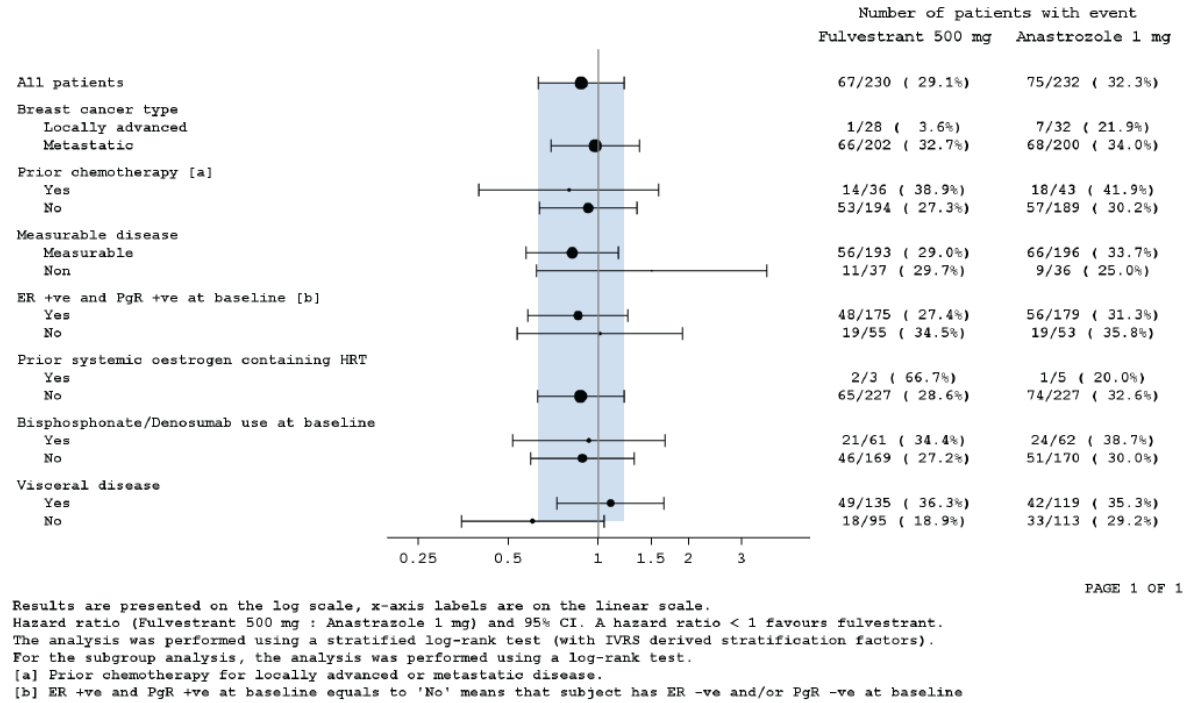
The OS data were immature at the time of the interim analysis (31%), to the extent that median OS could not be calculated. A further analysis of OS will be conducted when these data are more mature. However, the available survival data numerically favour fulvestrant. There was no statistically significant difference in OS between the treatment arms (HR 0.875; 95% CI 0.629 to 1.217; 2-sided p=0.4277, Table 21) (7).

Table 21: Summary of OS and survival status at the time of PFS analysis (ITT analysis set)

	Fulvestrant 500mg (n=230)	**Anastrozole 1 mg (N=232)**
Number (%) of subjects with events	67 (29.1)	75 (32.3)
Hazard ratio (95% CI)	0.875 (0.629, 1.217)	
1-sided p-value	0.2138	
2-sided p-value	0.4277	
Total number of deaths	67	75
25th percentile OS (months) a	22.2	21.1
95% CI for 25th percentile	(18.20, 28.19)	(17.31, 25.69)
Still in survival follow up b	137 (59.6)	131 (56.5)
Terminated prior to death c	26 (11.3)	26 (11.2)
Voluntary discontinuation by subject	19 (8.3)	23 (9.9)
Subject lost to follow-up	5 (2.2)	1 (0.4)
Other	2 (0.9)	2 (0.9)
a Calculated using the Kaplan-Meier technique. b Included subjects known to be alive at data cut-off. c Included subjects with unknown survival status or subjects who were lost to follow-up. Note: The analysis was performed using a stratified log-rank test with factors for prior chemotherapy for locally advanced or metastatic disease (yes/no) and measurable disease at baseline (yes/no). A hazard ratio of <1 favours fulvestrant. CI confidence interval; NC not calculable due to insufficient data; OS overall survival.		

An OS sensitivity analysis was conducted which demonstrated results consistent with the overall analysis of OS (Figure 21).

Figure 21: Overall survival at the time of the PFS analysis, Forest plot, by subgroup (ITT analysis set (68))



[a] Prior chemotherapy for locally advanced or metastatic disease.

[b] ER +ve and PgR +ve at baseline equals to 'No' means that subject has ER-ve and/or PgR –ve at baseline.

Analysis performed using a stratified log-rank test (with IVRS derived stratification factors).

Median duration of follow-up for OS was 25.00 months (range: 0.1 to 38.3 months) in the fulvestrant arm and 24.79 months (range: 0 to 37.9 months) in the anastrozole arm. The total duration of follow-up for OS was similar in the fulvestrant (5263.6 months) and anastrozole (5262.4 months) arms.

4.9 Meta-analysis

The methods and results of a network meta-analysis are presented in Section 4.10.

4.10 Indirect and mixed treatment comparisons

Search strategy

The search strategy is fully described in Section 4.1 and Appendix A.

Study selection

The study selection criteria are described in Section 4.1. Of the 44 studies included in the master network, 38 were excluded from further consideration due to a variety of reasons (terminated or discontinued studies, clinically non-relevant comparators, no extractable data and no link to an evidence network) to provide a core network of 6 studies (Figure 6, Figure 22 and Table 22).

Figure 22: Core relevant evidence network.

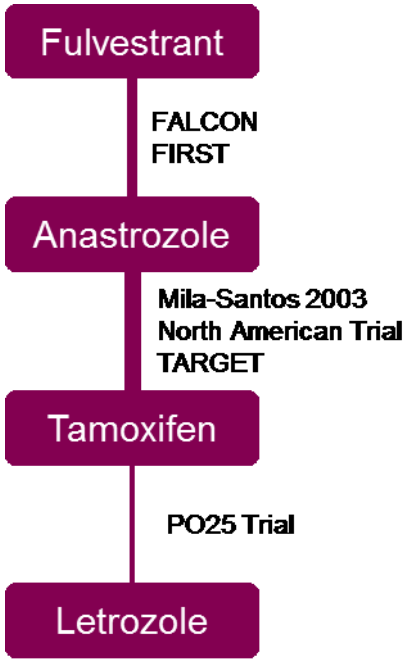


Table 22: Summary of the trials used to carry out the indirect or mixed treatment comparison

References of trial	Fulvestrant 500mg	Anastrozole 1mg	Tamoxifen 40 or 20mg	Letrozole 2.5mg
FALCON (7)	Yes	Yes		
FIRST (5)	Yes	Yes		
Milla-Santos 2003 (66)		Yes	40mg	
North American Trial (10)		Yes	20mg	
TARGET (11)		Yes	20mg	
PO25 Trial (12)			20mg	Yes

Varied types of efficacy measures were reported across the studies contributing to the relevant evidence network. The key efficacy and tolerability outcomes reported across these studies are summarized in Table 23.

Table 23: Outcomes reported across the studies to be included in the NMA

Study Name	PFS	OS	ORR	CBR	OS rate	PFS rate	DoR	TTF	Safety
FALCON trial (7)	✓	-	✓	✓	✓	✓	✓	-	✓
FIRST study (5)	✓	✓	✓	✓	✓	✓	-	✓	✓
Milla-Santos 2003 (66)	✓	✓	✓	✓	✓#	✓#	-	-	✓
North American trial (10)	✓	✓**	✓	✓	✓**#	✓#	✓	✓	✓
TARGET trial* (11)	✓	✓**	-	-	✓**#	✓	-	-	-
PO25 trial* (12)	✓	✓	✓	✓	-	-	-	-	-

OS: Overall survival; PFS: Progression-free survival; ORR: Overall response rate; CBR: Clinical benefit rate; DoR: Duration of response; TTF: Time to treatment failure

*Studies reporting subgroup data of interest

**OS data reported from combined analysis of North American trial and TARGET trial and not for individual studies

#Data reported graphically and were captured using Engauge software

Prior to conducting an NMA, a heterogeneity assessment is important to evaluate the degree of comparability among the studies that form the evidence network. Heterogeneity assessment is important since the studies included in the analysis have to be of sufficient clinical and methodological homogeneity to render the results of analysis meaningful and valid. The results for heterogeneity assessment for each comparison per outcome have been discussed in the following pages.

Data pertaining to PFS or time-to progression (TTP) were reported for all 6 studies. Five of these 6 studies reported TTP instead of PFS and the definitions reported for PFS or TTP across the studies are provided in Table 24 and demonstrate the similarity of definitions between the included studies.

Table 24: Definitions of the outcome of PFS/TTP across studies included in the network of PFS

Study Name	Outcome reported (PFS/TTP)	Definition
FALCON trial (7)	PFS	Time from randomisation until objective disease progression as defined by RECIST 1.1, surgery or radiotherapy to manage worsening of disease or death by any cause (in the absence of progression)
FIRST study (5)	TTP	Time from randomization to the time of the earliest evidence of objective disease progression or death from any cause prior to documented progression
Milla-Santos 2003 (66)	TTP	The time to objective disease progression or death, whichever occurred first
North American trial (10)	TTP	TTP represented the time to objective disease progression or death, whichever occurred first
TARGET trial* (11)	TTP	Time to objective disease progression or death, whichever occurred first
PO25 trial* (12)	TTP	Interval between the date of randomization and the earliest date of disease progression. Discontinuation of treatment due to clinical deterioration or death (any cause) were also accounted for disease progression

PFS: Progression-free survival; TTP: Time to progression;

*Studies reporting subgroup data of interest and not for the whole study population

Table 25: Summary of methodological characteristics among the included trials

Study name	Publication type (Primary)	Sample size	Randomization	Blinding	Phase	Primary efficacy end-point	Geographic locations
FALCON trial (7)	CSR	462	Adequate (IVRS/IWRS)	Double blind	III	PFS	USA, Argentina, Brazil, Canada, China, Czech Republic, Italy, Japan, Mexico, Peru, Poland, Romania, Russia, Slovakia, South Africa, Spain, Taiwan, Turkey, Ukraine, UK
FIRST study (5)	CSR	205	Adequate (Central randomization)	Open label	II	CBR	Brazil, Bulgaria, Czech Republic, France, Italy, Poland, Spain, UK and USA
Milla-Santos 2003 (66)	Journal article	238	Unclear	Unclear	III	Response rates (ORR and CBR), TTP and OS	NR
North American trial (10)	Journal article	353	Adequate (Central randomization)	Double blind	III	TTP and ORR	USA and Canada
TARGET trial* (11)	Journal article	668 (298)	Adequate (Central randomization)	Double blind	III	TTP and ORR	Europe, Australia, New Zealand, South America, and South Africa
PO25 trial* (12)	Journal article	916	Adequate (Computer generated randomization)	Double blind	III	TTP	NR

PFS: Progression-free survival; TTP: Time to progression; ORR: Objective response rate; CBR: Clinical benefit rate; OS: Overall survival; CSR: Clinical study report; IVRS: Interactive voice response system; IWRS: Interactive web response system
*Studies reporting subgroup data of interest. Baseline characteristics reported for whole population; in sample size, number in brackets represents subgroup population of interest

Clinical characteristics

In terms of median age of patients and the proportion of patients with metastatic disease at baseline, the studies were largely similar (Table 26). Performance status measurements (i.e. ECOG or Karnofsky status) were less routinely reported, but where information was available, studies were broadly similar in having the majority of subjects with high performance scores (i.e. 0-1 ECOG or >70 Karnofsky scores).

Receptor status and exposure to prior endocrine therapies

Two of the 6 included studies reported less than 85% patients who were HR+ had been recruited and HER2 status was only reported in the 2 studies investigating fulvestrant in ABC. It is important to note that a third of patients recruited to the PO25 study were not HR+ (12), suggesting that the ITT population in this study may not be as similar to the other studies.

All 6 studies recruited a majority of patients (>70%) who were endocrine naïve. Indeed, excluding the FIRST study ((5) for which patient level data was available), the minimum proportion of endocrine naïve patients in the remaining studies was 80%, indicating a reasonable level of homogeneity across studies in terms of exposure to previous therapies of interest.

Other potential sources of heterogeneity

Three of the 6 studies reported data pertaining to race/ethnicity of the recruited patients (Table 28). The studies reporting such data were largely similar as the majority of recruited patients across these studies were White. The proportion of White patients across these studies ranged from 76% (7) to 97% (5).

All 6 studies reported data pertaining to metastatic sites(Table 28). The studies were largely comparable in terms of metastatic sites of the disease. The proportion of patients with visceral metastasis ranged from about 30 (11) to 59% (7). Two studies (11, 66) recruited more than 40% patients with bone metastasis while bone metastasis was less evident in the remaining studies with two studies (5, 7) recruiting less than 10% patients with bone metastasis.

Table 26: Summary of clinical characteristics among the included trials for PFS

Study name	Treatment arms	Median age (years)	Measurable disease at baseline (%)		Disease at baseline (%)		ECOG/WHO performance status (%)				Karnofsky performance status (%)				
			Yes	No	Locally advanced	Metastatic	0	1	≥2	0-1	90-100	80-90	70-80	60-70	<60
FALCON trial (7)	FUL	64	84	16	12	88	51	46	3	-	NR	NR	NR	NR	NR
	ANA	62	85	14	14	86	50	45	5	-					
FIRST study (5)	FUL	66	87.3	12.7	18.6	81.4	NR	NR	NR	NR	NR	NR	NR	NR	NR
	ANA	68	90.3	9.7	17.5	82.5									
Milla-Santos 2003 (66)	ANA	60.2	NR	NR	-	100	81	12	7	-	NR	NR	NR	NR	NR
	TAM	60.6	NR	NR	-	100	78	14	9	-					
North American trial (10)	ANA	68	68.4	31.6	-	99#	NR	NR	NR	NR	NR	NR	NR	NR	NR
	TAM	67	76.9	23.1	-	99#									
	TAM	65.9	76	22	-	98#					25	55	-	16	3
TARGET trial* (11)	ANA	67	89	11	-	100#	NR	NR	NR	NR	NR	NR	NR	NR	NR
	TAM	66	87	13	-	100#									
PO25 trial* (12)	LET	65	NR	NR	-	93	NR	NR	NR	NR	56	-	38	-	7
	TAM	64	NR	NR	-	92					58	-	33	-	9

#Proportion of patients with metastatic disease were calculated by addition of patients reported with various metastatic sites as dominant site of metastasis

*Studies reporting subgroup data of interest. Baseline characteristics reported for whole population

ECOG PS: Eastern Cooperative Oncology Group Performance Status; NR: Not reported

FUL: Fulvestrant; ANA: anastrozole; LET: letrozole; TAM: tamoxifen

Table 27: Summary of clinical characteristics among the included trials for PFS

Study name	Receptor status (%)				Endocrine naïve (%)	Prior Therapies		
	HR+	ER+	PgR+	HER2-		Surgery	Radiotherapy	Chemotherapy
FALCON trial (7)	100	99	77	99.8	99.4	59	22.5	35 (19.2% in neo/adjuvant and 17% in advanced setting)
FIRST study (5)	100	97	80	47	74	NR	NR	26% in adjuvant setting
Milla-Santos 2003 (66)	100	100	NR	Unclear	100	NR	NR	28% CMF and 15% Doxorubicin in adjuvant setting
North American trial (10)	89	85	69	Unclear	80	NR	NR	27% in adjuvant setting
PO25 trial* (12)	66	NR	NR	Unclear	82	NR	NR	32% (22% in adjuvant and 10% in advanced setting)
TARGET trial* (11)	45	43	26	Unclear	89	NR	NR	23% in adjuvant setting

*Studies reporting subgroup data of interest. Baseline characteristics reported for whole population

CMF: Cyclophosphamide, methotrexate and 5-fluoro-uracil; ER: Oestrogen receptor; HR: Hormone receptor; HER2: Human Epidermal Growth Factor Receptor-2; NR: Not reported; PgR: Progesterone receptor

Table 28: Summary of clinical characteristics among the included trials for PFS

Study name	Treatment arms	Race				Metastatic sites#						Median DFI (months)	Disease free interval (DFI)		
		White	Black	Asian	Others	Visceral	Soft tissue	Bone	Lungs	Liver	Other		<12 months	>12 months	>24 months
FALCON trial (7)	FUL	76	2	16	7	59	4	10	-	-	-	NR	NR	NR	NR
	ANA	75	2	15	9	51	3	10	-	-	-				
FIRST trial (5)	FUL	95	3	-	2	47	2	10	29	15	1	NR	NR	NR	NR
	ANA	99	-	-	1	56	-	8	41	14	-				
Milla-Santos 2003 (66)	ANA	NR	NR	NR	NR	-	15	38	47	-	-	NR	NR	NR	NR
	TAM					-	13	42	45	-	-				
North American trial (10)	ANA	NR	NR	NR	NR	49	23	40	44	8	4	NR	NR	NR	NR
	TAM					48	28	33	37	17	5				
TARGET trial* (11)	ANA	NR	NR	NR	NR	30	68	46	22	9	-	NR	NR	NR	NR
	TAM					38	69	48	31	10	-				
PO25 trial* (12)	LET	86	-	-	-	43	25	32	-	13	-	70.8	-	-	55
	TAM					46	25	29	-	12	-	66	-	-	54

#Data overlapping and might not add up to 100%

*Studies reporting subgroup data of interest. Baseline characteristics reported for whole population

ANA: anastrozole; FUL: fulvestrant: LET; letrozole: TAM; tamoxifen

Further considerations for network meta-analysis

- Dose of tamoxifen was pooled for this analysis as FDA has approved both 20 mg and 40 mg dose of tamoxifen, while EMA has only approved 20 mg dose of tamoxifen for the treatment in breast cancer. The Milla-Santos study (66) was the only one of the 4 included studies that used the higher dose and it is unclear what effect this had on the generalizability of the outcomes from that study with the rest of the evidence network.

- OS results from individual studies (North American and TARGET trial (10, 11)) were not available; therefore, combined OS results (71) from these trials were considered in the analysis.

- The inclusion of Milla-Santos study (66) led to heterogeneity when analysis was conducted for OS outcome, i.e. I^2=84.2%, which according to Cochrane is considered substantial heterogeneity (>60%). Similarly, for PFS outcome, inclusion of Milla-Santos study (66) in base-case as well as sensitivity analysis resulted in substantial heterogeneity, i.e. I^2=96.1%. This heterogeneity is most likely a result of the biased reporting of PFS (or TTP) and OS which were only calculated for patients achieving a CB (complete response, partial response or stable disease). Therefore, the analyses for OS and PFS outcomes were conducted without considering the Milla-Santos study (66) in the network.

4.10.1 Method of network meta-analysis

Patient-level data was available for the following studies: FALCON, FIRST, and the combined North American and TARGET trials (hereafter referred to as NorthAmTarget). For the PO25 trial (12), the reported Kaplan-Meier curves were digitised (WebPlotDigitizer version 3.6), and the algorithm presented in Guyot et al 2012(72) was run in the statistical package R to reconstruct patient-level data.

For those trials identified in the systematic literature review and where patient-level data was available (FIRST and NorthAmTarget) the inclusion and exclusion criteria from the FALCON trial was applied to each treatment arm in both trials to better

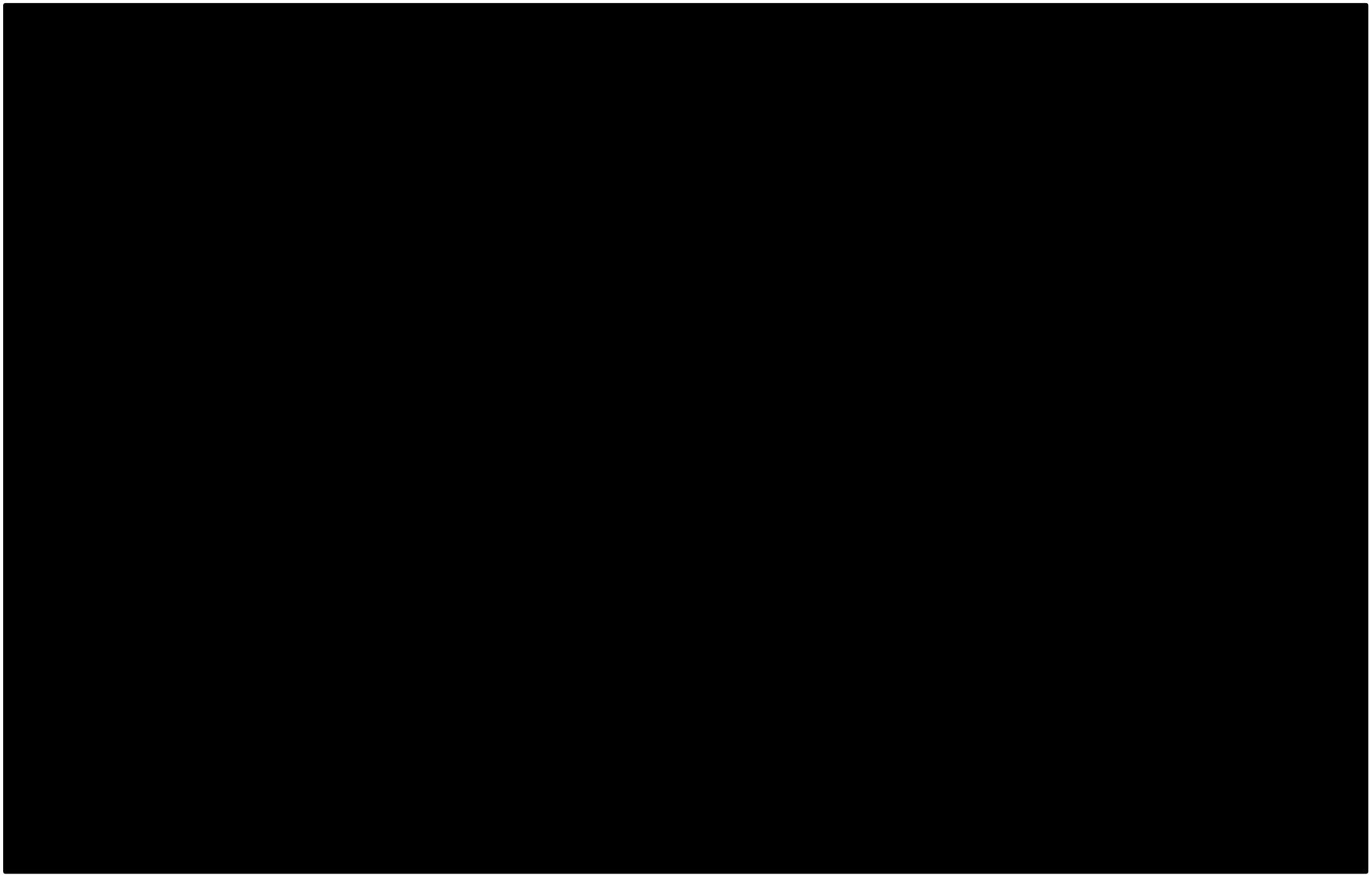
match the FALCON trial population (7). This couldn't be accomplished with the PO25 trial as only reconstructed patient-level data was available (12).

The Kaplan-Meier plots of PFS and OS from FALCON, FIRST, NorthAmTarget, PO25 are presented in Figure 23 and

Figure 24, respectively. The plots for FIRST and NorthAmTarget represent the trial data after the inclusion and exclusion criteria for FALCON had been applied (7).

Figure 23: PFS KM plots from FALCON and studies identified in the SLR

Figure 24: OS KM plots from FALCON and studies identified in the SLR



Visual inspection of the PFS Kaplan-Meier plots indicated that the treatment arms separated and remained separated over the course of each trial. Visual inspection of the OS Kaplan-Meier plots indicated that in both the PO25 trial and the NorthAmTarget trial the plots crossed, whilst OS in the FIRST study showed separation took place around 21 months. This suggests that traditional methods for NMA might not be appropriate, and alternative methods need to be explored.

Traditional methods for NMA utilize the summary data available for each study (hazard ratios in this instance) and estimates the difference in treatment effect in terms of the impact on these summary data. This assumes a constant relative treatment effect over time (i.e. proportional hazards). The proportional hazards assumption is, in this instance, likely violated due to the crossing of Kaplan-Meier plots in at least two studies for OS (PO25 and NorthAmTarget), and a late separation of the curves for FIRST OS data.

Evaluation of the log cumulative hazard plots for PFS for FALCON, FIRST, PO25 and NorthAmTarget (see Figure 25) suggest that the assumption of proportional hazards is not reasonable across all the trials included in the NMA. A similar conclusion was reached for OS (see Figure 26).

The use of hazard ratios limits the choice of distributions that can be used to extrapolate key trial outcomes, as it would not be theoretically possible to apply a hazard ratio in the case of the lognormal or log-logistic distributions. It was therefore judged inappropriate to derive an NMA using standard methods using reported summary data. Alternative methods are available which use patient-level data (available or estimated through digitised Kaplan-Meier data) to estimate the effect of treatment on the parameters (shape and scale) of the fitted parametric survival distributions(13). This allows for the synthesis and comparison of data from disparate sources and the inclusion of the lognormal and log-logistic distributions in a statistically valid manner.

The alternative methodology developed by Ouwens et al(13), allows a simultaneous extrapolation and network meta-analysis of Kaplan-Meier curves for all relevant comparators to be derived from available RCTs. This is achieved by relating the Kaplan-Meier curves of each of the competing interventions directly to the

parameters of each of the parametric distributions tested. Although the Kaplan-Meier plots were only observed to cross for OS data, the methodology developed by Ouwens et al was also applied for PFS, both for consistency and to allow the full range of traditional parametric survival curves to be explored.

In fixed-effects meta-analyses, it is assumed that treatment effects can be estimated directly from the trial data, while in random-effects meta-analyses it is assumed that the treatment effects are drawn from a common distribution with a variance parameter equal to the between-studies variance, or heterogeneity. A random effects model is more complex than a fixed-effects model as it requires more parameters, and therefore the added flexibility means it will usually provide a better fit to the data; however, in this instance, given the limited number of trials included in each network, a fixed effects analysis was deemed more appropriate. A fixed effects model was used to simultaneously extrapolate Kaplan-Meier data over time by means of each of the parametric distributions included (Weibull, Gompertz, log-logistic, lognormal and generalised gamma), to synthesize and to indirectly compare the different treatments The scale and non-location (hereafter referred to as 'shape') parameters for each of the distributions were estimated for the baseline comparator, and were used as the anchor to obtain estimates for the shape and scale for the other technologies included in the economic evaluation. This approach accounts for the possible differences in both shape and scale within-trial without breaking randomisation.

In the 1 and 2-parameter models, the difference in location and other parameters are modelled against this baseline treatment (anastrozole) and baseline study (FALCON) by using arm and study as indicators on the predictive scales. For the Generalized Gamma, only the difference in mean and sigma are modelled at the predictive scale. Allowing this higher flexibility allows all models, except exponential, to be modelled without assumptions of proportional hazard ratios/odds/acceleration factors.

For completeness, the following two types of analyses were undertaken:

- 'All shapes' model: Above described scenario.

- ‘No shape arm’ model: The shape parameter is regarded as fixed between treatment arms – tantamount to assuming a proportional treatment effect [proportional hazards ratio/ proportional acceleration factor].

Please note that the results are only adjusted for between-study differences for validation purposes (assessing the model fit) and is treated as a nuisance variable in the main analysis. We visually inspect the fit of the parametric distributions to individual trial data. For the purposes of the economic evaluation, the results are only adjusted for differences in shape parameters between trial arms at the predictive scale, if required.

The ‘no shape arm’ model is more assumptive and restrictive than the ‘all shapes’ model as it does not allow the shape parameter to differ between treatment arms. This model does not appear to lend itself to the synthesis and extrapolation of OS data due to the observed crossing of curves in the PO25 and NorthAmTarget data. The ‘no shape arm’ could, potentially, be appropriate for the extrapolation of PFS, as there is no evidence of crossing curves in any of the trials included in the network.

Based on evaluation of the log-cumulative hazard plots, the statistically significant differences in shape parameter for letrozole observed in the results of the fixed effects NMA for OS (see Table 29), and visual inspection of the improved curve fits resulting from the ‘all shapes’ models compared with the ‘no shape arm’ models to the PO25 trial data (see Figure 54; Appendix A), the ‘all shapes’ model was chosen to provide the base case survival curves for PFS and OS used in the economic model. The resulting curves from the ‘no shape arm’ models are tested in sensitivity analysis.

Due to the complexity in the interpretation of setting two of the three-parameter generalised gamma model equal, this distribution was not included in the ‘no shape arm’ models.

Additional considerations for PO25

The PO25 trial was a large, randomised, double-dummy trial, which was powered to demonstrate a 20% reduction in the risk of progression with letrozole (12). The study was designed such that upon disease progression or discontinuation of therapy due

to an adverse event, a patient could be switched over to the alternative treatment in a double-blind manner. In PO25, 53% of patients starting on letrozole crossed over to tamoxifen, 44% of patients starting on tamoxifen crossed over to letrozole, and the two survival curves crossed at around 3 years, at which point cross-overs where almost complete (12). There is therefore a risk that the OS analysis could be confounded.

The authors report that whilst a statistically significant difference between treatment arms was not observed, there was a significant survival advantage associated with letrozole in the first two years of the trial. However, as the authors note, as cross-over was not randomised and was not independent of treatment, the interpretation of a long-term survival benefit associated with letrozole should be considered speculative (12).

Patient-level data from the PO25 trial was not available (12); the Kaplan-Meier curves were digitised and an algorithm run in R to reconstruct the patient-level data; therefore, methods to adjust for potential bias due to crossover were not able to be implemented. Results of the OS fixed effects network meta-analysis for letrozole should be therefore be considered with caution. In the economic model, a scenario analysis is presented where the efficacy of letrozole is assumed to be equivalent to that of anastrozole (Table 101). This assumption has been used in many previous NICE appraisals, most recently in the ongoing appraisal of pabloclicib in combination with letrozole (73), is widely accepted by clinicians (54) and has recently been shown in a large (n=4136) randomised study to not have significantly superior efficacy or safety compared with anastrozole in postmenopausal patients with HR+, node +ve early breast cancer (74).

Figure 25: Log cumulative hazard plots (PFS)

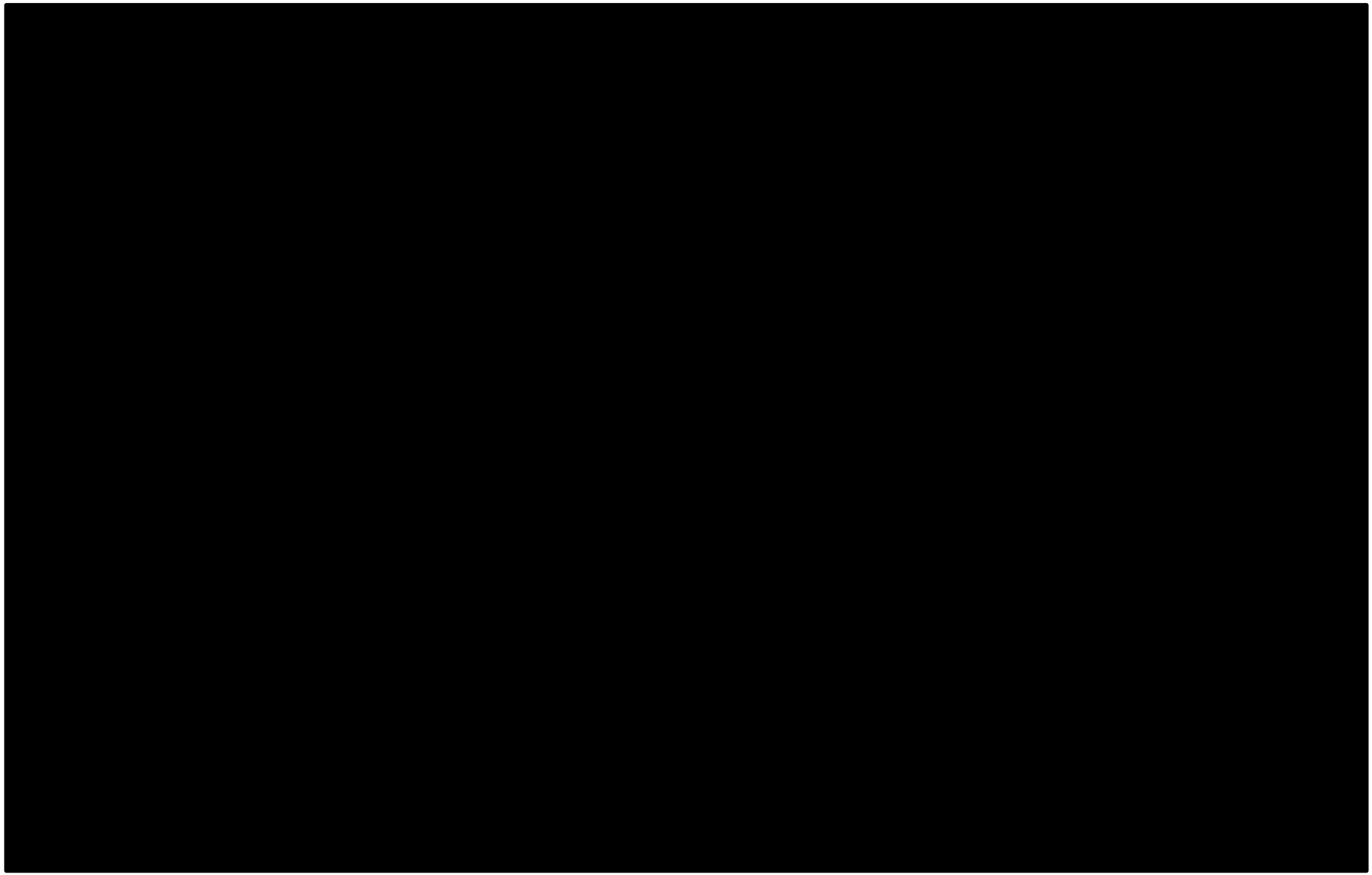
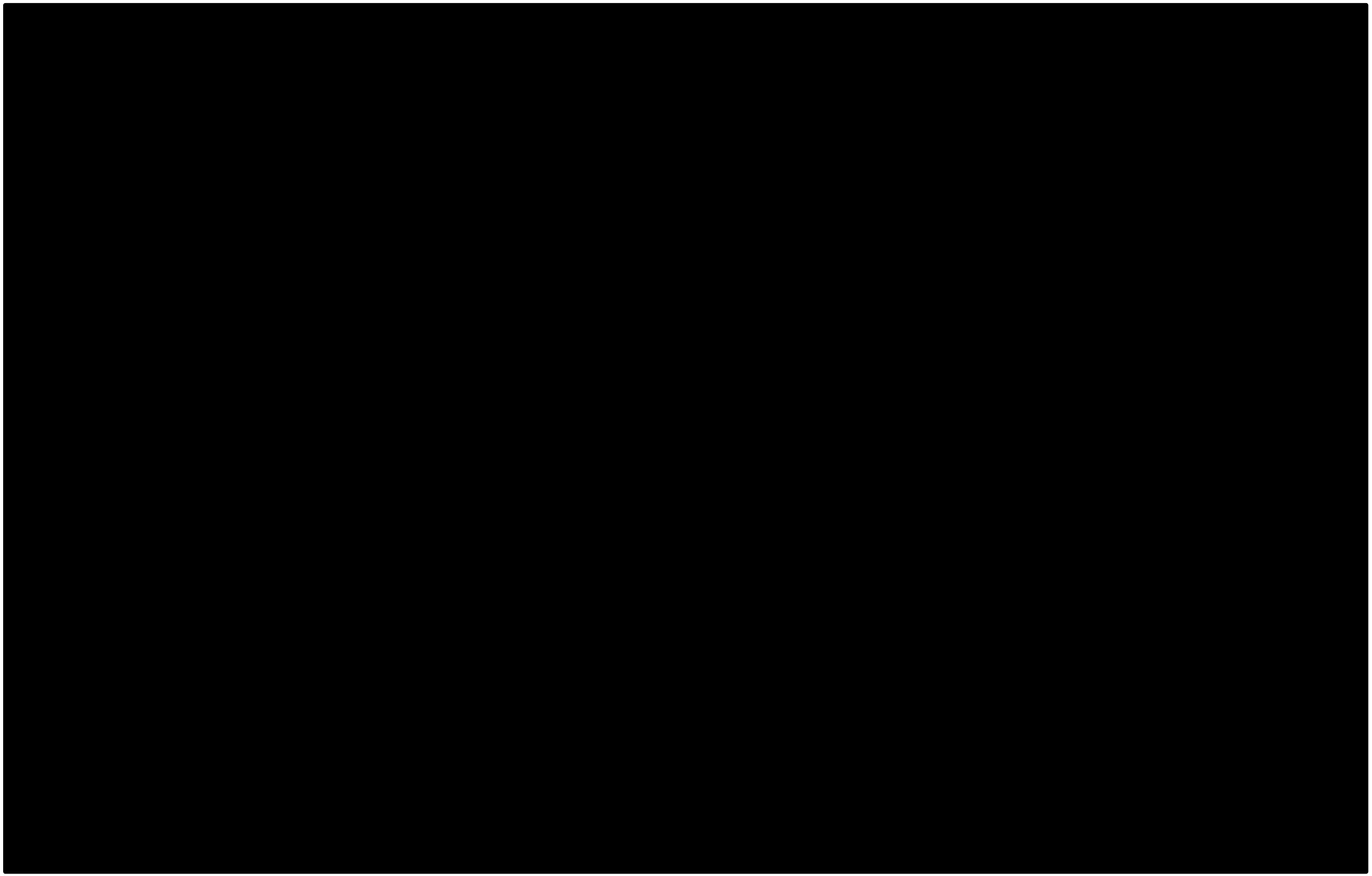


Figure 26: Log cumulative hazards plots (OS)



4.10.2 Network meta-analysis results

The results of the network meta-analysis for the ‘all shapes’ model are presented below. The results of the network meta-analysis when using the ‘no shape arm’ model are presented in Appendix B.

Table 29 presents the results of the PFS NMA: baseline shape and scale and difference from baseline for each of the treatment alternatives versus (FALCON) anastrozole. Fulvestrant and tamoxifen demonstrated statistically significant differences in the scale parameter when compared against anastrozole for the Weibull, log-logistic, lognormal and generalised gamma distributions. Both fulvestrant and tamoxifen are also associated with statistically significant differences in the shape parameter of the log-normal distribution when compared against anastrozole. Letrozole did not demonstrate any statistically significant differences in either shape or scale across any of the distributions when compared with anastrozole.

Table 29: Fixed effect network meta-analysis PFS results: baseline parametric distribution parameters and difference from baseline for treatment alternatives versus (FALCON) anastrozole

Weibull	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Gompertz	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Log-logistic	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Lognormal	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Generalised gamma	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Common parameter	[redacted]					
Q	[redacted]					

Abbreviations: L, lower; PFS, progression-free survival; U, upper.

Figure 27: PFS as estimated from fixed effects network meta-analysis models

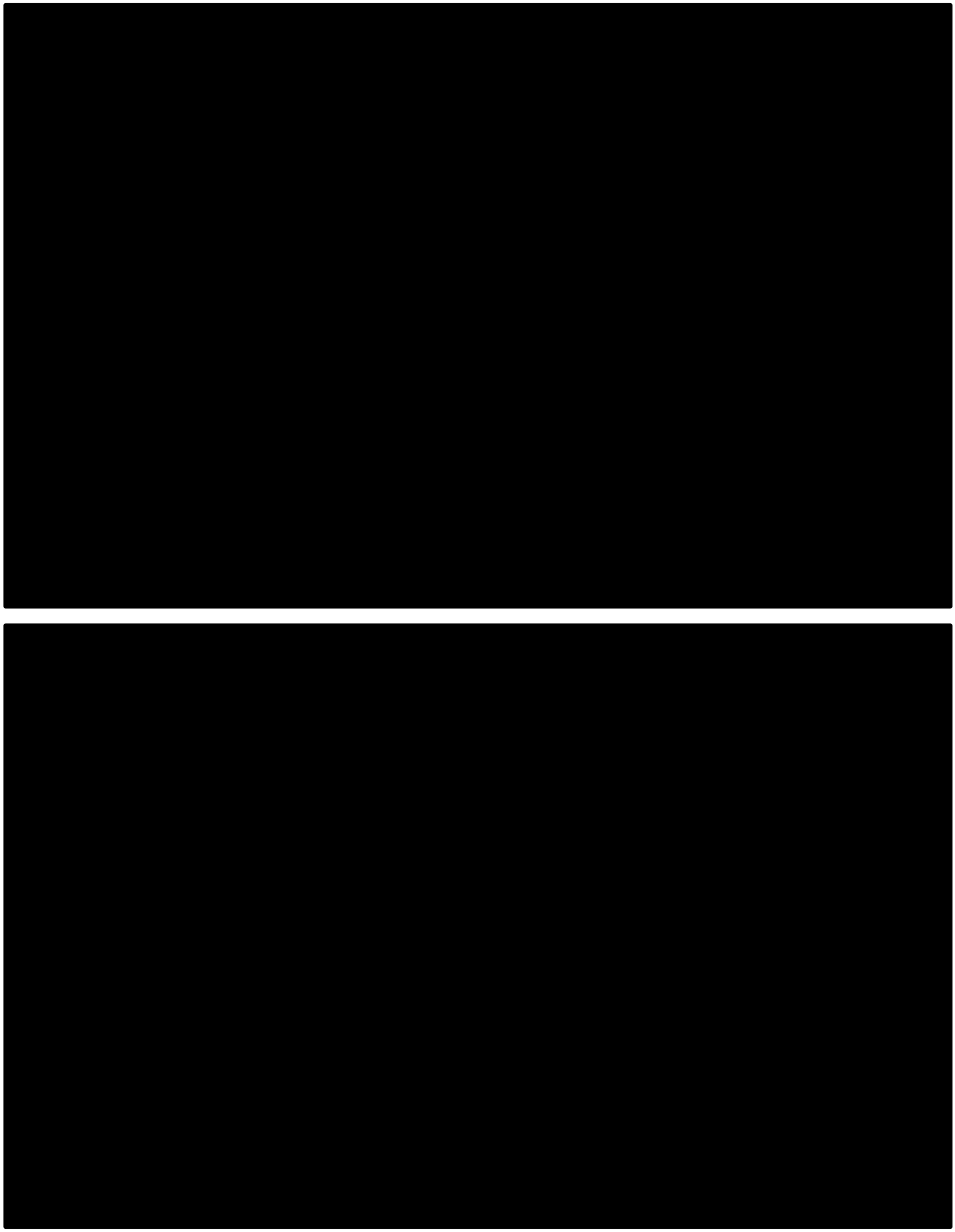


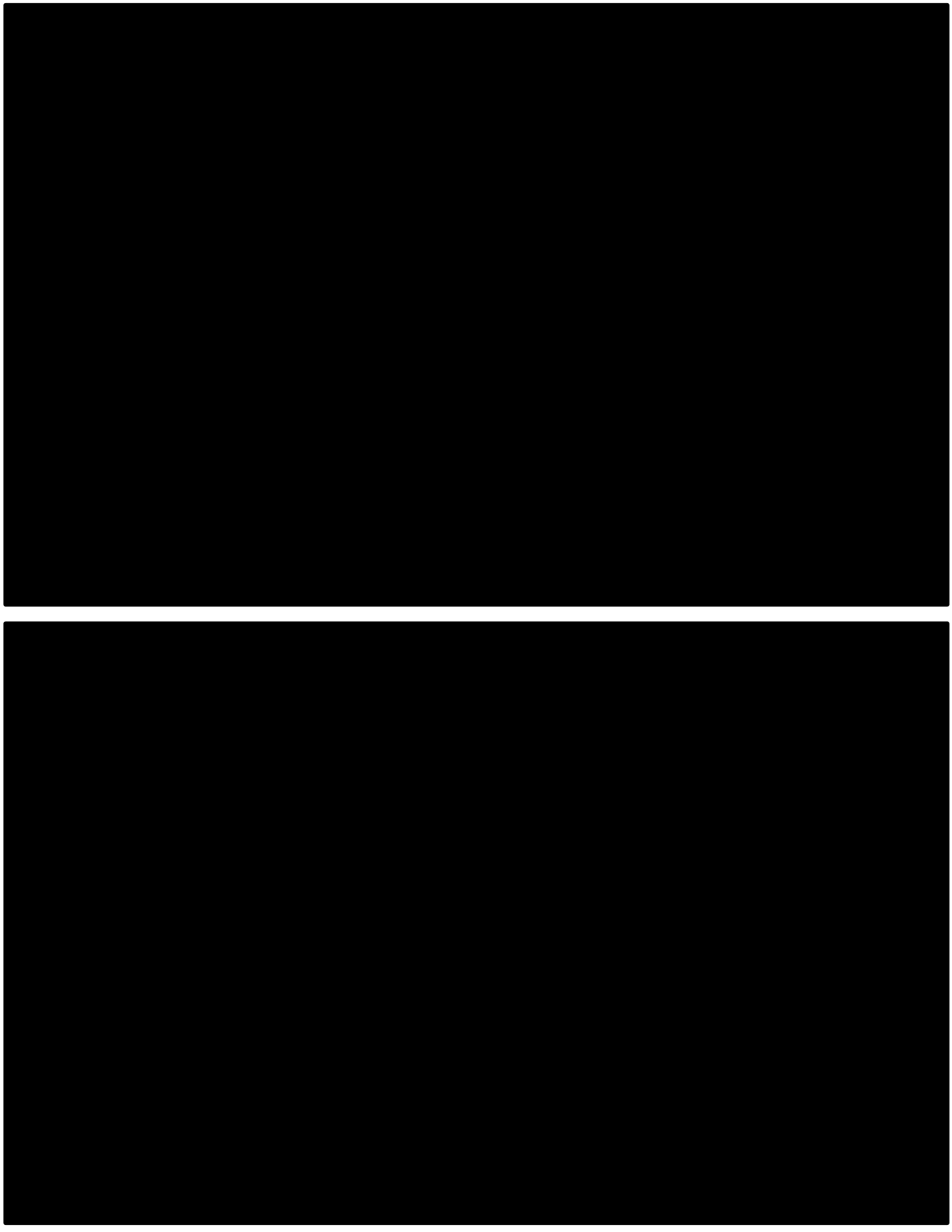
Table 30 presents the results of the NMA for OS. Letrozole demonstrated a statistically significant difference in shape compared against anastrozole for the Weibull, Gompertz, log-logistic and generalised gamma distributions. For the Gompertz distribution, letrozole also demonstrated a statistically significant difference in scale. Figure 28 presents the estimated parametric survival curves for OS from the NMA.

Table 30: Fixed effect network meta-analysis OS results: baseline parametric distribution parameters and difference from baseline for treatment alternatives versus (FALCON) anastrozole

Weibull	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Gompertz	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Log-logistic	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Lognormal	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Generalised gamma	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Common parameter	[redacted]					
Q	[redacted]					

Abbreviations: L, lower; OS, overall survival; U, upper.

Figure 28: OS as estimated from fixed effects network meta-analysis models



4.10.3 Process for selecting parametric survival curves

For the purpose of the economic modelling, it was necessary to extrapolate OS and PFS beyond the duration of the FALCON clinical study (7). The process for selecting parametric survival curves fitted to patient level data from the trials comprising the PFS and OS networks was based on the methods outlined in Technical Support Document 14 prepared by the Decision Support Unit for NICE(75). The assumption of proportional hazards was assessed via visual inspection of log-cumulative hazards plots for PFS and OS for each of the trials included in the NMA (see section 4.10.1). To assess the fit of each distribution to the NMA dataset, the Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) were compared across distributions. As the AIC and BIC only reflect the goodness of fit to the observed data, they do not provide information with which to inform the most appropriate extrapolation of each distribution beyond the observed data. Additional visual inspection of the distributions and clinical validation of the extrapolated output with UK clinical experts was also performed.

4.10.4 Progression-free survival extrapolation

4.10.4.1 Statistical goodness of fit

The results of fitting the standard parametric distributions to the NMA PFS dataset are shown in Table 31. The AIC and BIC statistics show that the log-logistic distribution provided the best fit, followed by the generalised gamma and the lognormal distributions; the Gompertz distribution is considered to have the least-best fit.

Table 31: AIC and BIC statistics for PFS based on fixed effects NMA model

Distribution	AIC	AIC rank	BIC	BIC rank
Log-logistic	8624.747	1	8703.403	1
Generalised gamma	8627.055	2	8711.329	2
Lognormal	8636.065	3	8714.721	3
Weibull	8687.484	4	8766.140	4
Gompertz	8720.786	5	8799.441	5

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; NMA, network meta-analysis; PFS, progression-free survival.

4.10.4.2 Visual inspection

Figure 29 presents the estimated survival curves for fulvestrant and anastrozole fitted to the PFS data from FALCON. For visual validation of the fitted survival curves against the non-FALCON trial data, the between-study differences, relative to FALCON, were incorporated in the survival functions.

The Gompertz and Weibull distributions display more conservative extrapolations of PFS than the log-logistic, generalised gamma and lognormal, and provide a better visual fit in the tail of the FALCON PFS data; however, the Gompertz distribution provides visually poor fits to the FIRST and PO25 trials relative to the Weibull and other distributions (see Figure 30 and Figure 32). The log-logistic and lognormal distributions provide a good visual fit to all of the trial data apart from FIRST, but the curves appear to flatten in later time periods and both distributions display long 'tails'. The generalised gamma distribution provides a reasonable visual fit to the observed data and displays a more conservative projection than the log-logistic or lognormal distributions (see Figure 29, Figure 30, Figure 31 and Figure 32).

Figure 29: FALCON PFS study fit with fixed effects 'all shapes' network meta-analysis model

Figure 30: FIRST PFS study fit with fixed effects 'all shapes' network meta-analysis model adjusted for between-study differences

Figure 31: NorthAmTarget PFS study fit with fixed effects 'all shapes' network meta-analysis model adjusted for between-study differences

Figure 32: PO25 PFS study fit with fixed effects 'all shapes' network meta-analysis model adjusted for between-study differences

4.10.4.3 Expert clinical opinion

Seven clinicians in England provided expert opinion on the proportion of those patients included in the FALCON trial who are expected to be progression-free at 1, 2, 5 and 10 years when treated with anastrozole (54). The clinician opinions are summarised in Table 32. Clinical expert opinion indicates that the log-logistic, generalised gamma and lognormal distributions provide realistic projections at 5 and 10 years for those patients treated with anastrozole.

Table 32: KOL opinion on PFS at 1, 2, 5 and 10 years (54)

	1 year	2 years	5 years	10 years
KOL estimate	50-60%	30-40%	5-10%	1-5%

Abbreviation: KOL, key opinion leader.

4.10.4.4 Survival curve selection

The generalised gamma distribution was chosen as the most appropriate method of extrapolating PFS based on visual inspection; the AIC and BIC values (second best fit) and clinical expert opinion for anastrozole. Guidance from NICE's Decision Support Unit recommends that the same parametric models are applied for all treatment arms per outcome(75); therefore, the generalised gamma distribution was chosen for all treatment arms. The parameters for the generalised gamma distribution are shown in Table 33. A plot of the curves for all comparators is shown in Figure 33. Alternative parametric functions for PFS were explored in sensitivity analysis.

Table 33: Generalised gamma parameter estimates for PFS based on fixed effects NMA model

Generalised gamma	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Common parameter	[redacted]					
Q	[redacted]					

Abbreviations: L, lower; PFS, progression-free survival; U, upper.

Figure 33: PFS as estimated with fixed effects generalised gamma NMA model

4.10.4.5 Sensitivity analysis of alternative parametric curves

The goodness-of-fit statistics indicated that the log-logistic distribution had the best fit to observed data (lowest AIC and BIC values), but was rejected based the flattening of the projected curve in later time periods and the long tail. The lognormal distribution had the third best fit to the observed data based on AIC and BIC but, like the log-logistic, was rejected based on the observed flattening of the projected curve in later time periods and long tail.

The Weibull distribution had the fourth best fit to the observed data based on AIC and BIC. Based on visual inspection the Weibull curve had a superior fit to the tail of the FALCON Kaplan-Meier data for fulvestrant than the log-logistic, generalised gamma and log-normal, but was judged to provide too conservative a projection at 5 years (1.52%) based on a comparison with expert clinical opinion (5-10%, Table 32).

The Gompertz distribution was associated with the worst fit to the observed data based on AIC and BIC statistics. Based on visual inspection the Gompertz curve provides a reasonable fit to the observed Kaplan-Meier data from FALCON, but was rejected on the grounds it provides too conservative a projection at 5 and 10 years

(1.16% and 0%, respectively) when compared with expert clinical opinion (5-10% and 1-5%, respectively, Table 32). Alternative distributions are tested in sensitivity analysis.

4.10.5 Overall survival extrapolation

4.10.5.1 Statistical goodness of fit

The results of fitting the standard parametric distributions to the observed data for OS are shown in Table 34. The AIC and BIC statistics for PFS based on the observed data incorporated into the NMA show that the Weibull distribution provided the best fit, followed by the generalised gamma and the Gompertz distributions; the lognormal distribution is considered to have the least-best fit.

Table 34: AIC and BIC statistics for OS based on NMA

Distribution	AIC	AIC rank	BIC	BIC rank
Weibull	10499.131	1	10577.848	1
Generalised gamma	10500.300	2	10584.640	2
Gompertz	10508.995	3	10587.713	3
Log-logistic	10513.882	4	10592.599	4
Lognormal	10552.618	5	10631.335	5

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; NMA, network meta-analysis; PFS, progression-free survival.

4.10.5.2 Visual inspection

Figure 34 presents the estimated survival curves for fulvestrant and anastrozole from the fixed-effects NMA, fitted to the OS trial data from FALCON. For visual validation of the fitted survival curves against the non-FALCON trial data, the between-study differences, relative to FALCON, were incorporated in the survival functions.

The Gompertz, Weibull and generalised gamma distributions display more conservative OS projections than the log-logistic and lognormal. The log-logistic and lognormal distributions both display long 'tails' with projected OS between 10-15% at 15 years for anastrozole; both the log-logistic and lognormal curves provide similar visual fits to across the trials incorporated into the NMA (see Figure 34, Figure 35, Figure 36 and Figure 37). The generalised gamma and Weibull distributions provide similar OS projections with the Weibull curve providing slightly more conservative estimates; this observation is seen across all the trials incorporated into the NMA. The Gompertz distribution displays the most conservative survival estimates with

100% of the cohort in any of the treatments arms dead at 10 years. The Gompertz distribution provide a very poor visual fit against the individual trial data incorporated in the NMA.

Figure 34: FALCON OS study fit with fixed effects 'all shapes' network meta-analysis model

Figure 35: FIRST OS study fit with fixed effects 'all shapes' network meta-analysis model

Figure 36: NorthAmTarget OS study fit with fixed effects 'all shapes' network meta-analysis model

Figure 37: PO25 OS study fit with fixed effects 'all shapes' network meta-analysis model

4.10.5.3 Expert clinical opinion

Seven clinicians in England provided expert opinion on the proportion of those patients included in the FALCON trial (7) who are expected to be alive at 1, 2, 5 and 10 years when treated with anastrozole (54). The clinician opinions are summarised

in Table 35. Clinical expert opinion indicates that the Weibull, generalised gamma and Gompertz distributions provide realistic projections at 5 years for those patients treated with anastrozole; at 10 years, only the Weibull and generalised gamma distributions provided estimates of OS that were aligned with expert clinical opinion.

Table 35: KOL opinion on OS at 1, 2, 5 and 10 years (54)

	1 year	2 years	5 years	10 years
KOL estimate	75-85%	55-70%	20-30%	5-10%

Abbreviation: KOL, key opinion leader.

4.10.5.4 Survival curve selection

The Weibull distribution was chosen as the most appropriate method of extrapolating OS based on visual inspection; the AIC and BIC values (best fit) and clinical expert opinion for anastrozole. Guidance from NICE's Decision Support Unit recommends that the same parametric models are applied for all treatment arms per outcome(75); therefore, the Weibull distribution was chosen for all treatment arms. The parameters for the Weibull distribution are shown in Table 36. A plot of the curves for all comparators is shown in Figure 38. Using alternative parametric functions that provide plausible OS estimates (generalised gamma) were explored in sensitivity analysis.

Table 36: Weibull parameter estimates for OS based on fixed effects NMA model

Weibull	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: L, lower; OS, overall survival; U, upper.

Figure 38: OS as estimated with fixed effects Weibull NMA model

4.10.5.5 Sensitivity analysis of alternative parametric curves

The goodness-of-fit statistics indicated that the generalised gamma had the second-best fit to the observed data, but was rejected based on the observation that the Weibull curve, which provides a similar fit and projection to the generalised gamma, was more closely aligned with clinical expert opinion of OS at 5 and 10 years for anastrozole (30.7% vs 20-30% and 5.5% vs 5-10%, respectively, Table 35), and provided slightly more conservative estimates of OS for fulvestrant over time.

The Gompertz distribution had the third best fit to the observed data based on AIC and BIC but was rejected based on visual inspection of its fit across all the trials, and for under-projecting OS for anastrozole at 10-years (0.03%) when compared with what was considered clinically plausible by expert clinical opinion (5-10%, Table 35).

The log-logistic and lognormal distributions were ranked as fourth and fifth best fit, respectively, according to the AIC and BIC statistics. Based on visual inspection of the extrapolated sections of the curves, both distributions were rejected due to the projected survival at 5 and 10 years (38-42% and 18-24%, respectively) being in excess of what was considered clinically plausible by expert clinical opinion (20-30% and 5-10%, respectively, Table 35). Alternative parametric distributions that provide plausible long-term estimates of OS are tested in sensitivity analysis.

4.11 Non-randomised and non-controlled evidence

There are no non-randomised or non-controlled studies relevant to this submission.

4.12 Adverse reactions

4.12.1 Safety and Tolerability of fulvestrant

FIRST

Assessment of the safety and tolerability of fulvestrant 500mg and anastrozole was a secondary endpoint in the FIRST study (5). Laboratory tests and incidence of adverse events (AEs) as well as the frequency of 10 pre-specified AEs, were recorded throughout the study. Tolerability was assessed by serious adverse event (SAE) monitoring for up to 8 weeks after the last dose of fulvestrant 500mg or for 30 days after the last dose of anastrozole. Results were reported at 3 timepoints:

1. at first data cut-off, 10 January 2008 (5),
2. first follow-up, 26 March 2010 (75% TTF, (6)) and
3. the final assessment of OS, 15 July 2014 (65% OS, (6)).

The number of patients remaining on randomized treatment at the time of first data cut off was 64 (62.7%) for fulvestrant 500mg and 53 (51.5%) for anastrozole. Median follow-up was 8 months (242.5 days) and 5.9 months (179 days), with median drug exposures of 9.2 months (range, 1 to 20.5 months) in the fulvestrant 500mg group and 6.1 months (range, 0 to 19.8 months) in the anastrozole group. Both fulvestrant 500mg and anastrozole were well tolerated. A total of 143 (70.1%) patients experienced at least one AE; the incidence of serious AEs was 11.9% with fulvestrant 500mg and 9.7% with anastrozole. Only three patients in each group (fulvestrant, 3.0%; anastrozole, 2.9%) discontinued treatment because of an AE. Overall, 11 patients (5.4%) died during the study; the predominant cause of death was disease progression. Only one patient (from the anastrozole group) died because of an AE, which was not considered to be treatment-related.

There were no significant differences between treatments in the incidence of any of the 10 prespecified AEs (Table 3) and there were no clinically important changes in hematologic or clinical chemistry parameters with either treatment.

Table 37: Analysis of pre-specified AE categories within the treatment period at first data cut-off in FIRST (n (%))(5)

Prespecified Adverse Event	Fulvestrant 500mg (n=101)	Anastrozole 1 mg (n=103)	P Two-sided Fisher's exact test
Endometrial dysplasia	0 (-)	0 (-)	1.000
GI disturbances	28 (27.7)	23 (22.3)	0.420
Hot flashes	13 (12.9)	14 (13.6)	1.000
Ischaemic cardiovascular disorders	0 (-)	1 (1.0)	1.000
Joint disorders	14 (13.9)	10 (9.7)	0.391
Osteoporosis	0 (-)	0 (-)	1.000
Thromboembolic events	0 (-)	0 (-)	1.000
Urinary tract infections	4 (4.0)	1 (1.0)	0.210
Vaginitis	0 (-)	0 (-)	1.000
Weight gain	1 (1.0)	0 (-)	0.495

At data cut-off for first follow-up analysis, median duration of follow-up for TTP was 18.8 months in the fulvestrant group and 12.9 months in the anastrozole group. For the period between first data cut-off and this follow-up analysis, World Health Organization-Performance Status (WHO-PS) and serious adverse events (SAEs) were reported for fulvestrant and anastrozole. Twelve SAEs were reported in seven patients in the fulvestrant group and 10 SAEs were reported in seven patients in the anastrozole group during the period after the primary data cut-off. Each SAE by preferred term was only reported in one patient. One SAE (pulmonary embolism) was considered treatment-related by the investigator in the fulvestrant group. No treatment-related SAEs were reported in the anastrozole group. There were no clinically important differences in terms of WHO-PS.

The occurrence of SAEs during the main study period and the follow-up period combined is detailed in Table 38. No new safety or tolerability issues were reported

from this phase of the study. The majority of SAEs were considered by the investigator to be unrelated to the treatment. Two SAEs considered to be treatment related were documented (one case of hypertension and one case of pulmonary embolism, both in the fulvestrant 500 mg treatment group).

Table 38: Incidence of SAEs and deaths in FIRST study at final data cut-off (65% OS)(9)

SAE	Fulvestrant 500mg	Anastrozole 1mg
	N=101	N=103
Any SAE	24 (23.8)	22 (21.4)
Any SAE related to death	3 (3.0)	5 (4.9)
Any SAE with outcome other than death	21 (20.8)	18 (17.5)
Any causally related SAE	2 (2.0)	0 (-)
Most commonly reported SAEs (>=2 patients)		
Atrial fibrillation	1 (1.0)	1 (1.0)
Cardiac failure	2 (2.0)	0 (-)
Death	0 (-)	2 (1.9)
Decreased appetite	2 (2.0)	0 (-)
Dehydration	2 (2.0)	0 (-)
Dyspnoea	2 (2.0)	0 (-)
Femur fracture	1 (1.0)	2 (1.9)
Neuralgia	1 (1.0)	1 (1.0)
Transient ischaemic attack	0 (-)	2 (1.9)

FALCON

Safety and tolerability assessments in FALCON included adverse events (graded according to Common Terminology Criteria for Adverse Event [CTCAE], version 4·0), serious adverse events, discontinuations because of adverse events, deaths because of adverse events, and predefined adverse events of special interest (joint disorders and back pain). Laboratory variables, electrocardiogram recordings, physical examination, and vital signs were monitored at prespecified timepoints throughout the study (7).

At data cut-off (April 11, 2016), when the target number of PFS events (306) was expected to have been met, median duration of actual exposure to fulvestrant was 14·7 months (range 0·9–37·7) and to anastrozole was 13·9 months (range 0·2–36·0). 166 (73%) of 228 patients in fulvestrant group and 173 (75%) of 232 patients

in the anastrozole group reported adverse events (Table 39). Serious adverse events were reported by 30 (13%) of 228 patients receiving fulvestrant versus 31 (13%) of 232 patients receiving anastrozole.

Table 39: Adverse events in FALCON with a frequency of more than 5% in any treatment group (7)

	Fulvestrant 500mg (n=228)	**Anastrozole 1mg (n=232)**
Patients with any adverse event	166 (73%)	173 (75%)
Arthralgia	38 (17%)	24 (10%)
Hot flush	26 (11%)	24 (10%)
Fatigue	26 (11%)	16 (7%)
Nausea	24 (11%)	24 (10%)
Back pain	21 (9%)	14 (6%)
Alanine aminotransferase increased	16 (7%)	7 (3%)
Myalgia	16 (7%)	8 (3%)
Hypertension	15 (7%)	21 (9%)
Insomnia	15 (7%)	13 (6%)
Diarrhoea	14 (6%)	13 (6%)
Constipation	13 (6%)	11 (5%)
Pain in extremity	13 (6%)	10 (4%)
Aspartate aminotransferase increased	12 (5%)	8 (3%)
Cough	12 (5%)	8 (3%)
Anaemia	9 (4%)	20 (9%)
Dyspnoea	9 (4%)	13 (6%)
Oedema peripheral	9 (4%)	13 (6%)

Data are n (%). Adverse events were graded according to Common Terminology Criteria for Adverse Events version 4.0.

Overall, 16 (7%) of 228 patients in the fulvestrant group and 11 (5%) of 232 patients in the anastrozole group discontinued because of adverse events (Table 40). Grade 3 or worse adverse events were reported by 51 (22%) of 228 patients receiving fulvestrant and 41 (18%) of 232 patients receiving anastrozole; none occurred in more than 5% of patients in either group. 6 (3%) of 228 patients in the fulvestrant group and 7 (3%) of 232 patients in the anastrozole group died because of adverse events. No deaths because of adverse events were considered causally related to treatment.

Table 40: Discontinuations due to AEs by organ class

Characteristic	Fulvestrant 500mg (n=228)	Anastrozole 1mg (n=232)
Patients with any AE leading to discontinuation	16 (7.0)	11 (4.7)
Infections and infestations	1 (0.4)	0 (-)
Neoplasms benign, malignant and unspecified	3 (1.3)	2 (0.9)
Immune system disorders	2 (0.9)	0 (-)
Nervous system disorders	4 (1.8)	0 (-)
Cardiac disorders	2 (0.9)	5 (2.2)
Vascular disorders	1 (0.4)	2 (0.9)
Respiratory, thoracic and mediastinal disorders	2 (0.9)	0 (-)
Gastrointestinal disorders	1 (0.4)	0 (-)
Hepatobiliary disorders	0 (-)	1 (0.4)
Musculoskeletal and connective tissue disorders	0 (-)	1 (0.4)
General disorders and administration site conditions	1 (0.4)	0 (-)
Investigations	1 (0.4)	0 (-)

Adverse events of special interest (joint disorders and back pain) were reported by 59 (26%) of 228 patients in the fulvestrant group and 42 (18%) of 232 patients in the anastrozole group. All adverse events of special interest were mild or moderate in severity (grade 1 or 2), with the exception of one patient (<1%) in the fulvestrant group who had grade 3 back pain. No adverse events of special interest led to treatment interruption, or had a fatal outcome. No serious adverse events of special interest were reported. Overall, no clinically significant changes in laboratory variables, electrocardiogram recordings, physical examination, or vital signs were observed in either group.

Oher studies

Of the other studies identified in the systematic literature review for clinical efficacy (see Section 4.10), only the North American trial reported specific adverse events (Table 41), while 3 studies reported any data for withdrawals (Table 42).

Table 41: Summary of adverse events reported in included studies

Adverse event (any grade)	Tamoxifen 20 mg (N=182)	Anastrozole 1 mg (N=170)
Diarrhea	12.6	17.1
Fatigue	3.3	1.2
Nausea	34.1	30.6
Asthenia	35.7	31.8
Hot flashes	24.2	**36.5**
Vomiting	12.1	14.7

Table 42: Studies reporting data pertaining to withdrawals

Study name	Intervention	All withdrawals	Withdrawals due to AEs	Withdrawals due to death	Comments
P025 trial (76)	Tamoxifen 20 mg (N = 458)	43.4			• Data reported for patients who terminated first line treatment without cross over; • Includes patients who died on first-line therapy, patients lost to follow-up during first-line therapy, and patients who went to follow-up for survival (includes patients who went to chemotherapy or other treatments not specified by protocol)
	Letrozole 2.5 mg (N = 458)	35.4			
TARGET trial (11)	Tamoxifen 20 mg (N = 328)		5.8	1.8	
	Anastrozole 1 mg (N = 340)		4.4	2.1	
North American trial (10)	Tamoxifen 20 mg (N = 182)		4.4	0.5	
	Anastrozole 1 mg (N = 171)		5.3	1.8	

AE: Adverse Events

4.13 Interpretation of clinical effectiveness and safety evidence

Data from the pivotal phase III FALCON study adds to the extensive data for the efficacy of fulvestrant in patients with advanced breast cancer and consolidates the evidence for the superior efficacy for fulvestrant over a third-generation AI (7), initially raised by the results of the phase II FIRST study, where most patients (approximately 75%) were also endocrine-naïve (5, 6, 8). The primary endpoint of the study was met, with patients receiving fulvestrant having a significant reduction in the risk of progression or death compared with patients receiving anastrozole (HR 0.797, 95% CI 0.637 – 0.999, p=0.0486), supporting the hypothesis that fulvestrant is a more efficacious treatment than anastrozole in postmenopausal women with HR+ ABC who have not received previous treatment with endocrine therapy.

The main strengths of this study are the inclusion of a diverse patient population, the double-dummy study design, and the use of a standard-of-care comparison group. Unlike many other studies where patients were allowed to receive previous adjuvant endocrine therapy, patients in the FALCON study were completely endocrine therapy-naïve (7). Therefore, this study provides a direct comparison of the therapeutic efficacy between the SERD fulvestrant and a third-generation AI without the confounding effects of previous adjuvant endocrine therapy exposure of any type. In addition to the primary endpoint results, predefined subgroup analyses were conducted and suggested that treatment effects in terms of PFS were largely consistent across the subgroups analysed.

The adverse event profile observed was generally consistent with the known safety profiles of fulvestrant and anastrozole. The most common adverse event reported with fulvestrant in the FALCON study was arthralgia, which occurred at a higher frequency to that noted in FIRST (38 [17%] of 228 in FALCON vs 9·9% in FIRST) (7, 8); however, no patients discontinued treatment as a result. More patients in the fulvestrant group had myalgia than in the anastrozole group. Less than 2% of patients in either treatment group had serious adverse events causally related to treatment or discontinued treatment because of adverse events, and no treatment-related deaths occurred.

An alternative to first-line fulvestrant has been established by the results of the Palbociclib Ongoing Trials in the Management of Breast Cancer (PALOMA-2) trial (NCT01740427), which excluded patients resistant to aromatase inhibitors, and the Mammary Oncology Assessment of LEE011's (ribociclib) Efficacy and Safety (MONALEESA-2 trial, NCT01958021). These studies investigated the efficacy of the cyclin-dependent kinases 4 and 6 (CDK4 or CDK6) inhibitors palbociclib or ribociclib plus letrozole, respectively, versus letrozole alone in postmenopausal women who had not received previous systemic treatment for ABC (77, 78). Both studies have shown that addition of a second drug from a different class is associated with not only improved efficacy but also additional toxicity. Significant improvements in PFS were observed for both combination treatments versus letrozole alone: HR 0·58, 95% CI 0·46–0·72, p<0·0001 in PALOMA-2, and HR 0·56, 0·43–0·72, p<0·0001 in MONALEESA-2. The incidence of grade 3 and 4 serious AEs and permanent treatment discontinuation because of AEs (both haematological and non-haematological AEs) was greater with palbociclib plus letrozole and ribociclib plus letrozole than with letrozole alone [Finn 2016]. Thus, when considered in the context of the results from FALCON, fulvestrant monotherapy provides a lower toxicity option for first-line therapy than combination therapy.

Identification of patients likely to gain most benefit from treatment with endocrine monotherapy is important. Patients who achieved clinical response to fulvestrant had a longer duration of response compared with anastrozole. Thus, patients with endocrine-sensitive disease might not always require a combination treatment that is associated with greater toxicity. The FALCON and PALOMA-2/MONALEESA-2 trials are not directly comparable and are immature from an OS perspective. OS results could provide additional evidence to support decisions between the use of a first-line CDK4 or CDK6 inhibitor with an AI versus fulvestrant monotherapy, particularly given the OS advantage already observed for fulvestrant compared with anastrozole in the FIRST study (HR 0.63, 95% CI 0.43 - 0.94), in patients who were endocrine-therapy naïve (6).

A comprehensive network of evidence was available to potentially compare fulvestrant 500mg with all the comparators of interest in the final scope; anastrozole, tamoxifen and letrozole. Visual inspection of the Kaplan-Meier survival plots

indicated ‘crossing of survival curves’ and suggested that the assumption of proportional hazards was not valid and that traditional methods for network meta-analysis (NMA) using pooled HR were not appropriate. An alternative method of NMA advocated in NICE DSU TSD 14 (75), was used to estimate the effect of treatment on the shape and scale of parametric survival distributions derived from all the available RCT evidence (13). The results of this NMA were broadly aligned with prior beliefs regarding the efficacy of fulvestrant, AIs and tamoxifen. Fulvestrant and tamoxifen were observed to demonstrate statistically significant differences in PFS when compared with anastrozole, whilst letrozole did not. This assumption has been used in many previous NICE appraisals, most recently in the ongoing appraisal of pabloclib in combination with letrozole (73), is widely accepted by clinicians (54) and has recently been shown in a large (n=4136) randomised study to not have significantly superior efficacy or safety compared with anastrozole in postmenopausal patients with HR+, node +ve early breast cancer (74).

Overall, the FALCON study results support the conclusion that fulvestrant is more efficacious than anastrozole on the basis of a significant improvement in PFS in postmenopausal women with HR+ ABC who have not received previous endocrine therapy. Both treatments were associated with an acceptable tolerability profile. Collectively, the efficacy and tolerability findings support the clinical effectiveness of fulvestrant in this setting (7).

Fulvestrant 500mg in this indication is not considered an End of Life medicine.

4.14 Ongoing studies

Follow-up in the FALCON study is ongoing (7) and mature OS results (when >= 50% of patients have died) are expected to report in approximately 2 years (i.e. 2020).

The MONALEESA3 study (NCT02422615) is a randomized double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of postmenopausal women with HR+, HER2- ABC who have received no or only one line of prior endocrine treatment. Results of this study are anticipated in [redacted].

There are no other ongoing studies from which evidence will be available within the next 12 months for the indication being appraised.

5 Cost effectiveness

5.1 Published cost-effectiveness studies

A targeted review of submissions made to national reimbursement and technology assessment organisations was conducted to identify economic evaluations of therapies for the treatment of locally advanced or metastatic breast cancer. The objective of the economic review was to identify and assess published cost-effectiveness evidence (including information on modelling methodology, health-related quality-of-life, costs, and resource use).

The HTA review included a search of national reimbursement and technology assessment organisations for potentially relevant submissions. The websites of the organisations reviewed included the following:

- Canadian Agency for Drugs and Technologies in Health, and the pan-Canadian Oncology Drug Review, Canada
- NICE, England and Wales
- Pharmaceutical Benefits Advisory Committee, Australia
- Scottish Medicines Consortium, Scotland

The websites were searched in May 2016 for any submissions in ‘breast cancer’, and those related to advanced or metastatic breast cancer were included. No additional inclusion or exclusion criteria were applied. An overview of the identified HTA submissions is presented in Appendix E.

NICE is the only HTA agency that routinely publishes the full details of the submitted economic evaluations; therefore, a final set of 10 NICE technology appraisals, encompassing 12 economic models, relating to advanced or metastatic breast cancer were included and extracted. A summary of the interventions and indications of the 10 technology appraisals is presented in Table 43. A description of the aims, methods and results for each study is presented in Table 44 and Table 45.

Table 43: NICE HTA submissions included in the economic review

Intervention	Indication	Source
Trastuzumab emtansine	HER2+, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane	TA371(79)
Everolimus in combination with exemestane	Postmenopausal women with advanced HER2- HR+ breast cancer that has recurred or progressed following treatment with a NSAI	TA421(80)
Bevacizumab with capecitabine	First-line treatment of metastatic breast cancer when other chemotherapy (including taxanes or anthracyclines) is not appropriate, or taxanes or anthracyclines have been used as part of adjuvant treatment within the past 12 months	TA263(81)
Lapatinib plus letrozole	Postmenopausal women with metastatic HR+ breast cancer that overexpresses HER2	TA257(82)
Trastuzumab plus anastrozole	Postmenopausal women with metastatic HR+ breast cancer that overexpresses HER2	TA257(82)
Eribulin	Locally advanced or metastatic breast cancer that has progressed after at least two chemotherapy regimens for advanced disease	TA423(83)
Fulvestrant	Postmenopausal women with HR+, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-oestrogen therapy, or disease progression on therapy with an anti-oestrogen	TA239(84)
Bevacizumab plus weekly paclitaxel	First-line treatment of patients with metastatic breast cancer	TA214(85)
Gemcitabine plus paclitaxel	Metastatic breast cancer after relapse following adjuvant/neo-adjuvant chemotherapy; prior chemotherapy should have included anthracyclines unless clinically contraindicated	TA116(86)
Trastuzumab plus paclitaxel or trastuzumab monotherapy	Combination therapy: in combination with paclitaxel for metastatic breast cancer with no prior chemotherapy for metastatic disease and anthracycline is unsuitable, in combination with paclitaxel Monotherapy: for metastatic breast cancer after at least two chemotherapy regimens; prior chemotherapy must have included at least an anthracycline and a taxane, unless these treatments are inappropriate; patients who are HR+ must also have failed to respond to appropriate hormonal therapy	TA34(87)
Trastuzumab monotherapy	Metastatic breast cancer after at least two chemotherapy regimens; prior chemotherapy must have included at least an anthracycline and a taxane, unless these treatments are inappropriate; patients who are HR+ must also have failed to respond to appropriate hormonal therapy	TA34(87)
Pertuzumab with trastuzumab and chemotherapy	Neoadjuvant treatment of adults with HER2+ locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence	TA424(88)

Abbreviations: HER2, human epidermal growth factor 2; HR, hormone receptor; NSAI, non-steroidal aromatase inhibitor; TA, technology assessment.

Table 44: Overview of manufacturer submissions to NICE in advance/metastatic breast cancer

NICE submission	Indication	Intervention and comparators	Model design	Perspective	Time horizon; cycle length	Health states	Resource use considered	Main source of utility data	Main source of clinical data
First-line therapies									
TA263 (Fleeman 2011)(81)	First-line treatment of metastatic breast cancer when other chemotherapy (including taxanes or anthracyclines) is not appropriate, or taxanes or anthracyclines have been used as part of adjuvant treatment within the past 12 months	Bevacizumab with capecitabine vs. Capecitabine	Partition survival analysis	NHS/PSS	15 years; 1 month	Progression-free Progressed disease (with tunnel states) Death	Drug costs (first-line treatment only) Administration and pharmacy costs AEs (deep vein thrombosis and hypertension) Cost of PFS Cost of progressed disease	Lloyd et al. (2006)(89)	All efficacy and treatment duration parameters were derived from the subgroup of patients from the RIBBON-1 trial who had previously received a taxane
TA257 (Fleeman 2010)(82)	Postmenopausal women with metastatic HR+ breast cancer that overexpresses HER2	Lapatinib plus letrozole vs. Letrozole Trastuzumab plus anastrozole Anastrozole	Partition survival analysis	NHS/PSS	10 years; cycle length not reported	Alive and no disease progression Alive with progression Death	Drug costs Drug administration Patient monitoring AEs Pre-progression cost Post-progression cost	The utility value for the 'alive and no disease progression' state was estimated using data from the FACT-B questionnaires administered during the EGF30008 trial; an algorithm was used to map to patient preference-based utilities. The utility value for the 'alive with progression' state was taken from Lloyd et al. (2006)(89). Utility decrements were applied for Grade 3+ AEs	The key clinical data comparing lapatinib plus letrozole with letrozole alone came from the EGF30008 trial. To compare lapatinib plus letrozole with other technologies, the manufacturer used the results of the indirect comparison

NICE submission	Indication	Intervention and comparators	Model design	Perspective	Time horizon; cycle length	Health states	Resource use considered	Main source of utility data	Main source of clinical data
TA257 (Fleeman 2010)(82)	Postmenopausal women with metastatic HR+ breast cancer that overexpresses HER2	Trastuzumab plus anastrozole vs. Anastrozole Letrozole Lapatinib plus letrozole	Partition survival analysis	NHS/PSS	15 years; 1 month	Progression-free Progressed disease Death	Drug costs Total subsequent monthly cost (administration, cardiac monitoring, pharmacy prep) Progressive disease costs (second line treatment with exemestane monotherapy) PFS BSC Post-progression BSC End of life	Cooper et al. (2003)(90)	TAnDEM trial used for trastuzumab plus anastrozole compared with anastrozole alone. Based on the results from the indirect comparison it was assumed that letrozole and anastrozole have a 'class effect' and therefore the PFS and OS curves for anastrozole were used for letrozole. The clinical estimates for lapatinib plus letrozole came from the EGF30008 trial.

NICE submission	Indication	Intervention and comparators	Model design	Perspective	Time horizon; cycle length	Health states	Resource use considered	Main source of utility data	Main source of clinical data
TA214 (Rodgers 2010)(85)	First-line treatment of patients with metastatic breast cancer	Bevacizumab plus weekly paclitaxel vs. Weekly paclitaxel Docetaxel Gemcitabine plus 3-weekly paclitaxel	Markov	NHS/PSS	10 years; 1 month	Progression-free Progressed disease Death	Drug costs (two-base case analyses: one used list prices in accordance with NICE reference case from BNF; the other used an average NHS cost for paclitaxel based on the average price paid by NHS trusts over a 4-month period, and a PAS for bevacizumab) Drug administration PFS health state supportive care Progressed health state supportive care AEs	Cooper et al. (2003)(90); decrements for febrile neutropenia and peripheral sensory neuropathy were applied	E2100 clinical trial provided the probability of a patient remaining within the PFS health state for each cycle of the model and the risk of death post-progression. Due to the very low number of events observed in the study for patients dying within the PFS health state, UK mortality rates were used to supplement the trial data. It was assumed that the E2100 paclitaxel weekly arm was a reasonable proxy for the docetaxel monotherapy and for gemcitabine in combination with paclitaxel comparisons
TA34 (NICE 2002)(87)	Metastatic breast cancer with no prior chemotherapy for metastatic disease and anthracycline is unsuitable, in combination with paclitaxel	Trastuzumab plus paclitaxel vs. Paclitaxel	Health state transition model	NHS	5 years; cycle length NR	NR	Drug costs Outpatient costs AE costs	Hutton et al. (1996)(91)	RCT of first-line trastuzumab combination therapy (Roche study H0648g)

NICE submission	Indication	Intervention and comparators	Model design	Perspective	Time horizon; cycle length	Health states	Resource use considered	Main source of utility data	Main source of clinical data
TA424 (Squires 2016)(88)	Neoadjuvant treatment of adults with HER2+ locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence	Pertuzumab plus trastuzumab and chemotherapy vs. Standard neoadjuvant therapy without pertuzumab for HER2+ breast cancer	N/A	NHS/PSS	N/A	N/A	N/A	Lloyd et al. (2006)(89)	NeoSphere and TRYPHAENA phase II RCTs
Second-line therapies									
TA371 (Squires 2014)(79)	HER2+, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane	Trastuzumab emtansine vs. Lapatinib plus capecitabine Trastuzumab and capecitabine Trastuzumab and vinorelbine Capecitabine Vinorelbine	Partition survival analysis/state transition Markov cohort model	NHS/PSS	10 years; 1 week	Progression-free Progressed disease Death	Drug costs Administration and pharmacy costs AEs (diarrhoea and fatigue) Supportive care	Lloyd et al. (2006)(89); disutilities associated with treatment-related Grade 3, 4, or 5 AEs from the EMILIA trial were applied	EMILIA trial for trastuzumab emtansine vs. lapatinib plus capecitabine. For the comparators for which there was no head-to-head evidence, a Bayesian MTC was used. It was assumed that vinorelbine and trastuzumab plus vinorelbine, which could not be compared with trastuzumab emtansine in the MTC, were clinically equivalent to capecitabine and trastuzumab plus capecitabine respectively

NICE submission	Indication	Intervention and comparators	Model design	Perspective	Time horizon; cycle length	Health states	Resource use considered	Main source of utility data	Main source of clinical data
TA421(80)	Postmenopausal women with advanced HER2-HR+ breast cancer without symptomatic visceral disease, that has recurred or progressed after a NSAI	Everolimus in combination with exemestane vs. Exemestane alone Tamoxifen Fulvestrant Docetaxel Doxorubicin Capecitabine Vinorelbine	State-transition Markov model[1]	NHS/PSS	10 years; 1 month[1]	Stable disease Progressed disease Death[1]	Drug costs Drug administration Cost of progressed disease (community home nurse, clinical nurse specialist, GP home visits, therapist) Costs of 4 subsequent chemotherapies: bevacizumab, paclitaxel, capecitabine and vinorelbine Costs associated with AEs only in the base-case analysis when comparing everolimus plus exemestane with chemotherapies (costs not included when compared with endocrine therapies) [1]	Utility values from Lloyd et al. (2006)(89) were used in the original submission. An alternative utility value for the 'progressed disease' health state was derived from Launois et al. (1996)(92). Disutitilies associated with AEs were applied to the analysis comparing everolimus plus exemestane with chemotherapies, but not with endocrine therapies [1]	The BOLERO-2 trial was used to estimate OS in the comparison of everolimus plus exemestane with exemestane alone. For the analysis of everolimus plus exemestane compared with tamoxifen, data from the TAMRAD trial were used. For everolimus plus exemestane compared with fulvestrant or chemotherapy, indirect treatment comparisons were used
TA239 (Henry 2011)(84)	Postmenopausal women with HR+, locally advanced or metastatic breast cancer with disease relapse on or after adjuvant anti-ooestrogen therapy, or disease progression on therapy with an anti-ooestrogen	Fulvestrant 500mg vs. Fulvestrant 250 mg Anastrozole Letrozole	Time-in-state	NHS/PSS	13 years; 1 month	Pre-progression Post-progression Death	Second-line hormonal treatment used during the pre-progression phase Subsequent treatments during the post-progression phase including third-line hormonal therapy Supportive palliative care Chemotherapy	Lloyd et al. (2006)(89)	Results of a base-case network meta-analysis of the clinical effectiveness data on TTP and OS

NICE submission	Indication	Intervention and comparators	Model design	Perspective	Time horizon; cycle length	Health states	Resource use considered	Main source of utility data	Main source of clinical data
							Treatment-related AEs		
TA116 (Jones 2007)(86)	Metastatic breast cancer after relapse following adjuvant/neo-adjuvant chemotherapy; prior chemotherapy should have included anthracyclines unless clinically contraindicated	Gemcitabine plus paclitaxel vs. Docetaxel Paclitaxel Docetaxel plus capecitabine	Markov state-transition	NHS/PSS	3 years; 3 weeks	Stable – no change Response – this is based on reduction in tumour size and is defined as complete or partial Progressive – defined as increase in tumour size or spread to other sites Death	Drug costs Drug administration Supportive care, including management of AEs Palliative care	Survey of 100 members of the general public who completed valuation tasks using visual analogue scales and the SG technique	Median OS estimate for gemcitabine plus paclitaxel was taken from the RCT comparing gemcitabine plus paclitaxel with paclitaxel monotherapy. For paclitaxel monotherapy, the average of the pooled, weighted absolute survival data from single arms of 15 different studies was used.

NICE submission	Indication	Intervention and comparators	Model design	Perspective	Time horizon; cycle length	Health states	Resource use considered	Main source of utility data	Main source of clinical data
						Each health state (other than death) is sub-divided to allow for the experience of treatment-related toxicity, which is broken down further by whether the toxicity is life-threatening, requires hospitalisation or is chronic. There are 19 health states in the model.			

NICE submission	Indication	Intervention and comparators	Model design	Perspective	Time horizon; cycle length	Health states	Resource use considered	Main source of utility data	Main source of clinical data
Third-line or subsequent therapies									
TA423 (Fleeman 2016)(83)	Locally advanced or metastatic breast cancer that has progressed after at least two chemotherapy regimens for advanced disease	Eribulin vs. Treatment of physician's choice (combined comparator including vinorelbine, gemcitabine, anthracyclines, and taxanes)	Semi-Markov state transition model[1]	NHS/PSS	Trial duration time horizon (no extrapolation of trial outcomes was carried out, and when the trial ended after 2.89 years all patients who were alive moved into a 'terminal' state); 21 days[1]	Treated Progressive Death (patients entered a "terminal" state for one cycle before the death state) [1]	Drug costs Pre-medication costs Drug administration Treated health state (medical personnel, tests and diagnostics, radiotherapy) Progressive health state (medical personnel, tests and diagnostics, radiotherapy) Terminal (medical personnel, tests and diagnostics, radiotherapy, care setting) [1]	Study 301, a clinical trial for eribulin, using a mapping algorithm published by Crott and Briggs (2010)(93)	EMBRACE trial

NICE submission	Indication	Intervention and comparators	Model design	Perspective	Time horizon; cycle length	Health states	Resource use considered	Main source of utility data	Main source of clinical data
TA34 (Lewis 2002)(87)	Metastatic breast cancer after at least two chemotherapy regimens; prior chemotherapy must have included at least an anthracycline and a taxane, unless these treatments are inappropriate; patients who are HR+ must also have failed to respond to appropriate hormonal therapy	Trastuzumab vs. Vinorelbine	Cost-effectiveness analysis with benefits measured as LYG	NHS	2 years; cycle length NR	NR	Drug costs Outpatient costs Hospital costs for AEs	Benefits measured in terms of LYG	Dffectiveness data relating to trastuzumab were derived from a non-randomised study (Roche study H0649g). Some supportive data were also derived from preliminary analysis of a study using trastuzumab as first line therapy for metastatic breast cancer (Roche study H0650g). The data relating to vinorelbine were taken from an RCT

Abbreviations: AE, adverse events; BSC, best supportive care; FACT-B, functional assessment of cancer therapy – breast; GP, general practitioner; HER2, human epidermal growth factor; HR, hormone receptor; LYG, life-years gained; MTC, mixed treatment comparison; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; NR, not reported; NSAI, non-steroidal aromatase inhibitors; OS, overall survival; PFS, progression-free survival; PSS, Personal Social Services; RCT, randomised control trial; SG, standard gamble; TTP, time to treatment progression.

[1]Based on the original submission

Table 45: Base case summary results of manufacturer submissions to NICE in advance/metastatic breast cancer

NICE submission	Intervention and comparators	Baseline age ± SD (years)	Base-case results		
			Total QALYs	Cost year and total costs (£)	ICER
First-line therapies					
TA263 (Fleeman 2011)(81)	Bevacizumab with capecitabine vs. Capecitabine	53.4	Bevacizumab with capecitabine: 1.34 Capecitabine: 0.83	Cost year: 2010 Bevacizumab with capecitabine: 51,577 Capecitabine: 12,721	£77,318 per QALY gained
TA257 (Fleeman 2010)(82)	Lapatinib plus letrozole vs. Letrozole Trastuzumab plus anastrozole Anastrozole	N/A	Lapatinib plus letrozole: 2.39 Letrozole:1.92 Trastuzumab plus anastrozole: 2.14 Anastrozole: 1.79	Cost year: 2009 Lapatinib plus letrozole: 60,614 Letrozole: 25,878 Trastuzumab plus anastrozole: 55,101 Anastrozole: 24,620	£74,448 per QALY gained compared with letrozole; £21,836 per QALY gained compared with trastuzumab; £59,895 per QALY gained compared with anastrozole
TA257 (Fleeman 2010)(82)	Trastuzumab plus anastrozole vs. Anastrozole Letrozole Lapatinib plus letrozole	N/A	Trastuzumab plus anastrozole: 1.87 Anastrozole: 1.29 Letrozole: 1.29 Lapatinib plus letrozole: 1.71	Cost year: 2009 Trastuzumab plus anastrozole: 54,749 Anastrozole: 23,341 Letrozole: 23,328 Lapatinib plus letrozole: 51,883	£54,312 per QALY gained compared with anastrozole; £54,336 per QALY gained compared with letrozole; £18,347 per QALY gained compared with lapatinib plus letrozole
TA214 (Rodgers 2010)(85)	Bevacizumab plus weekly paclitaxel vs. Weekly paclitaxel Docetaxel Gemcitabine plus 3-weekly paclitaxel	55.5	Bevacizumab plus weekly paclitaxel: 1.50 Weekly paclitaxel: 1.24 Docetaxel: 1.23 Gemcitabine plus 3-weekly paclitaxel: 1.24	Cost year: 2007/2008; costs below are based on NHS list price Bevacizumab plus weekly paclitaxel: 56,473 Weekly paclitaxel: 26,004 Docetaxel: 25,057 Gemcitabine plus 3-weekly paclitaxel: 29,115	Based on NHS list prices: £117,803 per QALY compared with paclitaxel; £115,059 per QALY compared with docetaxel; £105,777 per QALY compared with gemcitabine plus paclitaxel

					Based on average prices paid by NHS over a 4-month period and the PAS: all results indicated a lower cost per QALY though ICERs remained above £57,000 per QALY gained
TA34 (NICE 2002)(87)	Trastuzumab plus paclitaxel vs. Paclitaxel	N/A	N/A	Cost year: 2000 Trastuzumab plus paclitaxel: 28,600 Paclitaxel: 10,900	£29,448 per QALY gained compared with paclitaxel
TA424 (Squires 2016)(88)	Pertuzumab plus trastuzumab and chemotherapy vs. Standard neoadjuvant therapy without pertuzumab for HER2+ breast cancer	N/A	N/A	N/A	N/A (ERG estimated an ICER of £23,467 per QALY gained)
Second-line therapies					
TA 371 (Squires 2014)(79)	Trastuzumab emtansine vs. Lapatinib plus capecitabine Trastuzumab and capecitabine Trastuzumab and vinorelbine Capecitabine Vinorelbine	52.7	Trastuzumab emtansine:1.91 Lapatinib plus capecitabine: 1.45 Trastuzumab and capecitabine: 1.31 Trastuzumab and vinorelbine: 1.31 Capecitabine: 1.03 Vinorelbine: 1.03	Cost year: 2013 Trastuzumab emtansine: 111,162 Lapatinib plus capecitabine: 34,170 Trastuzumab and capecitabine: 37,629 Trastuzumab and vinorelbine: 39,047 Capecitabine: 13,173 Vinorelbine: 18,874	£167,236 per QALY gained compared with lapatinib plus capecitabine £111,095 per QALY gained compared with capecitabine
TA421(80)	Everolimus in combination with exemestane vs. Exemestane alone Tamoxifen Fulvestrant Docetaxel Doxorubicin Capecitabine Vinorelbine	62 ± 10.14 [1]	N/A	N/A	N/A (ERG estimated an ICER of £68,00 per QALY gained compared with exemestane alone)

TA239 (Henry 2011)(84)	Fulvestrant 500mg vs. Fulvestrant 250 mg Anastrozole Letrozole	NR	Fulvestrant 500mg: 1.49 Fulvestrant 250 mg: 1.26 Anastrozole: 1.21 Letrozole: 1.11	Cost year: 2009/2010 Fulvestrant 500mg: 31,075 Fulvestrant 250 mg: 25,603 Anastrozole: 22,467 Letrozole: 18,836	Anastrozole and fulvestrant 250 mg were extendedly dominated by a combination of two other single-agent treatments, fulvestrant 500mg and letrozole; £31,982 per QALY gained compared with letrozole
TA116 (Jones 2007)(86)	Gemcitabine plus paclitaxel vs. Docetaxel Paclitaxel Docetaxel plus capecitabine	NR	N/A	Cost year: 2005/2006 Total costs N/A	£17,168 per QALY gained compared with docetaxel; £30,100 per QALY gained compared with paclitaxel; £23,200 per QALY gained compared with docetaxel plus capecitabine
Third-line or subsequent therapies					
TA423 (Fleeman 2016)(83)	Eribulin vs. Treatment of physician's choice (combined comparator including vinorelbine, gemcitabine, anthracyclines, and taxanes)	N/A	N/A	N/A	£35,624 per QALY gained compared with treatment of physician's choice
TA34 (NICE 2002)(87)	Trastuzumab vs. Vinorelbine	N/A	N/A	Cost year: 2000 Trastuzumab: 6,196 Vinorelbine: 1,812	£7,521 per LYG compared with vinorelbine

Abbreviations: ERG, evidence review group; HER2, human epidermal growth factor; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; N/A, not applicable; NHS, National Health Service; PAS, patient access scheme; QALYs, quality-adjusted life-years; SD, standard deviation.
[1]Based on the original submission

5.2 De novo analysis

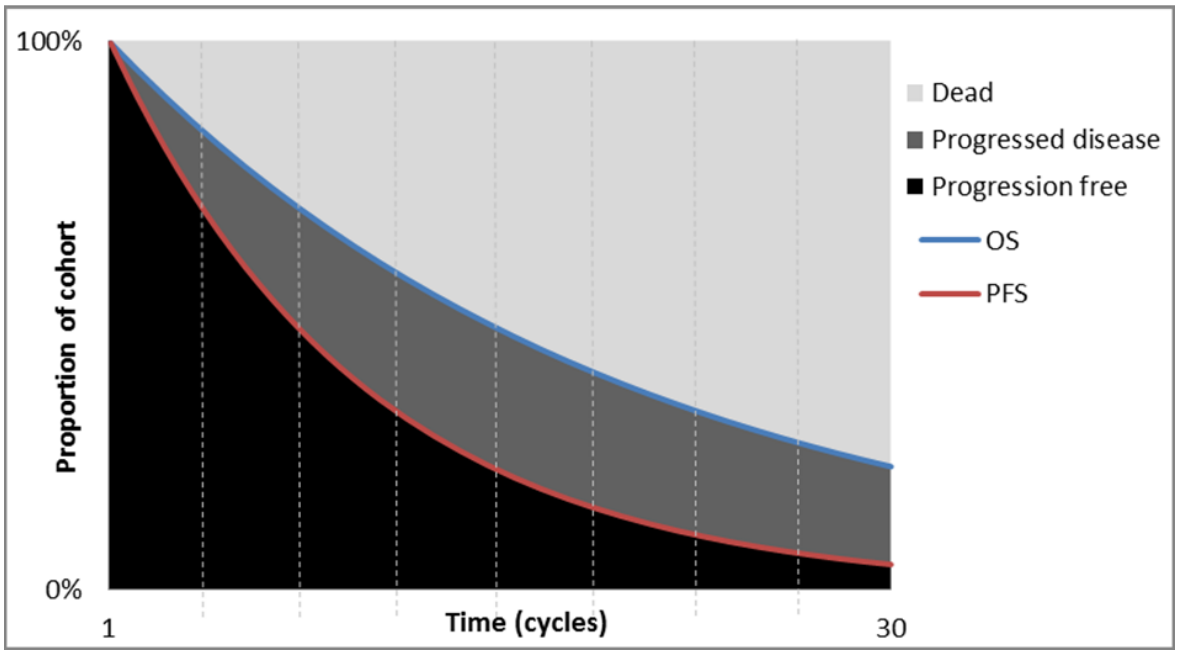
5.2.1 Patient population

The economic evaluation considers post-menopausal women with hormone receptor-positive locally advanced (not amenable to surgery or radiotherapy of curative intent) or metastatic breast cancer who have not previously been treated with any hormonal therapy. The patient population is consistent with the patient population included in the FALCON trial (7) used to support the update to the EU marketing authorization for fulvestrant, and is in-line with the NICE scope.

5.2.2 Model structure

A cohort-based partitioned survival model was developed in Microsoft Excel 2010 to evaluate the cost-effectiveness of fulvestrant 500mg. The model is comprised of three mutually exclusive health states: progression-free survival (PF) [receive first line hormonal therapy], progressed disease (PD) [receive subsequent therapies] and death (due to any cause). This model structure reflects the key clinical events in this disease area; i.e., progression – which usually results in moving the patient onto a new therapy – and death. The health state occupancy of the simulated cohort is estimated by extrapolating the cumulative survival probability of PFS and OS to a lifetime horizon. The extrapolated survival curves are used directly to estimate the proportion of the cohort who are alive and progression-free (Figure 39, black shaded area), the proportion of the cohort who are alive and have progressed (dark grey) and the proportion of the cohort who have died (light grey).

Figure 39: Partitioned survival analysis model structure



Within the context of the partitioned survival model, it is assumed that the health states represent the key sequence of events that patients experience over the course of their treatment for advanced breast cancer; i.e., progression of disease, subsequent treatment and death. In addition, it is assumed that these events are progressive, mutually exclusive and irreversible; i.e., a patient who experiences disease progression cannot transition back into the progression-free health state. This assumption is consistent with the definitions of PFS and OS from clinical trials, and the approaches used in previous NICE HTA submissions in advanced breast cancer and other cancers.

In accordance with the NICE reference case(94), the model adopts an NHS/PSS perspective and includes the resource use and costs associated with disease management, treatment acquisition, administration, adverse events and terminal care. In order to capture all relevant benefits of fulvestrant and comparator treatments, a lifetime time horizon is used in the base case analysis. The timeframe of the model is dependent on the OS data and stops when <1% of the population remain alive. As a result, the maximum length of the time horizon in the model is 30 years.

Costs and health-state utility values are allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle. The cycle

length is 4 weeks, which is considered the shortest time period in which a change in the disease course or symptoms would be observed in clinical practice(95). This is in accordance with the cycle length used in the previous cost-effectiveness analysis of fulvestrant and reflects the dosing schedule of non-steroidal aromatase inhibitors used in the FALCON trial (injections on Days 0, 14 [±3], 28 [±3], and every 28 [±3] days). The monthly cycle is also consistent with the follow-up visit schedule in the FALCON trial, which occur at Day 14, Weeks 4, 8, 12, 16, 20, 24, and every 12 weeks thereafter(96).

The model calculates mid-cycle estimates in each health state by taking the average between the number of patients present at the beginning of the cycle and the number of patients at the end of the cycle (half cycle correction). This prevents under or over estimation of costs and QALYs. An annual discount rate of 3.5% is applied to costs and outcomes in line with the NICE reference case (Table 46).

Table 46: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (maximum 30 years)	NICE reference case(94)
Cycle length	4 weeks	Considered to be shortest time in which a change in disease symptoms would be observed in clinical practice, and is consistent with the follow-up visit schedule in the FALCON trial
Starting age	63.5	Based on the average age of patients in FALCON
Half-cycle correction	Yes	Mitigates bias due to cycle length
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case(94)
Discount of 3.5% for utilities and costs	Yes	NICE reference case(94)
Perspective (NHS/PSS)	Yes	NICE reference case(94)

Abbreviations: NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years.

5.2.3 Intervention technology and comparators

The intervention of interest in the economic evaluation is fulvestrant 500mg.

The relevant comparators included in the economic analysis are aromatase inhibitors (anastrozole and letrozole) and tamoxifen, recommended in those patients where aromatase inhibitors are contraindicated or not tolerated. The relevant comparators for fulvestrant have been confirmed by a panel of UK Breast cancer oncologists and are aligned with those treatments included in the NICE scope for this appraisal.

5.3 Clinical parameters and variables

Results from the FALCON trial showed that fulvestrant 500mg significantly prolongs progression-free survival versus anastrozole (see section 4.7.2) and demonstrates, in the Phase II open-label study FIRST, a statistically significant improvement in OS (see section 4.7.1) (OS data from FALCON were immature at the time of interim analysis [only 31% of events had been reached], to the extent that median OS could not be calculated). The benefits of treatment in terms of QALYs gained are experienced through delaying disease progression (keeping patients in the progression-free health state longer, maintaining a higher quality of life), and extending the time alive for patients.

5.3.1 Parametric survival models

In order to estimate the proportion of patients in the modelled health states time horizon of the economic evaluation (lifetime [maximum 30 years]), it was necessary to extrapolate OS and PFS beyond the duration of the FALCON study. These extrapolations have been validated by estimates of PFS and OS provided by a panel of UK Breast cancer Oncologists (Expert clinical opinion), described in Table 32 and Table 35. Furthermore, it was also necessary to fulvestrant with alternative treatments that are in routine use within the NHS, included in the FALCON trial. This was accomplished by conducting a extrapolation and network meta-analysis of Kaplan-Meier curves for all comparators, derived from available RCTs. The NMA methodology and key trials that inform the PFS and OS networks are presented in section 4.10. The case survival curve parameter estimates and resulting plotted curves for PFS presented in Table 47 and Figure 40 respectively. The corresponding results for OS are reproduced in

Table 48 and Figure 41. The method of survival curve selection is detailed in section 4.10.4 and section 4.10.5 for PFS and OS respectively.

Table 47: Generalised gamma parameter estimates for PFS based on fixed effects NMA model

Generalised gamma	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in scale			Difference in shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Common parameter	[redacted]					
Q	[redacted]					

Abbreviations: L, lower; PFS, progression-free survival; U, upper.

Figure 40: PFS as estimated with fixed effects generalised gamma NMA model

Table 48: Weibull parameter estimates for OS based on fixed effects NMA model

Weibull	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in scale			Difference in shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					

Abbreviations: L, lower; OS, overall survival; U, upper.

Figure 41: OS as estimated with fixed effects Weibull NMA model

5.3.2 Adverse events

Adverse events were included in the evaluation to account for the potential cost and quality of life burden of experiencing events whilst on treatment. The impact of all AEs grade ≥ 3 according to the Common Terminology Criteria for Adverse Events (CTCAE), and experienced by at least 2% of patients in any treatment group, were included and the impact on costs and utilities accounted for. The incidence rate for AEs for patients on fulvestrant and anastrozole are sourced from the FALCON trial (7). Treatment-specific AE rates for letrozole and tamoxifen sourced from the literature. Due to data limitations, it was not possible to apply an indirect comparison of adverse event data. Therefore, it is possible that differences between treatments may partially be driven by differences between patient characteristics as well as follow-up periods in the respective studies. The incidence rates used in the model are reported in Table 49.

Table 49: Incidence rates of adverse events used in the model

Adverse event	Fulvestrant	Anastrozole	Letrozole	Tamoxifen
Source:	FALCON(97)	FALCON(97)	Finn 2016(98)	Paridaens 2008(99)
Sample size (n)	228	232	222	189
ALT increased	1.3%	0.0%	0.0%	4.2%
AST increased	1.3%	0.4%	0.0%	1.6%
Hypertension	1.8%	1.7%	0.0%	3.2%
Pleural effusion	2.2%	0.4%	0.0%	0.0%
Pain, bone	0.4%	0.4%	0.0%	5.8%
Pain, other	1.3%	0.9%	1.4%	3.2%
Dyspnoea	0.0%	0.9%	0.5%	2.6%
Bilirubin increased	0.0%	0.4%	0.0%	1.6%

Abbreviations: AE, adverse event; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase.

Adverse events were applied as one-off events in the first cycle of treatment. The alternative approach is to convert the events into monthly rates and apply throughout the time on treatment period. The advantages of employing the one-off event approach are as follows: the time element is already incorporated since costs and disutilities are defined as 'per event' and, as the rates are derived from the trials and applied to the population, the modelled results should more closely reflect the observed rates. In contrast, due to the patients progressing, the use of a monthly rate would likely underestimate the results observed in the clinical trials. The drawback of modelling adverse events as one-off events within the first cycle of treatment is that they are not discounted appropriately; however, since adverse events are not expected to last more than 1 year, the results of the model should not be affected.

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality-of-life data from clinical trials

Patient-Reported Outcomes (PROs) measurements and variables were not recorded in the FIRST study(5); however, the FALCON trial collected EQ-5D data using the 3L questionnaire (7). During the primary analysis, the questionnaire was administered at baseline and every 12 weeks until disease progression and at treatment discontinuation. During the survival follow-up phase, the questionnaire was administered every 12 weeks for those subjects still on randomised treatment; for patients who had discontinued treatment, the questionnaire was administered 3 months after objective disease progression and then at 6-monthly intervals. The EQ-

5D-3L index was calculated based on data for the five EQ-5D dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and the utility value set for the UK(100).

Health state utility values for progression-free and progressed disease were calculated. These were estimated using both summary statistics and repeated measures mixed effects regression models (MMRMs).

Table 50 presents the summary statistics for the full FALCON population (7). These values are based on the mean EQ-5D-3L index value per patient, calculated separately before and after progression. The mean EQ-5D-3L index values per patient were then again averaged for the total sample and by treatment group to obtain aggregated utility values for progression-free and progressed disease. The means per visit for the progression-free and progressed disease health state are presented in Table 50.

Table 50: Health state utility values based on summary statistics

	ITT		
	n	**Mean (SE)**	**95% CI**
Overall			
Progression-free	449	0.75 (0.01)	[0.73, 0.77]
Progressed disease	232	0.69 (0.02)	[0.65, 0.72]
Fulvestrant			
Progression-free	225	0.76 (0.01)	[0.73, 0.78]
Progressed disease	104	0.69 (0.03)	[0.63, 0.74]
Anastrozole			
Progression-free	224	0.74 (0.01)	[0.71, 0.76]
Progressed disease	128	0.69 (0.03)	[0.63, 0.74]

Abbreviations: CI, confidence interval; ITT, intention-to-treat; SE, standard error.

The mean EQ-5D values were similar across treatments and, with overlapping 95% confidence intervals between the two groups, no statistically significant difference was observed. This result was seen in both the progression-free and progressed disease estimates. This supported the use of the same utility values for both treatments.

A visual assessment of the means per visit of the EQ-5D-3L index from baseline (week 0) to the end of the study (week 56) are presented in Figure 65 and Figure 67 [Appendix F] for all patients and visits without and with progression, respectively. Similarly, the proportions of missing values of the EQ-5D-3L index for all patients and visits without and with progression are presented in Figure 66 and Figure 68 [Appendix F].

The summary statistics also showed similar values across health states. Whilst the health state utility value for progression-free (0.75) was higher than for progressed disease (0.69), the difference was small (0.06).

In order to take account of the repeated measures per patient, and estimate the association between utilities and clinical events in the FALCON study, mixed models with repeated measurements were estimated. For the purpose of these analyses, EQ-5D-3L index values were multiplied by 100 for ease of interpretation. Analysis was carried out using the NLME statistical package in the programming software R.

Included covariates were chosen based on the following:

- EMA and FDA recommended stratification factors in FALCON (metastatic disease, prior chemotherapy and measurable disease at baseline)
- The identified predictors of missing EQ-5D-3L index scores: identification was based on multiple consecutive nominal statistically significant associations in the logistic regression of missing EQ-5D-3L index (UK) scores for each visit on patient characteristics (see Table 130 [Appendix F])
- Clinically significant events: disease progression
- The research question: treatment group

The results of the regression analyses are presented in Table 51. In MMRM (1) the coefficient for disease progression was negative and statistically significant ($p<0.001$). In MMRM (2), similar results were observed concerning disease progression. In line with the summary statistics, the treatment coefficient was found not statistically significant. Treatment discontinuation was also found not statistically

significant; this may be due to multicollinearity with disease progression. All other covariates were also not statistically significant.

The resulting utility values for progression-free and progressed disease are PF=0.7511 and PD=0.6913 for MMRM (1), and PF=0.7570 and PD=0.7027 for MMRM (2). Both models provide estimates which are lower than the EQ-5D population norms for the relevant age and sex group: according to Kind (1999)(101), the EQ-5D index for a female aged 55-64 is 0.81 and for a female aged 65-74, it is 0.78. The additional covariates included in the MMRM (2) were not found to be statistically significant; therefore, based on parsimony, MMRM (1) was the preferred model.

It is noted that for the PD health state both models yield higher utility values than have been reported elsewhere (see Section 5.4.3); however, to best-align with the NICE reference case the use of patient-level EQ-5D-3L data, collected in a patient population specific to the decision problem, was preferred to literature based values.

Table 51: Mixed models with repeated measurements for EQ-5D index values

	MMRM (1)		MMRM (2)	
	Estimated coefficient (SE)		Estimated coefficient (SE)	
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Progression (Y=1; N=0)	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic disease (Y=1; N=0)	[redacted]		[redacted]	
Prior chemotherapy (Y=1; N=0)	[redacted]		[redacted]	
Measurable disease (Y=1; N=0)	[redacted]		[redacted]	
Visceral disease (reference=non-visceral disease)	[redacted]		[redacted]	
Stable disease (reference=progressive disease)	[redacted]		[redacted]	
Partial response (reference=progressive disease)	[redacted]		[redacted]	
Complete response (reference=progressive disease)	[redacted]		[redacted]	
Drug discontinuation (Y=1; N=0)	[redacted]		[redacted]	
Treatment group (reference=anastrozole)	[redacted]		[redacted]	
Observations	[redacted]		[redacted]	
AIC	[redacted]		[redacted]	
BIC	[redacted]		[redacted]	

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; MMRM, mixed models with repeated measurements; SE, standard error.
***p<0.001

5.4.2 Mapping

No mapping techniques were used to estimate health-related quality-of-life-data. FACT-B questionnaires were administered during the FALCON trial (7), however, as the EQ-5D-3L was also administered and represents the preferred measure of health-related quality of life in the NICE reference case, it was used instead.

5.4.3 Health-related quality-of-life studies

A structured review of utility studies was performed to identify sources of utility values for model inputs. Studies terms related to HRQoL and advanced or metastatic breast cancer were specified. The review was conducted within the Embase database using a search strategy published in a recent manufacturer's submission(79). The search was restricted to new publications from October 2013: the date the last NICE Technology Appraisal search was conducted. The search update was conducted on 6 June 2016; the search strategy is shown in Table 52.

Table 52: Embase search strategy for utilities in advanced or metastatic breast cancer

#	Search term	Results
1	'health related quality of life'	39,963
2	'quality adjusted life year' OR 'qaly' OR 'qalies'	20,796
3	'health related' NEAR/6 'quality of life'	40,307
4	'fact b' OR 'sf 36' OR 'sf 12' OR 'sq. 5d' OR 'eq 5d 5l' OR euroqol	37,349
5	'utility value' OR 'utility score'	1,015
6	tto OR 'time trade off' OR 'time tradeoff' OR sg OR 'standard gamble'	55,526
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	139,020
8	'breast cancer'	371,684
9	metastasis:de OR metastatic OR advanced OR inoperable	1,093,013
10	#7 AND #8 AND #9	983
11	#10 AND [4-10-2013]/sd NOT [25-5-2016]/sd	354

A total of 354 references were identified in the Embase search. Titles and abstracts were reviewed and the following exclusion criteria were applied to screen results to identify potentially relevant studies:

- Duplicates
- Not about breast cancer
- Non English language
- A trial protocol, letter or qualitative study
- No mention of EQ-5D or quality-adjusted life years (QALY)
- Poster or conference abstract that did not provide any values

After initial screening, 303 studies were excluded. The remaining studies were subsequently categorized as primary sources of utility data (13 studies), reviews of utility studies (10 studies), or secondary sources of utility data (18 studies).

Only two studies were included in the final data extraction table (Table 53). Most primary studies were excluded for not using EQ-5D to measure utilities and the majority of utility reviews were excluded for not identifying EQ-5D studies or studies published prior to 2013; reasons for exclusion are presented in Table 131 and Table 132 in Appendix G. A total of 47 utility references were tracked from the secondary utility source studies. All 47 studies were excluded (Table 133, Appendix G) due to either studies being published prior to 2013 or studies already having been identified earlier in the review. The review flow diagram is presented in Figure 42.

Figure 42: Review flow diagram

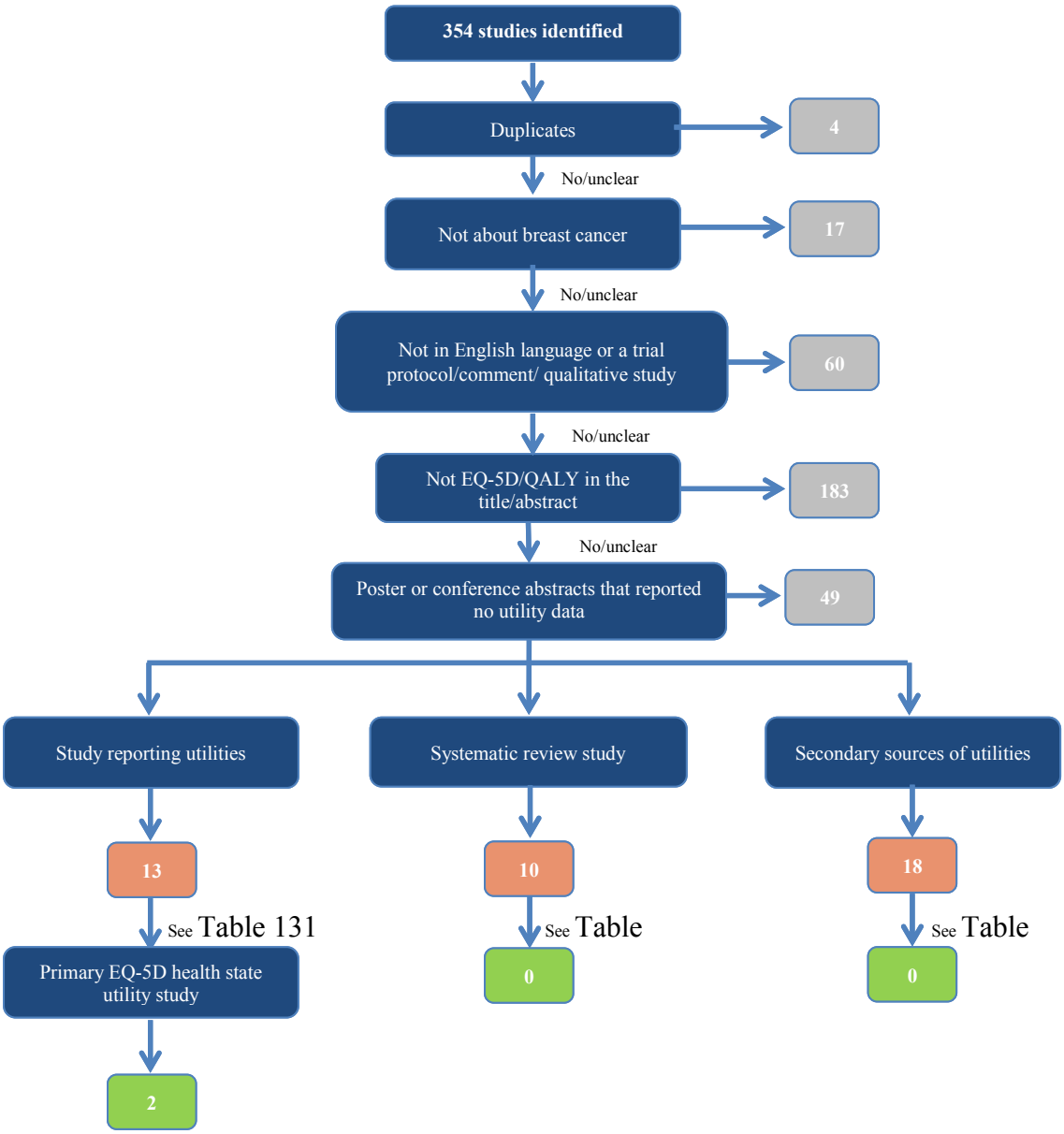


Table 53: Utility studies extraction

Study [country]	Population/disease area (sample size)	Study design/intervention	Population, method of elicitation (frequency) and valuation technique/tariff [e.g. SG, TTO, VAS]	Response rates to instrument provided?	Loss to follow-up; missing data	Health states and/or treatment description	Mean (SD/CIs)
Fukuda et al. (2015)(102) Takashima et al. (2016)(103) [Japan] (Fukuda 2015; Takashima 2016)	HER2- metastatic breast cancer, resistant to endocrine therapy (57% previous endocrine treatment after recurrence) Age (years), median (IQR): S-1 59.0 (53–65) and taxane 58.5 (51–65) Years since diagnosis: NR Life expectancy: NR ECOG: NR (n=618)	Randomised open-label phase III trial 1L taxane (docetaxel or paclitaxel) vs. S-1	Patients EQ-5D-3L (pre-treatment, 3 months after randomisation, every 6 months thereafter) Tariff: NR	(208 [S-1] + 175 [taxane]) /618 = 62% patients with EQ-5D responses Mean duration of response: 21 months	NR	Mean EQ-5D scores up to 60 months (S-1)	0.748
						Mean EQ-5D scores up to 60 months (taxanes)	0.741
						During 1L – mean EQ-5D up to 36 months (S-1)	0.810
						During 1L – mean EQ-5D up to 36 months (taxanes)	0.781
						Post-progression period (S-1)	0.729
						Post-progression period (taxanes)	0.703
Eyles et al. (2015) [England] (Eyles 2015)(104)	Metastatic breast cancer, stable disease Age (years): 37–65 Years since diagnosis, mean: 2.76 (0.5–7) Life expectancy: >6 months ECOG: 0–2 (n=19)	Feasibility study Mindfulness-based stress reduction for self-management of anxiety, depression, QoL, and fatigue	Patients EQ-5D-3L (baseline, during treatment [4 and 8 weeks] and follow-up [16 and 24 weeks]) Tariff: NR	19/20 patients analysed	Too ill to join (n=1)	Baseline	0.74
						End of follow-up	0.72
						End of follow-up (extreme outlier removed)	0.76

Abbreviation: 1L, first line; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EQ-5D, EuroQol-5 Dimension; HER2: Human epidermal growth factor; IQR, interquartile range; NR, not reported; QoL, quality of life; SD, standard deviation; SG, standard gamble; TTO, time trade off; VAS, visual analogue scale.

Fukuda et al (102) was judged to provide the most viable source of EQ-5D data against which the EQ-5D estimates from FALCON could be validated (7). It was a randomised trial with a large sample of comparable patients suffering from HER2-metastatic breast cancer receiving first-line therapy; however, 57% of patients in both arms had received prior endocrine therapy. The EQ-5D-3L values reported were analysed during first-line therapy for up to 36 months and also post-progression, which are comparable to the utility values related to the PF and PD health states estimated from FALCON (7). Nevertheless, caution should be taken when evaluating these values due to the lack of information around the baseline characteristics of the patients and, due to the small size of the sample and the mean EQ-5D response duration of 21 months, the PD health state value in particular.

Eyles et al(104) was also judged to serve as a valid source of validation for the PF utility value estimated from FALCON, as patients were described as having stable metastatic disease. The study sample size and follow-up was small and short respectively, and EQ-5D values were only reported at baseline and at the end of follow-up.

The utility values used in previous NICE Technology Appraisals in advanced breast cancer are presented in Table 54. Data from four primary utility sources were extracted after the following studies were excluded:

- Delea et al(105) and Dobrez et al(106) were excluded as they were mapping studies

- Cooper et al(90) was not a primary study; it used pooled utilities from published sources (Launois et al(92), Hutton et al(91), and Brown & Hutton(107)), where the utility values were obtained from oncology doctors and nurses using the standard gamble method.

Details on the remaining primary sources used in NICE Technology Appraisals in advanced breast cancer are presented in Table 55. The four remaining primary studies all used the standard gamble to elicit utilities from either the general public or oncology doctors/ nurses. Therefore, in contrast to the studies identified previously,

none of the studies met the preferred NICE reference case criteria regarding directly measuring HRQoL in patients.

Table 54: Utility sources used in NICE submissions

Treatment (submission)	PFS value	PFS source	PD value	PD source
Trastuzumab emtansine (TA371)(79)	0.78 (TRA) 0.72 (LAP+CAP)	Lloyd et al. (2006)(89)	0.5	Lloyd et al. (2006)(89)
Everolimus in combination with exemestane (TA295)(108)	0.7644 (EVE+EXE) 0.7571 (PLC+EXE)	Lloyd et al. (2006)(89)	0.65	Launois et al. (1996)(89)
Bevacizumab with capecitabine (TA263)(81)	0.784 (BEV+CAP) 0.774 (CAP)	Lloyd et al. (2006)(89)	0.496	Lloyd et al. (2006)(89)
Lapatinib plus letrozole (TA257)(82)	0.86	FACT-B from EGF30008 trial mapped (Delea et al. 2010 and Dobrez et al. 2007)	0.62	Lloyd et al. (2006)(89)
Trastuzumab plus anastrozole (TA257)(82)	0.73	Cooper et al. (2003)	0.45	Cooper et al. (2003)(90)
Eribulin (TA423)(83)	0.715 (stable) 0.790 (response)	Lloyd et al. (2006)(89)	0.443 0.16 (terminal)	Lloyd et al. (2006)(89) Cooper et al. (2003)(90)
Fulvestrant (TA239)(84)	0.72	Lloyd et al. (2006)(89)	0.44	Lloyd et al. (2006)(89)
Bevacizumab plus weekly paclitaxel (TA214)(85)	0.65 (stable) 0.81 (response)	Cooper et al. (2003)(90)	0.45	Cooper et al. (2003)(90)
Gemcitabine plus paclitaxel (TA116)(86)	0.72 (stable) 0.80 (response)	Survey of 100 members of the general public using VAS and SG	0.46	Survey of 100 members of the general public using VAS and SG
Trastuzumab plus paclitaxel (TA34)(87)	NR	Hutton et al. (1996)(91)	NR	Hutton et al. (1996)(91)

Abbreviations: BEV, bevacizumab; CAP, capecitabine; EVE, everolimus; EXE, exemestane; LAP, lapatinib; NR, not reported; PCL, placebo; SG, standard gamble; TA, technology appraisal; TRA, trastuzumab emtansine; VAS, visual analogue scale.

Table 55: Primary sources used in NICE Technology Appraisals in advanced breast cancer

Study	Country	Participants valuing health states (n)	Valuation technique	Analysis technique	Health state	Utility value
Lloyd et al.(89)	UK	General population [mean age 40.16 years; female 50%] (n=100)	SG	Mixed model with random effects including age and sex as coefficients	Stable metastatic breast cancer with no toxicities	0.715
					Treatment response	+0.075
					Disease progression	-0.272
					Febrile neutropenia	-0.150
					Diarrhoea and vomiting	-0.103
					Hand-foot syndrome	-0.116
					Stomatitis	-0.151
					Fatigue	-0.115
					Hair loss	-0.114
Hutton et al.(91)	UK, Spain, Germany, Italy, US, and Canada	Oncology nurses (n=129, 30 UK)	SG	No analysis	Partial response (UK only)	0.81 (0.84)
					Partial response & severe peripheral oedema (UK only)	0.75 (0.78)
					Stable disease (UK only)	0.62 (0.62)
					Before second-line therapy begins (UK only)	0.59 (0.56)
					Partial response and severe peripheral neuropathy (UK only)	0.53 (0.62)
					Progressive disease (UK only)	0.41 (0.33)
					Sepsis (UK only)	0.20 (0.16)
					Terminal disease (UK only)	0.16 (0.13)

Study	Country	Participants valuing health states (n)	Valuation technique	Analysis technique	Health state	Utility value
Launois et al.(92)	France	Oncology nurses (n=20)	SG	No analysis	Before starting chemotherapy	0.86
					Minor toxicities	0.76
					Severe skin reactions	0.72
					Severe arthralgia/myalgia	0.72
					Febrile neutropenia without hospitalization	0.66
					Early progression	0.52
					Gastrointestinal toxicity with hospitalization	0.48
					Febrile neutropenia with hospitalization	0.47
					Confirmed responder with..	0.81
					.. severe oedema	0.74
					.. treatment interrupted for severe oedema	0.64
					.. treatment interrupted for severe neuropathy	0.64
					.. severe neuropathy	0.57
					Stable with..	0.75
					.. severe oedema	0.73
					.. treatment interrupted for severe oedema	0.58
					.. treatment interrupted for severe neuropathy	0.58
					.. severe neuropathy	0.50

Study	Country	Participants valuing health states (n)	Valuation technique	Analysis technique	Health state	Utility value
					Progressed with..	0.65
					.. severe oedema	0.58
					.. treatment interrupted for severe oedema	0.53
					.. treatment interrupted for severe neuropathy	0.50
					.. severe neuropathy	0.45
					Terminal care	0.25
Brown & Hutton(107)*	US	Oncology nurses (n=29)	SG	N/A	Response	0.81
					Stable	0.65
					Progression	0.39
					Terminal	0.16

*Identified in Cooper et al.
Abbreviations: N/A, not applicable; SG, standard gamble; UK, United Kingdom; US, United States.

Lloyd et al(89) was the most common source of utility data across the HTAs. Although recognized as the best available data, several ERG reports have recognized some limitations of this study. As the health states described in the Lloyd study were based on literature reviews, exploratory interviews with physicians, an oncology focus group made up of specialist nurses; and that the health states were gender neutral and did not mention cancer, the derived utility values for the general public may not be fully reflective of patients with breast cancer or even the true general population(82).

The model by Lloyd et al(89) includes only six specific AEs and as such does not account for the full range of AEs experienced in a clinical trial(109). Furthermore, the study found that increasing age had a positive correlation with HRQoL, but this contradicts other established sources using larger samples of the general population, which suggest that HRQoL decreases with age(79). It has been highlighted in several submissions that the age parameter in Lloyd et al(89) refers to the age of the 100 participants involved in the exercise (40 years) and not the age of patients in the economic models(84). There is a lack of general agreement amongst economists as to the most appropriate value for the age parameter(82). Some believe that the mean age should be set to 47 years and the utility values adjusted accordingly in the model to be consistent with the standard UK EQ-5D tariff scores, as this is the mean of the original York study(101), but this adjustment was not always made(84, 109).

The ERG for the second-line fulvestrant submission stated that the utilities should be adjusted for age; the mean age should be set to 47, the mean age of the original York study(101). In line with this approach, age-adjusted utility values were calculated (Table 56).

Table 56: Health state utility values based on Lloyd et al(89)

Health state	Lloyd et al (2006)(89) – age-adjusted
Progression-free	0.7562
Progressed disease	0.4961

5.4.4 Adverse reactions

In addition to the health state utility values, utility decrements due to experiencing grade ≥3 adverse events were included in the base case analysis. Utility decrements

and the duration of AEs were sourced from previous NICE submissions; the estimates are presented in Table 57.

Table 57: Disutilities associated with adverse events

Adverse event	Utility decrement per event	Duration (days)	Source
ALT increased	-0.050	28.0*	Boehringer Ingelheim Ltd. (2014)(110)
AST increased	0.000	0.000	
Hypertension	-0.153	8.0	Swinburn et al. (2010)(111)
Pleural effusion	-0.371	3.0	Swinburn et al. (2010)(111)
Pain, bone	-0.069	17.0	Doyle et al. (2008)(112)
Pain, other	-0.069	17.0	Doyle et al. (2008)(112)
Dyspnoea	-0.103	12.7	Lloyd et al. (2006)(89)
Bilirubin increased	0.000	0.000	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
*Assumption

5.5.5 Health-related quality-of-life data used in cost-effectiveness analysis

The health state utility values used in the model are presented in Table 58 (disutilities associated with adverse events used in the model are presented in Table 57). In the base case analysis, utility values for the PF and PD health states were taken from MMRM (1) derived from the FALCON trial (7). The PF and PD utility values from MMRM (1) was considered to best match the NICE reference case and therefore the most appropriate estimates. It is acknowledged that the PD utility value may be an overestimation of the true HRQoL impact of disease progression in first-line metastatic patients; therefore, the impact of applying utility values from the summary statistics of the FALCON trial (7), from a combination of MMRM (1) and Lloyd model (the utility decrement associated with disease progression, estimated from the Lloyd model, was applied to the PF value from MMRM (1) to calculate the utility value for the PD health state), and from the Lloyd model directly were tested in scenario analyses; health state utility values tested in sensitivity analysis are presented in Table 59.

Table 58: Health state utility values used in the base case

Health state	Base case: MMRM (1)
Progression-free	**0.7511**
Progressed disease	**0.6913**

Abbreviations: MMRM, mixed models with repeated measurements.

Table 59: Health state utility values explored in sensitivity analysis

Health state	FALCON study summary statistics	MMRM (1) & Lloyd 2006	Lloyd 2006(89)
Progression-free	0.75	0.7511	0.7562
Progressed disease	0.69	0.4910	0.4961

Abbreviations: MMRM, mixed models with repeated measurements.

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Resource identification, measurement and valuation studies

The model uses 2016 prices in UK pounds sterling (£). Costs relating to earlier years were inflated to present values using the PSSRU Hospital and Community Health Services (HCHS) pay and price index(113). The model includes the following costs:

- Disease management
- Treatment acquisition
- Treatment administration
- Subsequent therapy
- Adverse events

5.5.2 Disease management costs

The disease management costs are health state-specific and not treatment-specific, and are split into progression-free, progressed disease (per 4 weeks), and terminal care.

The “Package 1” and “Package 2” methods reported in the NICE clinical guideline on ABC (CG81)(114) were applied to determine the PF and PD health state costs

respectively. Unit costs were inflated to 2015-2016 using the PSSRU HCHS pay and price index(113). The resource use and unit costs for the PF and PD health states are presented in Table 60 and Table 61.

Table 60: Costs of progression-free health state

Items	Resource usage per 4 weeks	Frequency	Unit cost (£) inflated to 2015/16	Total cost per month	Source*
Community nurse (home visit - 20 minutes)	2	1 per 2 weeks	£14.67	£29.34	PSSRU 2015/16 (113, 115)
GP contact (surgery visit – 11.7 minutes)	1	1 per month	£46.02	£46.02	PSSRU 2015/16 (113, 115)
Clinical nurse specialist (1 hour)	1	1 hour every month	£108.00	£108.00	PSSRU 2015/16 (113, 115)
Total progression-free cost per 4 weeks				£183.36	Calculation

Abbreviation: GP, General Practitioner.

*PSSRU 2015 used to provide duration of appointment time; PSSRU 2016 used to provide unit costs.

Table 61: Costs of progressed disease health state

Resource	Resource usage per 4 weeks	Frequency	Unit cost (£)	Total cost per 4 weeks (£)	Source*
Community nurse (home visit 20 minutes)	4	1 per week	£14.67	£58.67	PSSRU 2015/16 (113, 115)
Consultation with a GP (home visit)	2	1 per 2 weeks	£65.00	£130.00	PSSRU 2015/16 (113, 115)
Clinical nurse specialist (duration 1 hour)	4	1 per week	£108.00	£432.00	PSSRU 2015/16 (113, 115)
NHS community occupational therapist	2	1 per 2 weeks	£42.00	£84.00	PSSRU 2015/16 (113, 115)
Total progressed disease cost per 4 weeks				£704.67	Calculation

Abbreviations: GP, General Practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

*PSSRU 2015 used to provide duration of appointment time; PSSRU 2016 used to provide unit costs.

Terminal care costs were also included using the method described in the NICE CG81(114). In line with the guideline, it was assumed that 50% of patients die at

home, 40% in a hospital and 10% in a hospice. The unit costs were originally reported in 2006/2007 prices and have been inflated to 2015/16 values using the HCHS index(113). Terminal care costs are presented in Table 62. The cost of terminal care is applied as one lump sum upon death in the model.

Table 62: Terminal care costs

Terminal care setting	% of patients that died per setting	Unit cost (£)	Total cost (£)
Hospital	40%	£5,595.20	£2,238.08
Hospice	10%	£6,975.58	£697.56
Home	50%	£2,886.77	£1,443.39
Total terminal care costs (£)			**£4,379.03**

5.5.3 Intervention and comparators' costs and resource use

Drug acquisition costs are calculated based on available formulations; pack sizes, unit costs and price per mg for each treatment included in the model. The dosing information is sourced from the British National Formulary (BNF)(17) label for each treatment and the drug acquisition costs were sourced from eMit (116). The cost of fulvestrant is based on the BNF.

Treatment duration is assumed to be until objective disease progression. The PFS and time to treatment discontinuation KM curves are broadly comparable for both treatment arms (see Figure 43 and Figure 44). However, a small separation is seen for fulvestrant. Given that the most frequent reason for treatment discontinuation was disease progression and the proportion of other reasons for treatment discontinuation are small and comparable between arms, it is considered unlikely that these two endpoints are meaningfully different. The small separation observed for fulvestrant could be due to the fact that fulvestrant is dosed every 28 days and anastrozole is daily.

Figure 43: Comparison of time to treatment discontinuation and progression-free survival for the anastrozole arm of FALCON (7)

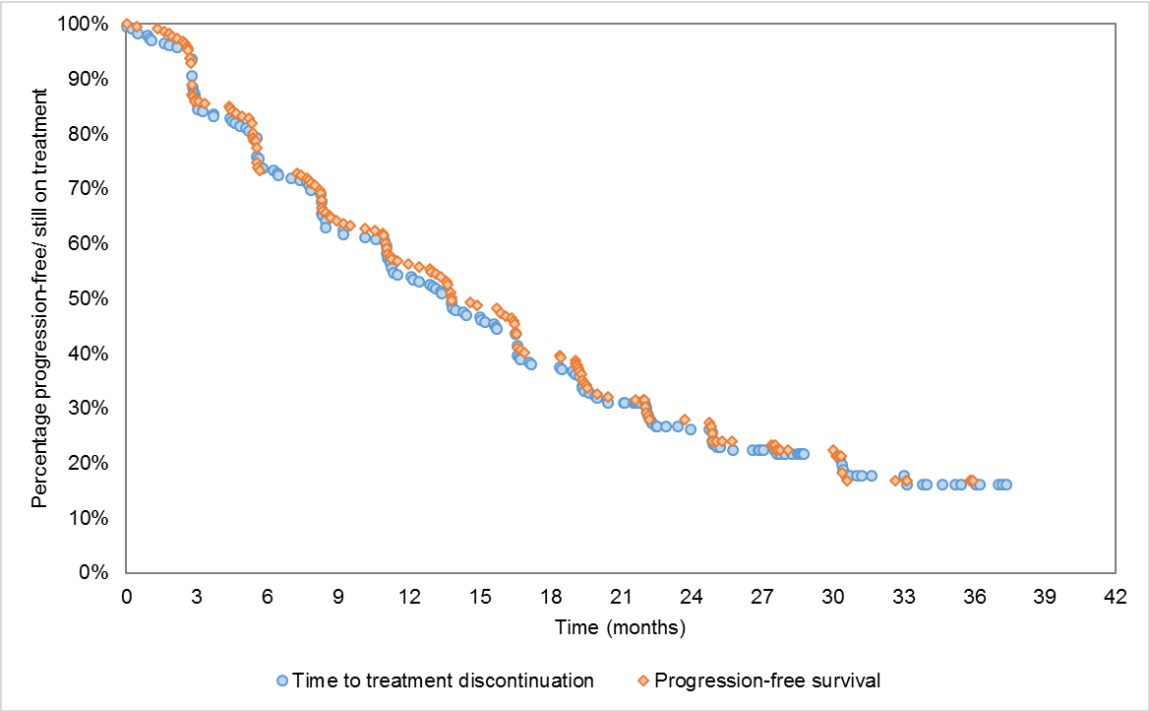
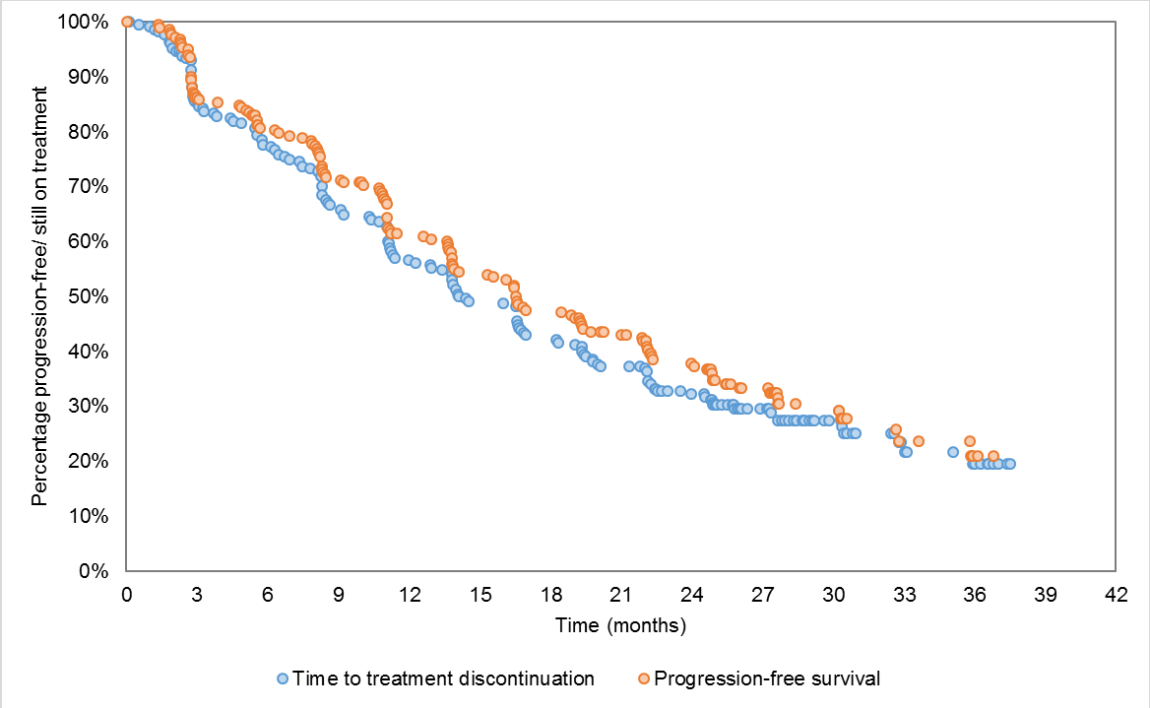


Figure 44: Comparison of time to treatment discontinuation and progression-free survival for the fulvestrant arm of FALCON (7)



The treatment acquisition cost is multiplied by the overall compliance to treatment. Table 63 summarises the treatment dosing, pack size and cost, and compliance for the treatments included in the model. The total treatment costs per 4-week cycle are presented in Table 64.

Table 63: Treatment dosing, administration and drug acquisition costs

		Fulvestrant (first 4 weeks)	Fulvestrant (after first 4 weeks)	Anastrozole	Letrozole	Tamoxifen
Label information	**Administration method**	IV	IV	Oral	Oral	Oral
	Dose per administration (mg)	500	500	1.0	2.5	2.5
	Administration frequency	2 per 4 weeks	1 per 4 weeks	1 per day	1 per day	1 per day
Package information	**Formulation (mg)**	250	250	1.0	2.5	20
	Pack size	2	2	28	28	30
	Cost per pack (£)	£522.41	£522.41	£0.75	£1.52	£1.62
Dosing required in model	**Required dose (mg)**	500	500	1.0	2.5	20
	Vials/ capsules per administration	1	1	0.04	0.04	0.03
Relative dose intensity/ compliance		1.00	0.99	0.99	1.00*	1.00*

Abbreviations: IV, intravenous.
*Assumption (data not available)

Table 64: Total drug acquisition per 4-week cycle

	Total cost per 4 weeks (£)*
Fulvestrant (first 4 weeks)	£1,044.82
Fulvestrant (after first 4 weeks)	£522.41*
Anastrozole	£0.75*
Letrozole	£1.52
Tamoxifen	£1.51

*Based on a compliance rate of 0.99(97)

Treatment administration costs are calculated separately for the first 4-week cycle and subsequent cycles due to differences in resource use. Treatment administration costs are consistent with the NICE submission for fulvestrant for the treatment of disease relapse on or after adjuvant anti-ooestrogen therapy or disease progression on therapy with an anti-ooestrogen, TA239(84). It was assumed that to initiate treatment on fulvestrant or any of the comparators, an initial consultation with an oncologist would be required to make an assessment and determine the appropriate treatment for the patient. It was assumed that if the patient was initiated on

fulvestrant, it would be administered after the initial oncologist visit by a nurse. If the patient was initiated on any of the comparators, the oncologist would provide a prescription during this initial visit. Subsequent administrations of fulvestrant may be delivered in the primary care setting (32.3%) or in the outpatient setting (67.7%).

In the primary care setting, fulvestrant was assumed to be delivered by a community nurse as a 15 minute appointment. If administered in the outpatient setting, it was assumed that a follow-up non-admitted visit with an oncologist would be required. Based on expert opinion, it was determined that repeat prescriptions for anastrozole, letrozole and tamoxifen are provided by GPs on a monthly basis as these are oral medications. A telephone consultation with a GP lasting 7.1 minutes was assumed.

Tamoxifen is not included in TA239 but as an oral therapy is assumed to have the same treatment administration costs as anastrozole and letrozole. Treatment administration costs for each drug based on the above resource use required to initiate treatment for initial and subsequent administrations are presented in Table 65. The administration costs for fulvestrant in the first cycle is £370 and £73 in subsequent cycles. The administration costs for all other comparators are £197 in the first cycle and £28 in subsequent cycles.

Table 65: Unit costs, resource use and total 4-week administration costs

Treatment (treatment cycle [weeks])	Cost item	Number per cycle (first)	Number per cycle (subsequent)	Percentage(to be used for weighed average of service in primary or secondary setting)	Unit cost (£)	Total cost first cycle (£)	Total cost sub-sequent cycle (£)	Source	Description
Fulvestrant	Oncologist visit	1	-	100%	196.64	196.64	0.00	NHS reference cost 2015-16(117)	NHS Trusts Consultant Led: First Attendance Non-Admitted Face to Face, Medical Oncology Code 370
	Oncologist visit follow-up	1	-	100%	99.97	99.97	0.00	NHS reference cost 2015-16(117)	NHS Trusts Non-Consultant Led: Follow up Attendance Non-Admitted Face to Face,Medical oncology Code 370
	Community nurse specialist 15 minutes	1	1	32%	18.75	6.06	6.06	PSSRU 2016(113)	Cost per working hour for Nurse Band 6 (PSSRU 2016) (ratio between working hour and hour of patient related work assumed the same as in PSSRU 2015)
	Oncologist visit follow-up	1	1	68%	99.97	67.68	67.68	NHS reference cost 2015-16(117)	NHS Trusts Non-Consultant Led: Follow up Attendance Non-Admitted Face to Face,Medical oncology Code 370
						370.35	**73.74**		
Oral therapies (anastrozole, letrozole, and tamoxifen)	Oncologist visit	1	-	100%	196.64	196.64	0.00	NHS reference cost 2015-16(117)	NHS Trusts Consultant Led: First Attendance Non-Admitted Face to Face, Medical Oncology Code 370
	GP telephone consultation	-	1	100%	27.93	0.00	27.93	PSSRU 2016(113)	GP consultation lasting 7.1 minutes (PSSRU 2015) based on GP hour cost including direct care staff costs with qualification costs (PSSRU 2016)
						196.64	**27.93**		

Abbreviations: GP, general practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

5.5.4 Subsequent therapy costs

The cost-effectiveness analysis includes the cost of treatments post-progression. The number of treatment options and proportions of patients receiving each of the treatment options were based on Kurosky 2015(118), a retrospective cohort study of postmenopausal patients with metastatic ER+, HER2- breast cancer in the UK, and a number of assumptions.

In line with advice given from the panel of UK breast cancer clinicians consulted by AstraZeneca (54), which stated that the number of lines of subsequent endocrine and chemotherapies, and their duration, would remain the same following either use of fulvestrant or an AI as a first line treatment, it was initially assumed that subsequent treatment options would be the same for all treatments. However, as Kurosky 2015 (118) documents, fulvestrant use in the second and third-line setting it was assumed, in the absence of evidence to the contrary, that patients starting on fulvestrant would not go on to receive it in later lines of therapy. Therefore, the same subsequent treatment options are applied to all treatments apart from fulvestrant, where subsequent fulvestrant use was assumed not to occur. The inclusion of subsequent fulvestrant treatment for those patients initiating fulvestrant as first-line therapy is tested in sensitivity analysis.

Two lines of treatments were considered:

- second-line therapy (after first-line)
- third-line therapy (after first- and second-line).

Second- and third-line therapies were categorized into endocrine and chemotherapies. A targeted therapy (everolimus plus exemestane) was also considered within the possible treatment options following progression from first-line. In-line with data presented in Kurosky 2015(118), targeted therapy is only considered second line.

Due to the small proportion of patients moving to chemotherapy in combination with or followed by endocrine therapy (13% in second-line and 4% in third-line) and the lack of data to cost these treatments, they were excluded as treatment options. The

percentage of patients receiving endocrine therapies, chemotherapies, and targeted therapies was consequently rescaled to 100%.

The percentage split of patients across therapies at second and third line are presented in Table 65. Kurosky 2015(118) reported that 100% of patients that initiated first-line therapy subsequently initiated second-line therapy. It was therefore assumed in the model that 100% of those patients who were alive and experienced disease progression would initiate second-line therapy. The proportion of patients who, having received treatment second-line, would go on to receive third-line treatment was calculated from the rescaled probabilities presented in Table 65: 54.41% (100% - 45.59%).

Table 66: Proportion of patients using subsequent treatments in the second- and third-line settings

From primary treatment to →→→ / Setting	Endocrine therapy (%)	Targeted therapy (%)	Chemotherapy (%)	No treatment (%)	Total (%)
Second-line	54.35%	8.08%	37.57%	0.00%	100.00%
Third-line	24.02%	0.00%	30.39%	45.59%	100.00%

The duration of subsequent treatments was also sourced from Kurosky 2015(118). On average, patients on endocrine therapy were assumed to receive treatment for 9.16 months in second-line and 6.17 months in third-line. Yardley 2013(119) reported the median duration of exposure to everolimus in the BOLERO-2 trial to be 23.9 weeks (range 1.0-123.3). An estimated mean duration of exposure of 9.89 months was estimated using the following formula:

$$Mean = \frac{(min + (2 * median) + max)}{4}$$

In the absence of data specific to targeted therapies in Kurosky 2015 and in-line with the estimated mean exposure from BOLERO-2, the duration of treatment for targeted therapy was assumed to be the same as that for endocrine therapies. Patients receiving chemotherapy were assumed to receive treatment for 6.1 months both in second- and third-line. The treatment durations are presented in Table 67.

Table 67: Mean (SD) treatment durations of subsequent treatments in the second- and third-line settings (months)

Setting	Endocrine therapy	Targeted therapy	Chemotherapy	No treatment
Second-line	9.16 (6.2)	9.16 (6.2)	6.1 (7.5)	N/A
Third-line	6.17 (7.9)	-	6.1 (4.4)	N/A

Abbreviations: SD, standard deviation.

For each class of therapy, the weighted average cost per 4-week cycle was estimated. The estimated costs include acquisition and administration costs (first and subsequent cycles), which are detailed in Table 68 and Table 69, respectively. Table 70 summarises the weighted average costs for first-line and second-line subsequent treatments. For non-generic costs or when the cost was not available in the NHS eMIT database, the unit costs were sourced from the BNF. The distribution within each treatment class was estimated based on Kurosky 2015(118).

For endocrine therapy, weighted averages including and excluding fulvestrant were calculated on the assumption that patients receiving fulvestrant as first-line therapy would not receive the same endocrine therapy in subsequent lines.

Table 68: Treatment dosing, administration and drug acquisition costs (additional subsequent treatments)

		Capecitabine	Docetaxel	Eribulin	Everolimus	Paclitaxel
Label information	Admin method	Oral	IV	IV	Oral	IV
	Dose per admin	1,250 mg/m²	75 mg/m²	1.4 mg/m²	10 mg	175 mg/m²
	Admin frequency	2 per day for 2 weeks, followed by 1 week off	1 per 3 weeks	2 per 3 weeks	1 per day	1 per 3 weeks
Package information	Formulation (mg)	500	140	0.88	10	330[1]
	Pack size	120	1	1	30	1
	Cost per pack (£)	£29.59	£17.77	£361.00	£2,673.00	£24.89[1]
Dosing used in model	Required dose per admin[2]	£2,250.00	£133.50	£2.49	£10.00	£311.50
	Vials / caps per admin	0.04	0.95	2.83	0.03	0.94
	Vials / caps per admin (without wastage)	0.04	1.00	3.00	0.03	1.00
Relative dose intensity/compliance		--	--	--	--	--
Cost per 4 weeks (£)		£40.97	£23.69	£2,888.00	£2,494.80	£33.19

Abbreviations: IV, intravenous.
[1]Includes 30mg and 300mg vial
[2]Based on a body surface area of 1.78m²

Table 69: Unit costs and resource use for administration costs (additional subsequent treatments)

Treatment	Cost item	Number per cycle (first)	Number per cycle (subsequent)	Unit cost (£)	Total cost first cycle (£)	Total cost subsequent cycle (£)	Source	Description
Capecitabine	Oncologist visit	1	-	£196.64	£196.64	-	NHS reference cost 2015-16(117)	Assumed zero cost in TA295, therefore assumed equal to endocrine oral therapies
	GP telephone consultation	0.33	1.33	£27.93	£9.31	£37.24	PSSRU 2016(113)	
Docetaxel **Eribulin**	SB12Z – Deliver Simple Parenteral Chemotherapy at First Attendance	1.33	1.33	£236.19	£314.92	£314.92	NHS reference cost 2015-16(117)	HRG code used in TA423
Paclitaxel	SB14Z – Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	1.33	1.33	£383.13	£510.84	£510.84	NHS reference cost 2015-16(117)	HRG code used in TA423
Everolimus plus exemestane	Oncologist visit	1	-	£196.64	£196.64	-	NHS reference cost 2015-16(117)	Assumed equal to exemestane monotherapy
	GP telephone consultation	-	1	£27.93	-	£27.93	PSSRU 2016(113)	

Abbreviations: GP, General practitioner; HRG, Healthcare Resource Group; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Table 70: Weighted average costs of subsequent treatments in the second- and third-line settings (per cycle)

Treatment class	Treatment	Treatment costs (per administration)				Second-line		Third-line	
		Acquisition (<4weeks) (£)	Acquisition (>4weeks) (£)	Administration (first) (£)	Administration (subs) (£)	Proportion of patients (incl. fulvestrant)	Cost per 4-week cycle (£)	Proportion of patients (incl. fulvestrant)	Cost per 4-week cycle (£)
Endocrine therapies	Fulvestrant	£1,044.82	£522.41	£475.78	£116.30	10.99%	**With fulvestrant**: First: £344.86 Subs: £97.77 **Without fulvestrant:** First: £199.70 Subs: £30.99	36.11%	**With fulvestrant**: First: £676.50 Subs: £250.25 **Without fulvestrant:** First: £199.39 Subs: £30.68
	Anastrozole	£0.75	£0.75	£196.64	£27.93	17.58%		13.89%	
	Letrozole	£1.52	£1.52	£196.64	£27.93	15.38%		-	
	Exemestane	£5.56	£5.56	£196.64	£27.93	37.36%		22.22%	
	Tamoxifen	£1.51	£1.51	£196.64	£27.93	18.68%		27.78%	
Targeted therapies	Everolimus plus exemestane	£2,500.36	£2,500.36	£196.64	£27.93	100%	First: £2,697.00 Subs: £2,528.29	-	-
Chemo-therapies	Docetaxel	£23.69	£23.69	£314.92	£314.92	28.00%	First: £343.85 Subs: £262.87	-	First: £849.38 Subs: £711.74
	Capecitabine	£40.97	£40.97	£205.95	£37.24	48.00%		81.58%	
	Paclitaxel	£33.19	£33.19	£510.84	£510.84	24.00%		-	
	Eribulin	£2,888.00	£2,888.00	£629.84	£629.84	-		18.42%	

Abbreviations: Incl., including; Subs, subsequent.

Table 71 presents the subsequent treatment costs applied in the model. The total acquisition and administration costs associated with subsequent treatment for all comparators bar fulvestrant are £3,371 and £1,319, respectively; for fulvestrant the total acquisition and administration costs are £2,775 and £1,202, respectively. Scenario analyses were run using the same subsequent treatments to all primary treatments.

Table 71: Weighted average costs of subsequent treatments in the second and third line settings (total duration)

Primary treatment	Acquisition	Administration	Total
Fulvestrant (including fulvestrant post-progression)	£2,775.28 (£3,370.75)	£1,202.29 (£1,318.50)	£3,977.57 (£4,689.25)
Anastrozole	£3,370.75	£1,318.50	£4,689.25
Letrozole	£3,370.75	£1,318.50	£4,689.25
Tamoxifen	£3,370.75	£1,318.50	£4,689.25

5.5.5 Adverse reaction unit costs and resource use

NHS reference costs were used to cost AEs and cost codes for each AE were adopted from those reported in previous NICE submissions. The costs associated with the adverse events included in the model are presented in Table 72. The Technology Appraisals from which the NHS reference costs' cost codes were sourced are also reported.

Table 72: Adverse event costs

Adverse event	Cost per event (£)	Description	Source
ALT increased	£1,757.79	GC17A-K Non-Malignant, Hepatobiliary or Pancreatic Disorders, without/with single/multiple Interventions, with CC Score 0-9+	NHS reference costs 2015-16(117); TA347(120)
AST increased	£1,757.79	GC17A-K Non-Malignant, Hepatobiliary or Pancreatic Disorders, without/with single/multiple Interventions, with CC Score 0-9+	Assumed to be the same as ALT increase due to both being associated with the liver
Hypertension	£729.87	EB04Z Hypertension	NHS reference costs 2015-16(117) TA378(121)
Pleural effusion	£1,830.68	DZ16H-R Pleural effusion with multiple/single/no intervention with CC score	NHS reference costs 2015-16(117) TA360(122)
Pain, bone	£1,038.08	HD216 D-G Musculoskeletal Signs or Symptoms, with CC Score 0 -12+	NHS reference costs 2015-16(117) TA391(123)
Pain, other	£626.97	Combination of all pain-related codes in NHS Reference Costs	NHS reference costs 2015-16(117) TA311(124), TA377(125), TA378(121)
Dyspnoea	£718.76	DZ19H-N Other Respiratory Disorders without Interventions, with CC Score 0-11+, without, with single or multiple interventions	NHS reference costs 2015-16(117) TA420(126)
Biliribulin increased	£1,757.79	GC17A-K Non-Malignant, Hepatobiliary or Pancreatic Disorders, without/with single/multiple Interventions, with CC Score 0-9+	Assumed to be the same as ALT increase due to both being associated with the liver

Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; NHS, National Health Service; TA, Technology Appraisal.

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Summary of base-case de novo analysis inputs

Details of all of the values used in the economic model are provided in Appendix H.

A summary of the key variables used in the model is presented in Table 73.

Table 73: Summary of variables applied in the economic model (base case analysis)

Area	Variable	Value	Reference to section in submission
Model settings/ patient characteristics	Time horizon	30 years	Section 5.2
	Model cycle length	4 weeks	Section 5.2
	Starting age	63.8 years	Section 5.2
	Discount rate costs	3.5%	Section 5.2
	Discount rate outcomes	3.5%	Section 5.2
Clinical efficacy data	OS - fulvestrant	[redacted]	Section 5.3
	OS - anastrozole	[redacted]	Section 5.3
	OS - letrozole	[redacted]	Section 5.3
	OS - tamoxifen	[redacted]	Section 5.3
	PFS - fulvestrant	[redacted]	Section 5.3
	PFS - anastrozole	[redacted]	Section 5.3
	PFS - letrozole	[redacted]	Section 5.3
	PFS - tamoxifen	[redacted]	Section 5.3
Resource use and costs	Cost of fulvestrant (per 2x vials)	£522.41	Section 5.5
	Cost of anastrozole (per pack)	£0.75	Section 5.5
	Cost of letrozole (per pack)	£1.52	Section 5.5
	Cost of tamoxifen (per pack)	£1.62	Section 5.5

Area	Variable	Value	Reference to section in submission
	Administration cost per dose (fulvestrant) – first 4 weeks	£370.35	Section 5.5
	Administration cost per dose (fulvestrant) – subsequent 4-week cycles	£73.74	Section 5.5
	Administration cost per dose (comparators) – first 4 weeks	£196.64	Section 5.5
	Administration cost per dose (comparators) – subsequent 4-week cycle	£27.93	Section 5.5
	Disease management costs – PF (per 4 weeks)	£180.29	Section 5.5
	Disease management costs – PD (per 4 weeks)	£704.67	Section 5.5
	Terminal care cost	£4,379.03	Section 5.5
Utility values	PF	0.7511	Section 5.4
	PD	0.6913	Section 5.4

Abbreviations: OS, overall survival; PF, progression-free; PFS, progression-free survival; PD, progressed disease.

5.6.2 Assumptions

- A year in the model is assumed to consist of 13 4-week cycles, and each month is 4.35 weeks long. The model applied half-cycle corrections
- The average treatment dosages used in the model are assumed to account for dose reductions and treatment gaps
- Treatment duration is assumed to be until objective disease progression
- Disease management costs:

    - Progression-free: 4-week resource usage multiplied by the respective unit cost
    - Progressed disease state: the proportion of patients that require the resource, multiplied by the respective unit cost

- A terminal care cost is applied to each patient upon death to reflect the additional resource usage. This cost is an aggregated cost of the medical costs in the final 4 weeks of a UK cancer patient. It is assumed that this is strictly in addition to standard care therefore there is no double counting
- The cost of subsequent treatment is a weighted average consisting of treatment costs (acquisition and administration), mean treatment duration after progression, and the distribution of patients on subsequent treatments following primary treatment discontinuation. No wastage is assumed for subsequent treatments
- In the absence of disaggregated data, a mix of subsequent treatments is assumed for all patients. The treatment mix is assumed to differ between fulvestrant and the comparators as fulvestrant is not included in the subsequent treatment mix for those patients initiating fulvestrant as first-line therapy
- The subsequent treatment cost is applied as a one-off cost upon progression. This is calculated using the new progressed disease population each cycle which tends to result in an underestimation of patients receiving subsequent treatment.
- Subsequent treatments are assumed to only impact on costs; any impact on survival is assumed to be captured in the OS estimates
- Both the costs and disutilities associated with AEs are assumed to occur as one-off costs/disutilities in the first cycle of the model.

5.7 Base-case results

5.7.1 Base-case incremental cost effectiveness analysis results

Total costs, life years gained (LYG), QALYs and incremental cost per QALY for that patients would experience whilst on either the intervention treatment (fulvestrant 500mg), or the comparator treatments (anastrozole, letrozole and for those patients in which aromatase inhibitors are not tolerated or are contraindicated, tamoxifen), over the model time horizon (30 years, lifetime). The Weibull distribution from the fixed effects NMA was used to extrapolate OS and the generalised gamma distribution estimated from the fixed effects NMA was used to extrapolate PFS in the base case analysis.

The results section presents the results of fulvestrant when compared against the AIs (anastrozole and letrozole) and the results of fulvestrant when compared against tamoxifen (in those patients in which AIs are not tolerated or are contraindicated) separately.

Pair-wise comparisons of fulvestrant vs anastrozole, letrozole and tamoxifen are presented in Table 74, Table 75 and Table 76.

Table 74: Fulvestrant vs. anastrozole

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Anastrozole	£30,261	3.736	2.676	-	-	-	-
Fulvestrant	£49,165	4.475	3.229	£18,904	0.739	0.553	£34,179

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

Table 75: Fulvestrant vs. letrozole

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Letrozole	£25,928	3.399	2.455	-	-	-	-
Fulvestrant	£49,165	4.475	3.229	£23,237	1.076	0.774	£30,025

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

Table 76: Fulvestrant vs. tamoxifen

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Tamoxifen	£31,941	3.479	2.469	-	-	-	-
Fulvestrant	£49,165	4.475	3.229	£17,223	0.996	0.760	£22,655

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

An incremental analysis of fulvestrant versus the aromatase inhibitors is presented in Table 77. Letrozole was associated with the lowest overall cost (£25,928), followed by anastrozole (£30,261) and fulvestrant (£49,165). Letrozole was used as the baseline comparator within the incremental analysis as it was associated with the lowest overall total cost. ICERs were calculated for each treatment versus the next least costly non-dominated option. This resulted in an ICER for anastrozole versus letrozole of £19,621, and for fulvestrant versus anastrozole of £34,179.

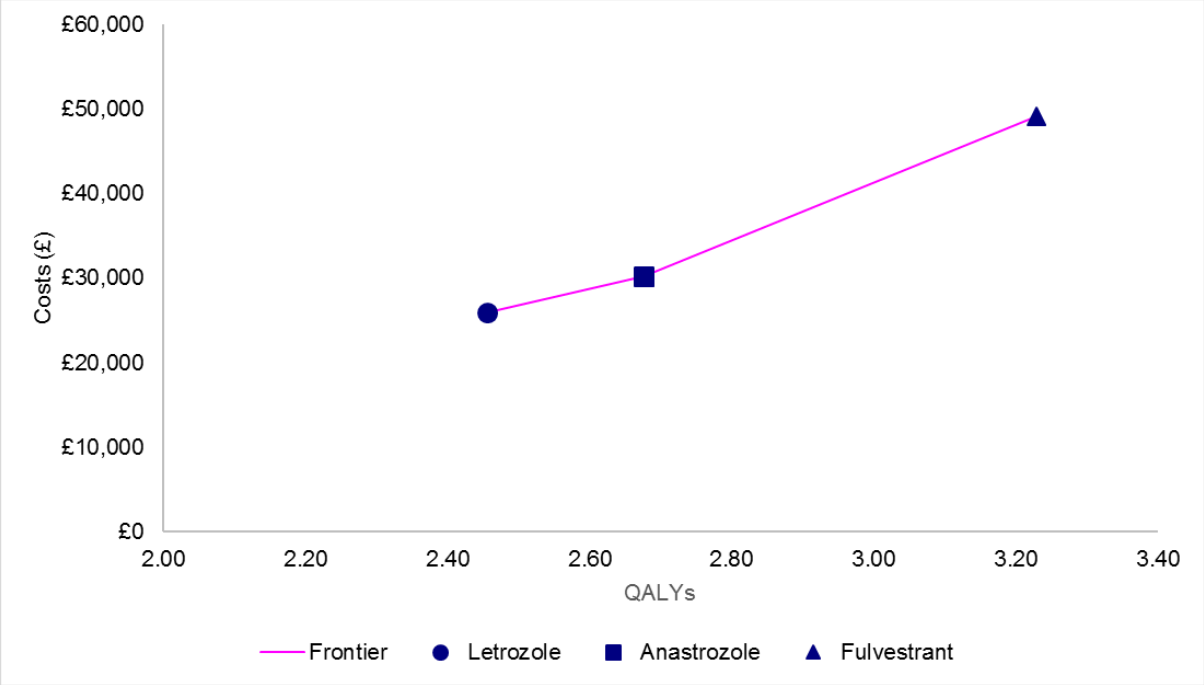
Figure 45 presents the cost-effectiveness frontier.

Table 77: Incremental analysis

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Letrozole	£25,928	3.399	2.455	-	-	-	-
Anastrozole	£30,261	3.736	2.676	£4,333	0.337	0.221	£19,621
Fulvestrant	£49,165	4.475	3.229	£23,237	1.076	0.774	£34,179

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

Figure 45: Deterministic cost-effectiveness plane comparing fulvestrant, anastrozole and letrozole



5.7.2 Clinical outcomes from the model

The predicted mean and median time to progression, time in progressed disease and time alive for each arm of the simulation are summarized in Table 78. The extrapolated survival showed good consistency with external data (see Table 79 and Table 80).

Table 78: Survival outcomes; time (mean and median) spent in health states, undiscounted

Treatment	Time in PFS (months)		Time in PD (months)		Time alive (months)	
	Median	Mean	Median	Mean	Median	Mean
Fulvestrant	16.56	29.58	31.28	30.51	47.84	60.08
Anastrozole	11.96	19.56	27.60	29.38	39.56	48.95
Letrozole	14.72	22.16	23.92	21.26	38.64	43.42
Tamoxifen	9.20	13.16	27.60	31.89	36.80	45.05

Abbreviation: PD, progressed disease; PFS, progression-free survival.

Table 79: Comparison of modelled outcomes (PFS) against other available sources

Treatment	Median PFS (months)		
	Model outcomes	Systematic literature review	Previous HTA assessments
Fulvestrant	16.56	Range: 16.6 – 25.9	NA
Anastrozole	11.96	Range: 12.9 – 14.8	NA
Letrozole	14.72	9.60	14.5[1]
Tamoxifen	9.20	Range: 5.9 – 10.4	NA

Abbreviations: HTA, Health Technology Assessment; NA, not available; PFS, progression-free survival.
[1]palbociclib NICE submission, Table 76, company submission(127)

Table 80: Comparison of modelled outcomes (OS) against other available sources

Treatment	Median OS (months)		
	Model outcomes	Systematic literature review	Previous HTA assessments
Fulvestrant	47.84	62.5	NA
Anastrozole	39.56	Range: 44.9 – 46.5	NA
Letrozole	38.64	34	33.3[1]
Tamoxifen	36.80	Range: 30.3 – 43.6	NA

Abbreviations: HTA, Health Technology Assessment; NA, not available; OS, overall survival.
[1]palbociclib NICE submission, Table 76, company submission(127)

5.7.3 Disaggregated results of the base case incremental cost-effectiveness analysis

Table 81, Table 82 and Table 83 summarises the breakdown of QALYs for each health state over the model time horizon in the base case analysis for fulvestrant vs anastrozole, letrozole and, for those patients in which aromatase inhibitors are not tolerated or are contraindicated, tamoxifen, respectively. Treatment with fulvestrant is associated with more QALYs in pre-progression and progressed disease when compared with each of the AIs. When compared against tamoxifen, fulvestrant results is associated with more QALYs in the pre-progression health state but less in the progressed disease health state.

Table 81: Summary of QALY gain by health state; fulvestrant vs. anastrozole

Health state	QALY intervention (fulvestrant)	QALY comparator (anastrozole)	Incremental QALYs	% absolute incremental QALYs
PF	1.71	1.18	0.53	95.85%
PD	1.52	1.50	0.02	4.17%
AE disutility	0.00	0.00	0.00	-0.02%
Total	3.23	2.68	0.55	100.00%

Abbreviation: AE, adverse events; PD, progressed disease; PF, progression-free.

Table 82: Summary of QALY gain by health state; fulvestrant vs. letrozole

Health state	QALY intervention (fulvestrant)	QALY comparator (letrozole)	Incremental QALYs	% absolute incremental QALYs
PF	1.71	1.33	0.38	48.86%
PD	1.52	1.13	0.40	51.17%
AE disutility	0.00	0.00	0.00	-0.02%
Total	3.23	2.46	0.77	100.00%

Abbreviation: AE, adverse events; PD, progressed disease; PF, progression-free.

Table 83: Summary of QALY gain by health state; fulvestrant vs. tamoxifen

Health state	QALY intervention (fulvestrant)	QALY comparator (letrozole)	Incremental QALYs	% absolute incremental QALYs
PF	1.71	0.81	0.90	117.82%
PD	1.52	1.66	-0.14	-17.87%
AE disutility	0.00	0.00	0.00	0.06%
Total	3.23	2.47	0.76	100.00%

Abbreviation: AE, adverse events; PD, progressed disease; PF, progression-free.

Table 84, Table 85 and Table 86 summarises the breakdown of costs in the base case analysis. The largest contributor to incremental costs between fulvestrant and each of the comparators is the drug acquisition cost, accounting for approximately 68-92% of the total incremental costs. Treatment with fulvestrant is associated with higher absolute disease costs compared with each of the comparators, which is driven by patients surviving longer on fulvestrant therapy.

Table 84: Summary of costs by health state; fulvestrant vs. anastrozole

Health state	Cost intervention (fulvestrant)	Cost comparator (anastrozole)	Incremental costs	% absolute increment
Disease management: PF	£5,419	£3,737	£1,682	8.90%
Disease management: PD	£20,167	£19,862	£306	1.62%
Terminal care	£3,719	£3,868	-£149	-0.79%
Treatment acquisition	£15,841	£15	£15,825	83.71%
Administration and monitoring	£2,458	£733	£1,725	9.12%
Subsequent treatment	£1,449	£1,994	-£545	-2.89%
Adverse events	£112	£52	£60	0.32%
Total	£49,165	£30,261	£18,904	100.00%

Abbreviation: PD, progressed disease; PF, progression-free.

Table 85: Summary of costs by health state; fulvestrant vs. letrozole

Health state	Cost intervention (fulvestrant)	Cost comparator (letrozole)	Incremental costs	% absolute increment
Disease management: PF	£5,419	£4,219	£1,200	5.16%
Disease management: PD	£20,167	£14,920	£5,247	22.58%
Terminal care	£3,719	£3,938	-£218	-0.94%
Treatment acquisition	£15,841	£35	£15,806	68.02%
Administration and monitoring	£2,458	£811	£1,647	7.09%
Subsequent treatment	£1,449	£1,993	-£544	-2.34%
Adverse events	£112	£12	£100	0.43%
Total	£49,165	£25,928	£23,237	100.00%

Abbreviation: PD, progressed disease; PF, progression-free.

Table 86: Summary of costs by health state; fulvestrant vs. tamoxifen

Health state	Cost intervention (fulvestrant)	Cost comparator (tamoxifen)	Incremental costs	% absolute increment
Disease management: PF	£5,419	£2,577	£2,843	16.50%
Disease management: PD	£20,167	£21,968	-£1,801	-10.45%
Terminal care	£3,719	£3,919	-£199	-1.16%
Treatment acquisition	£15,841	£21	£15,819	91.85%
Administration and monitoring	£2,458	£561	£1,897	11.01%
Subsequent treatment	£1,449	£2,588	-£1,139	-6.61%
Adverse events	£112	£309	-£197	-1.14%
Total	£49,165	£31,941	£17,223	100.00%

Abbreviation: PD, progressed disease; PF, progression-free.

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted in order to assess the parametric uncertainty associated with the base case model results. Those parameters where estimates of uncertainty were available were assigned probability distributions and point estimates were drawn using Monte Carlo simulation techniques. Where available, known correlation between parameters was preserved; e.g., the correlations for the baseline survival curve parameters (PFS and OS) were available from the survival analysis and included in the model (assuming a multivariate normal distribution). The parameters to which there was uncertainty, and the choice of distribution used is presented in Table 87.

Table 87: PSA distributions according to parameter

Parameter	Distribution	Comment
Survival distributions	Cholesky decomposition	Decomposition of a Hermitian, positive-definite matrix into the product of a lower triangular matrix and its conjugate transpose
Survival curve (shape, scale, and covariate parameters)	Multinomial normal	Incorporates the covariance between parameters estimated in a survival regression analysis
Costs	Gamma	Likely skewed nature of health care costs, and their constraint to positive values
AE rates (incidence)	Beta	Bounded between 0 and 1
Distribution of subsequent treatments	Dirichlet distribution	Normalised sum of independent gamma variables
Duration of subsequent treatment	Gamma	Bounded between 0 and infinity, and skewed
Utilities	Beta	Constrained to values between minus infinity and 1. Modelled as a disutility
AE disutilities	Lognormal	Bounded between 0 and infinity, and skewed

Abbreviation: AE, adverse event; PSA, probabilistic sensitivity analysis.

The PSA was run was 10,000 iterations for the base case analysis. Results from the PSA are presented in Table 88, Table 89 and Table 90 for fulvestrant vs. anastrozole, letrozole and tamoxifen, respectively. The probabilistic ICER for fulvestrant vs. anastrozole is £33,870 per QALY gained which compares with £34,179 in the deterministic analysis, a difference of 0.91%. The probabilistic ICER for fulvestrant vs. letrozole is £31,058, which is a 3.38% difference from the deterministic estimate of £30,025. The probabilistic ICER for fulvestrant vs. tamoxifen is £22,756 as compared with the deterministic estimate of £22,937, a 1.24% difference.

Table 88: Average results based on the probabilistic sensitivity analysis (10,000 iterations); fulvestrant vs. anastrozole

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Anastrozole	£30,434	3.761	2.694	-	-	-	-
Fulvestrant	£49,573	4.518	3.259	£19,139	0.757	0.565	£33,870

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

Table 89: Average results based on the probabilistic sensitivity analysis (10,000 iterations); fulvestrant vs. letrozole

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Letrozole	£26,376	3.480	2.513	-	-	-	-
Fulvestrant	£49,573	4.518	3.259	£23,197	1.038	0.747	£31,058

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

Table 90: Average results based on the probabilistic sensitivity analysis (10,000 iterations); fulvestrant vs. tamoxifen

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Tamoxifen	£32,239	3.527	2.504	-	-	-	-
Fulvestrant	£49,573	4.518	3.259	£17,334	0.992	0.756	£22,937

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

The results of the incremental analysis are presented in Table 91. Letrozole was used as the baseline comparator within the incremental analysis as it was associated with the lowest overall total cost. ICERs were calculated for each treatment versus the next least costly non-dominated option. This resulted in an ICER for anastrozole versus letrozole of £22,319, and for fulvestrant versus anastrozole of £33,870.

Table 91: Incremental analysis (PSA results)

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Letrozole	£26,376	3.480	2.513	-	-	-	-
Anastrozole	£30,434	3.761	2.694	£4,057	0.281	0.182	£22,319
Fulvestrant	£49,573	4.518	3.259	£19,139	0.757	0.565	£33,870

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

The cost-effectiveness planes (CEP) for fulvestrant compared with anastrozole, letrozole and tamoxifen are presented in Figure 46, Figure 47 and Figure 48, respectively.

Figure 46: Cost-effectiveness plane for fulvestrant vs. anastrozole

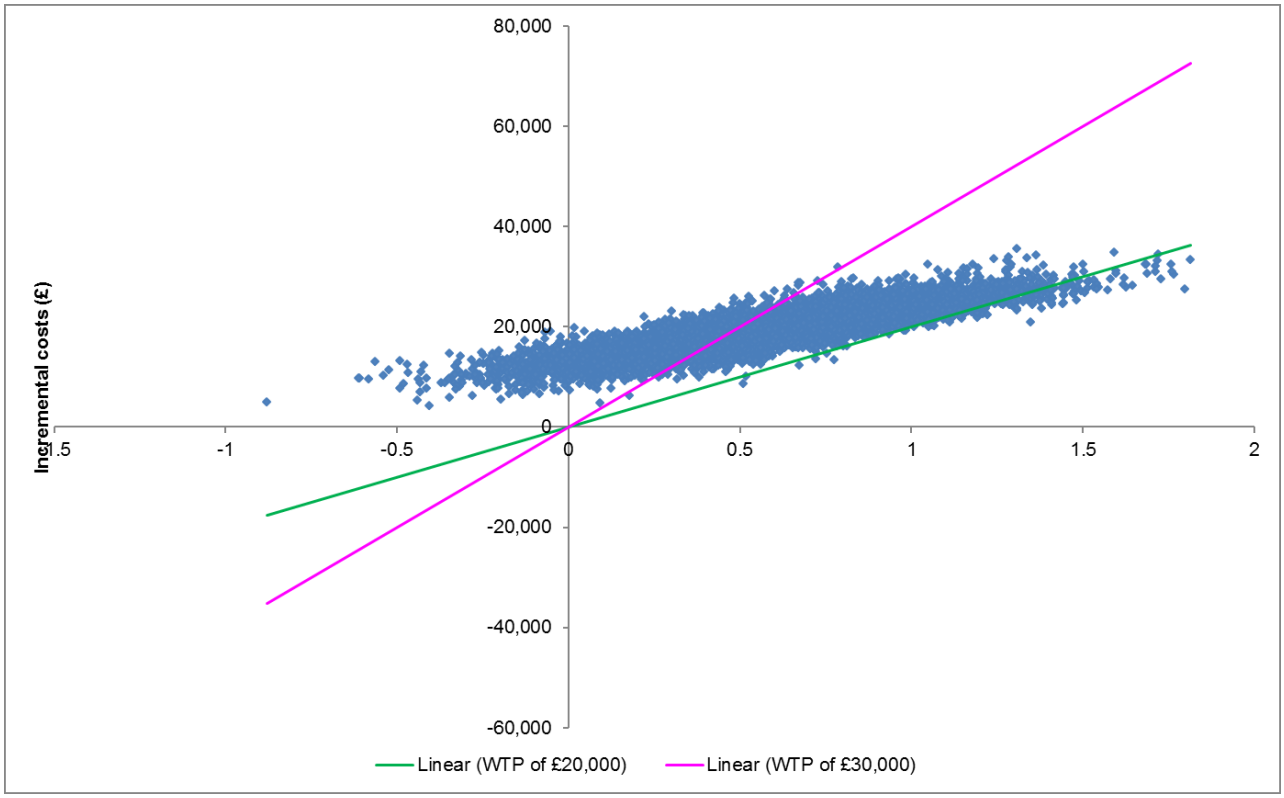


Figure 47: Cost-effectiveness plane for fulvestrant vs. letrozole

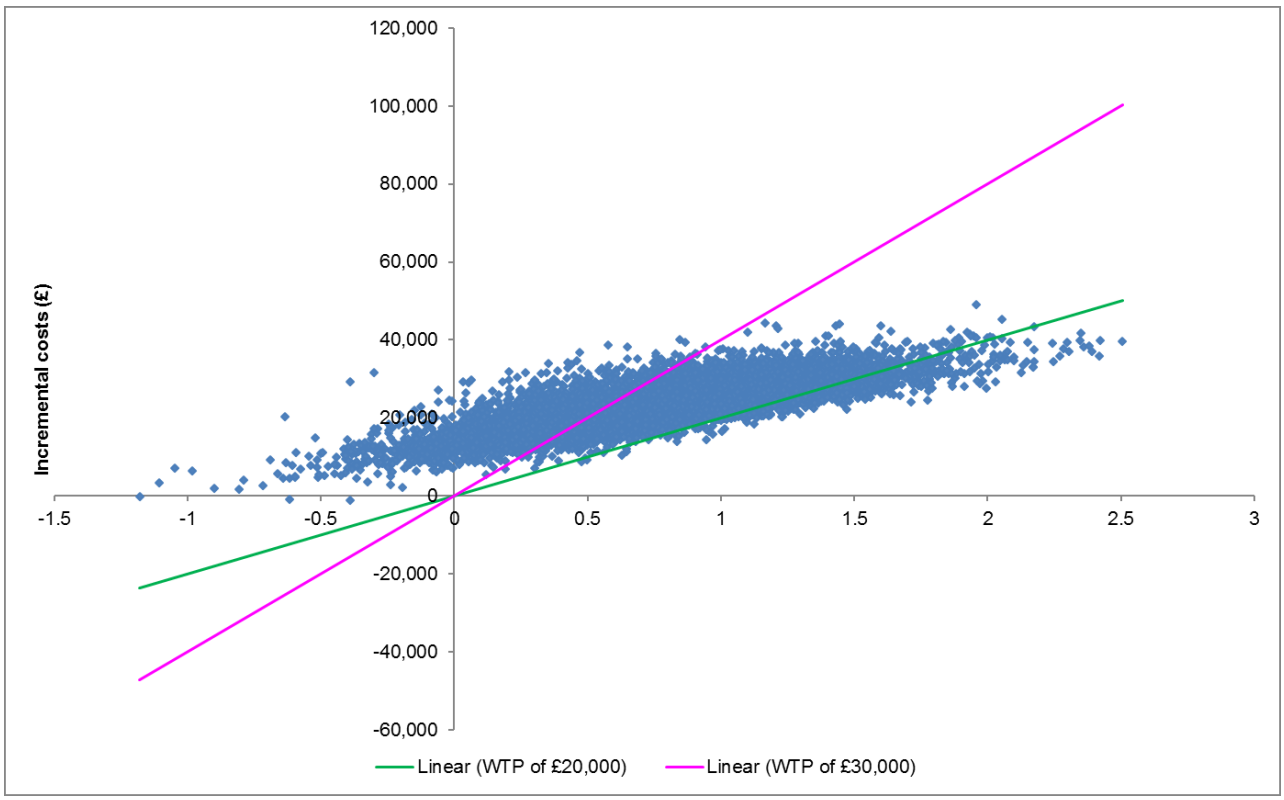


Figure 48: Cost-effectiveness plane for fulvestrant vs tamoxifen

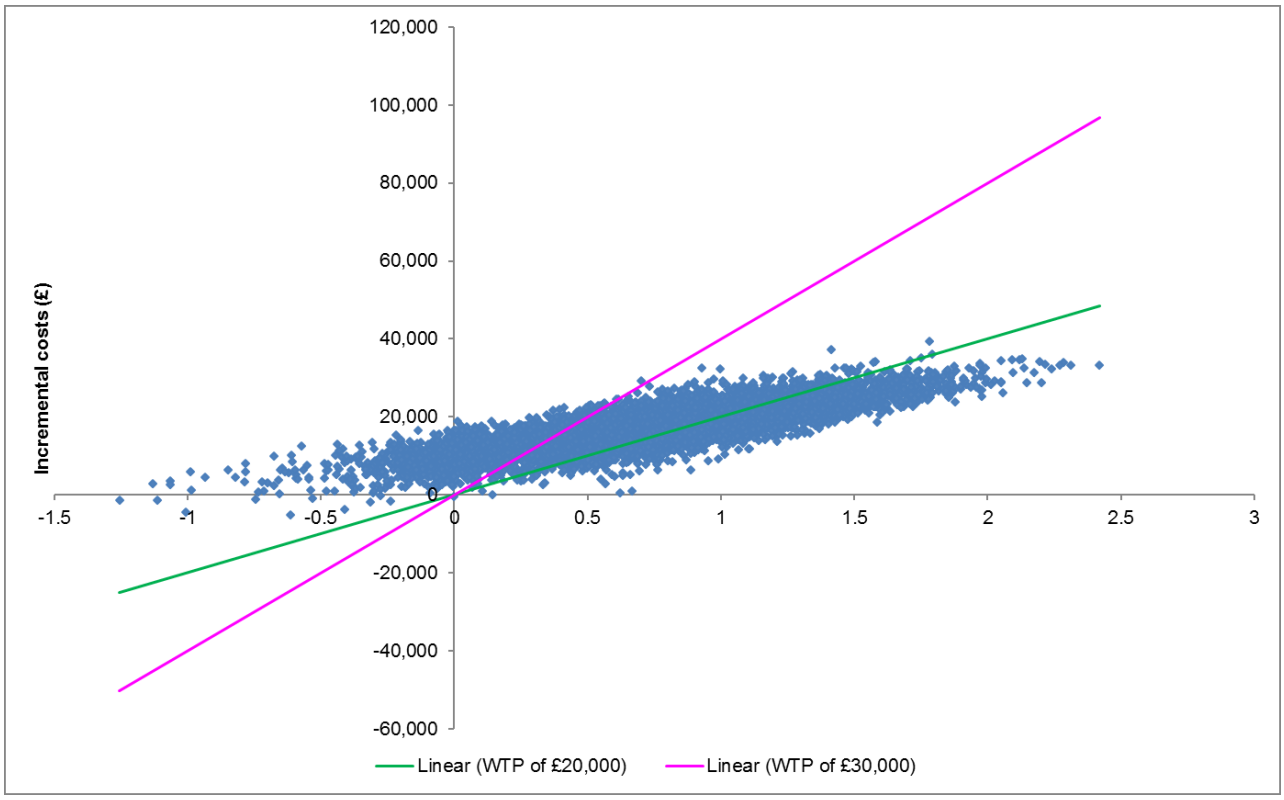


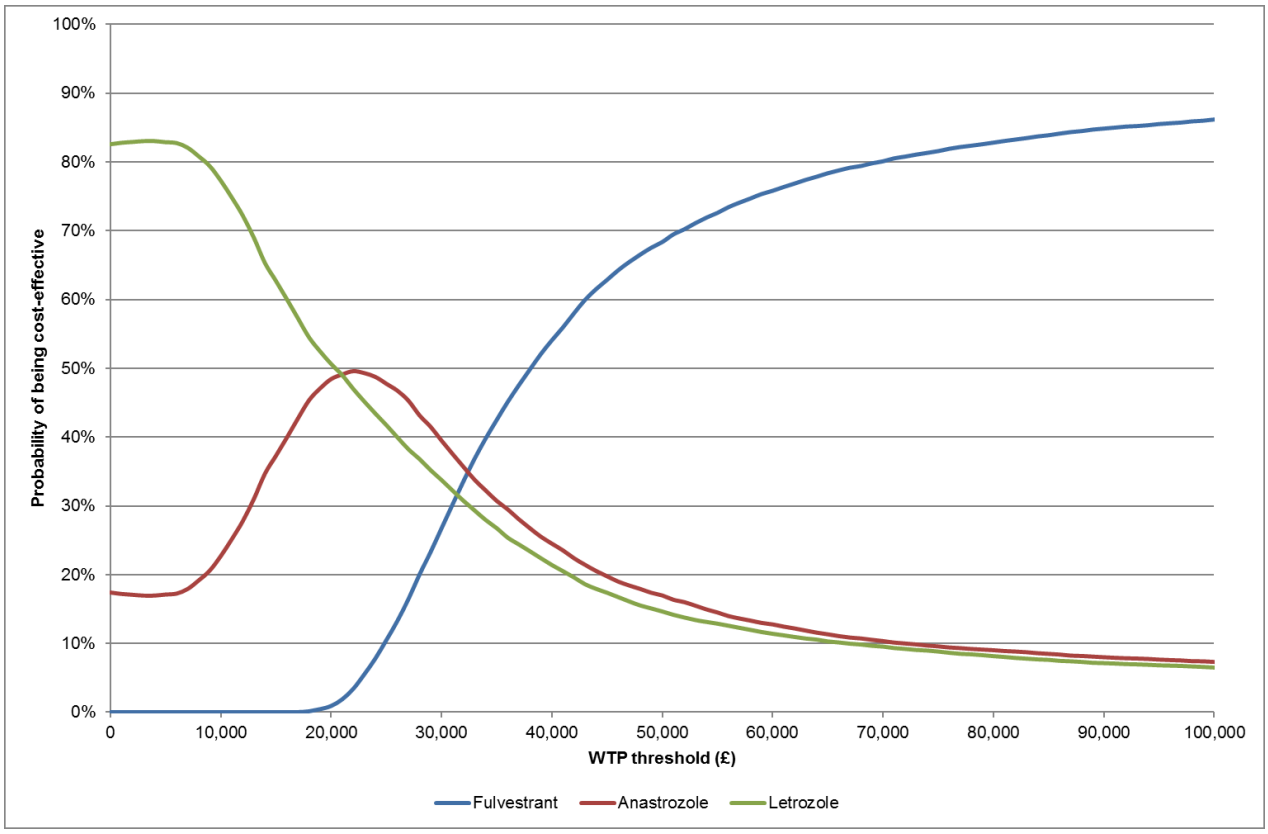
Table 92 and Figure 49 present the probability of fulvestrant, anastrozole and letrozole being the most cost effective at a series of WTP thresholds. At a WTP threshold of £20,000 per additional QALY, there is a 0.9% probability of fulvestrant being the most cost-effective treatment versus anastrozole or letrozole. This increases to 26.8% at a WTP threshold of £30,000 per QALY, and 68.4% at a WTP threshold of £50,000 per QALY.

Table 92: Probability of being the most cost-effective treatment (fulvestrant, anastrozole and letrozole) at WTP thresholds

Technology	WTP threshold		
	£20,000	£30,000	£50,000
Fulvestrant	0.9%	26.8%	68.4%
Anastrozole	48.5%	39.5%	17.0%
Letrozole	50.6%	33.8%	14.7%

Abbreviation: WTP, willingness to pay.

Figure 49: Cost-effectiveness acceptability curve (fulvestrant, anastrozole and letrozole)



Abbreviation: WTP, willingness-to-pay.

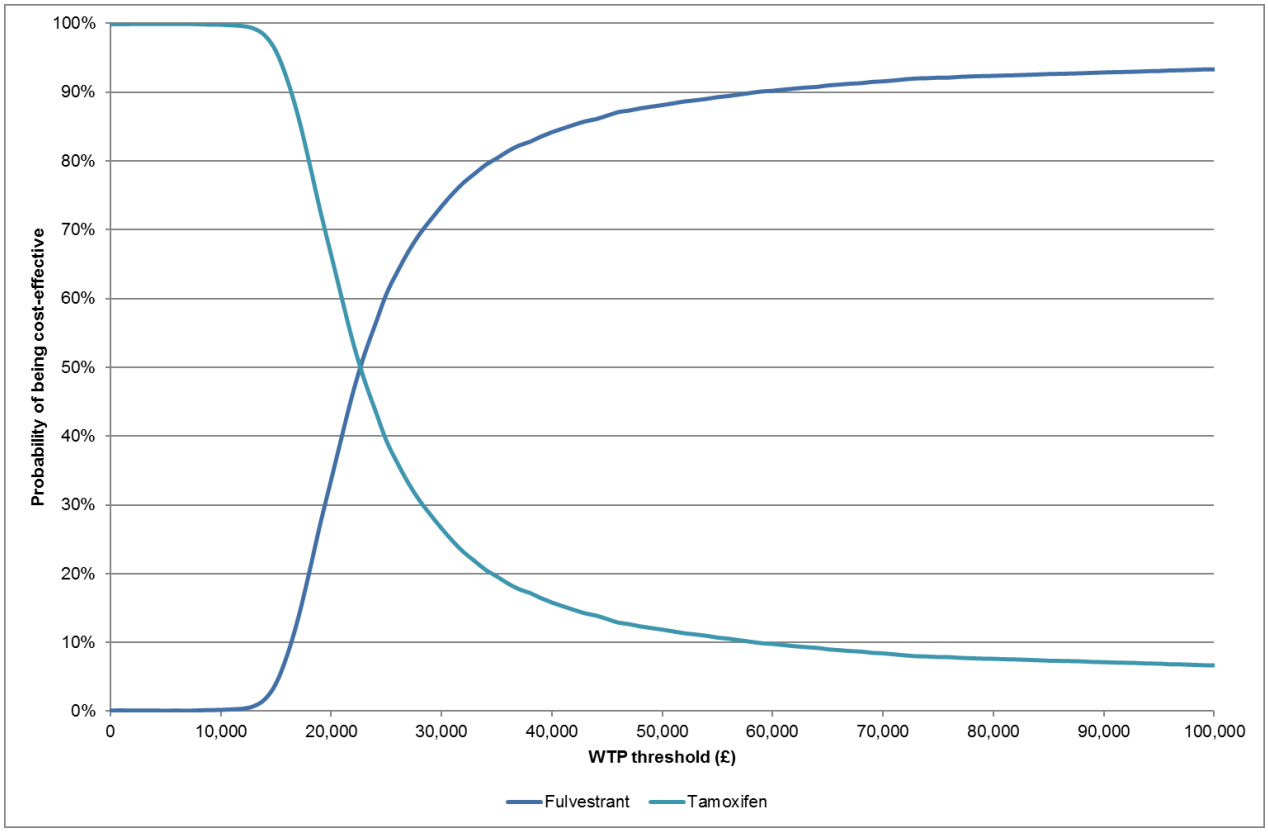
Table 93 and Figure 50 present the probability of fulvestrant and tamoxifen being the most cost effective at a series of WTP thresholds. At a WTP threshold of £20,000 per additional QALY, there is a 33.7% probability of fulvestrant being the most cost-effective treatment versus tamoxifen. This increases to 73.4% at a WTP threshold of £30,000 per QALY, and 88.1% at a WTP threshold of £50,000 per QALY.

Table 93: Probability of being the most cost-effective treatment (fulvestrant and tamoxifen) at WTP thresholds

Technology	WTP threshold		
	£20,000	£30,000	£50,000
Fulvestrant	33.7%	73.4%	88.1%
Tamoxifen	66.3%	26.6%	11.9%

Abbreviation: WTP, willingness to pay.

Figure 50: Cost-effectiveness acceptability curve (fulvestrant and tamoxifen)



Abbreviation: WTP, willingness-to-pay.

5.8.2 Deterministic sensitivity analysis

One-way sensitivity analysis was performed on the following key parameter groups:

- Parametric survival distribution parameters
- Disease management costs
- Terminal care/ end of life costs
- Treatment acquisition and administration (per 4 weeks)
- Health state utilities

Each parameter was varied according to its associated standard error or confidence/ credible intervals (if available); or by 20% if no information on uncertainty around the mean was available.

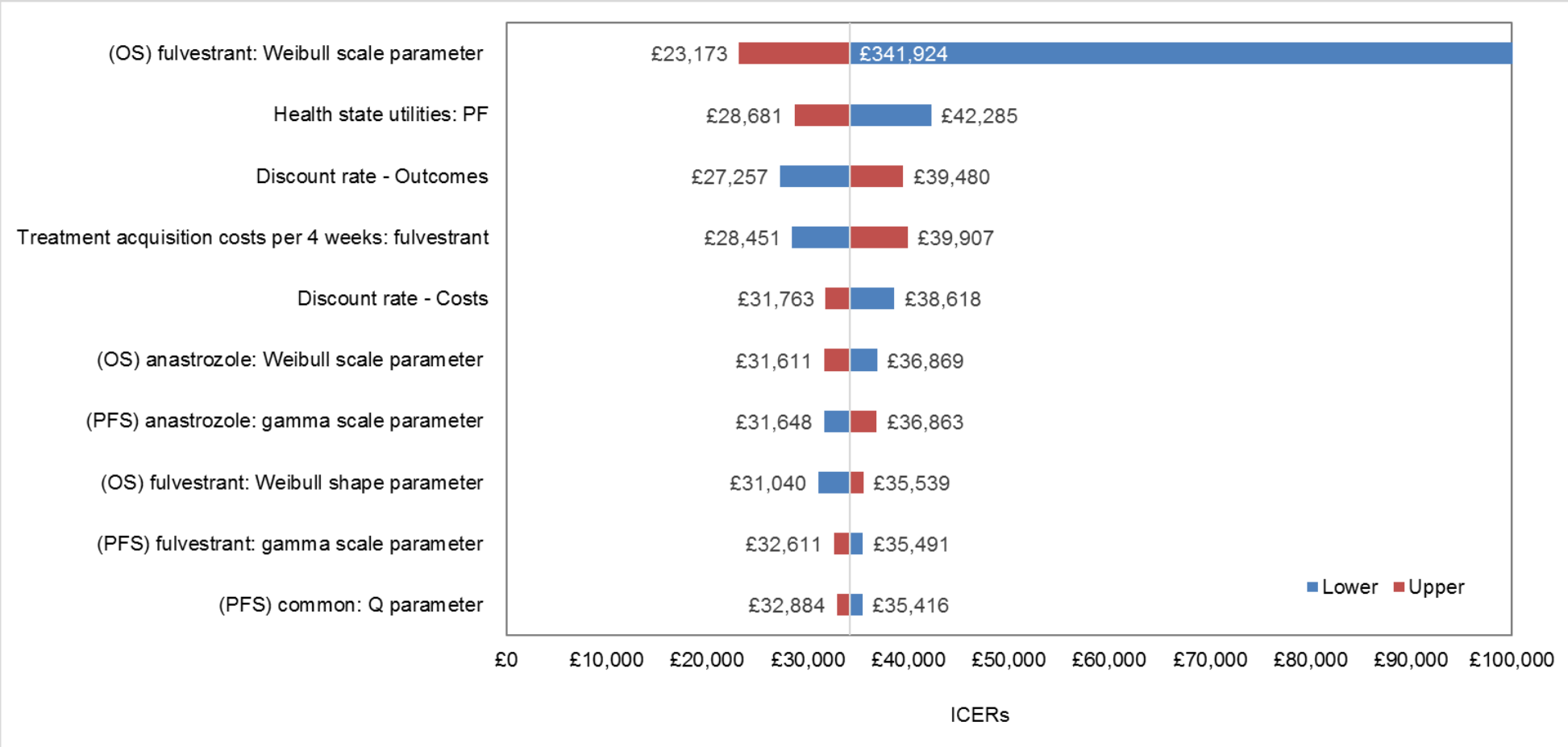
The top 10 sensitive parameters of the model for each comparison (fulvestrant 500mg vs anastrozole, letrozole and tamoxifen), defined as the parameters which caused the biggest absolute change in the ICER, were identified and plotted on a tornado diagram. The results of the deterministic sensitivity analysis for fulvestrant vs. anastrozole are presented in Table 94 and Figure 51, respectively. For fulvestrant versus anastrozole, the results show that the ICER is most sensitive to OS survival curve parameters, health state utility values for the PF health state and the discount rate applied to the QALY outcomes.

Table 94: Results of deterministic sensitivity analysis – fulvestrant vs. anastrozole

Parameter	Parameter value			Lower value (ICER)	Upper value (ICER)
	Lower value	Base case value	Upper value		
(OS) fulvestrant: Weibull scale parameter	[redacted]	[redacted]	[redacted]	£341,924	£23,173
Health state utilities: PF	0.6009	0.7511	0.9014	£42,285	£28,681
Discount rate - Outcomes	0.0%	3.5%	6.0%	£27,257	£39,480
Treatment acquisition costs per 4 weeks: fulvestrant	£417.93	£522.41	£626.89	£28,451	£39,907
Discount rate - Costs	0.0%	3.5%	6.0%	£38,618	£31,763
(OS) anastrozole: Weibull scale parameter	[redacted]	[redacted]	[redacted]	£36,869	£31,611
(PFS) anastrozole: gamma scale parameter	[redacted]	[redacted]	[redacted]	£31,648	£36,863
(OS) fulvestrant: Weibull shape parameter	[redacted]	[redacted]	[redacted]	£31,040	£35,539

Abbreviations: ICER, incremental cost-effectiveness ratio; PF, progression-free; PFS, progression-free survival; OS, overall survival.

Figure 51: Tornado diagram – fulvestrant vs. anastrozole



Abbreviations: ICERs, incremental cost-effectiveness ratio; PF, progression-free; PFS, progression-free survival; OS, overall survival.

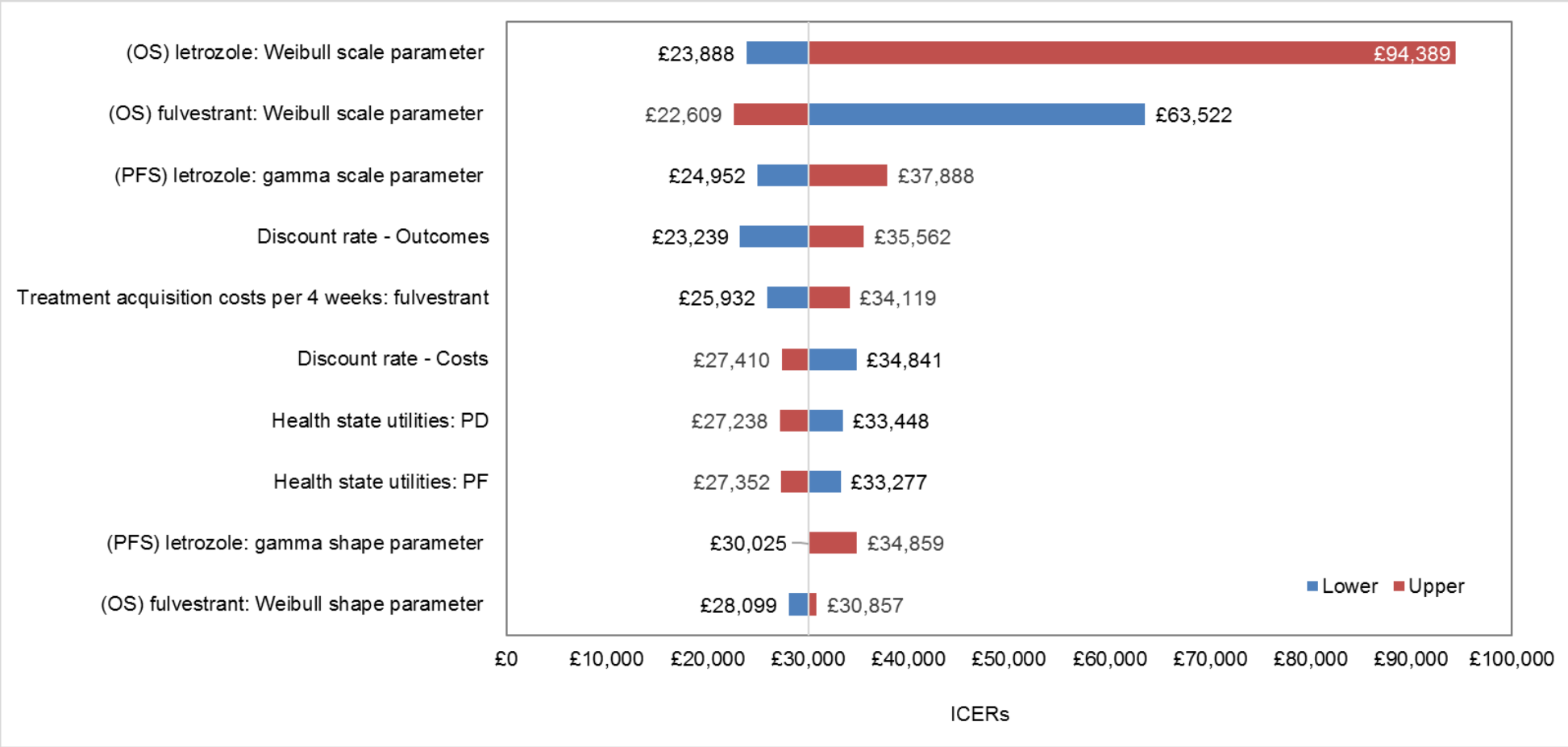
The results of the deterministic sensitivity analysis for fulvestrant vs. letrozole are presented in Table 95 and Figure 52, respectively. The results show that the ICER is most sensitive to OS and PFS survival curve parameters, the discount rate applied to the QALY outcomes and the treatment acquisition costs for fulvestrant.

Table 95: Results of deterministic sensitivity analysis – fulvestrant vs. letrozole

Parameter	Parameter value			Lower value (ICER)	Upper value (ICER)
	Lower value	Base case value	Upper value		
(OS) letrozole: Weibull scale parameter	[redacted]	[redacted]	[redacted]	£23,888	£94,389
(OS) fulvestrant: Weibull scale parameter	[redacted]	[redacted]	[redacted]	£63,522	£22,609
(PFS) letrozole: gamma scale parameter	[redacted]	[redacted]	[redacted]	£24,952	£37,888
Discount rate - Outcomes	0.0%	3.5%	6.0%	£23,239	£35,562
Treatment acquisition costs per 4 weeks: fulvestrant	£417.93	£522.41	£626.89	£25,932	£34,119
Discount rate - Costs	0.0%	3.5%	6.0%	£34,841	£27,410
Health state utilities: PD	0.5530	0.6913	0.8296	£33,448	£27,238
Health state utilities: PF	0.6009	0.7511	0.9014	£33,277	£27,352

Abbreviations: ICER, incremental cost-effectiveness ratio; PF, progression-free; PFS, progression-free survival; OS, overall survival.

Figure 52: Tornado diagram – fulvestrant vs. letrozole



Abbreviations: ICER, incremental cost-effectiveness ratio; PF, progression-free; PFS, progression-free survival; OS, overall survival.

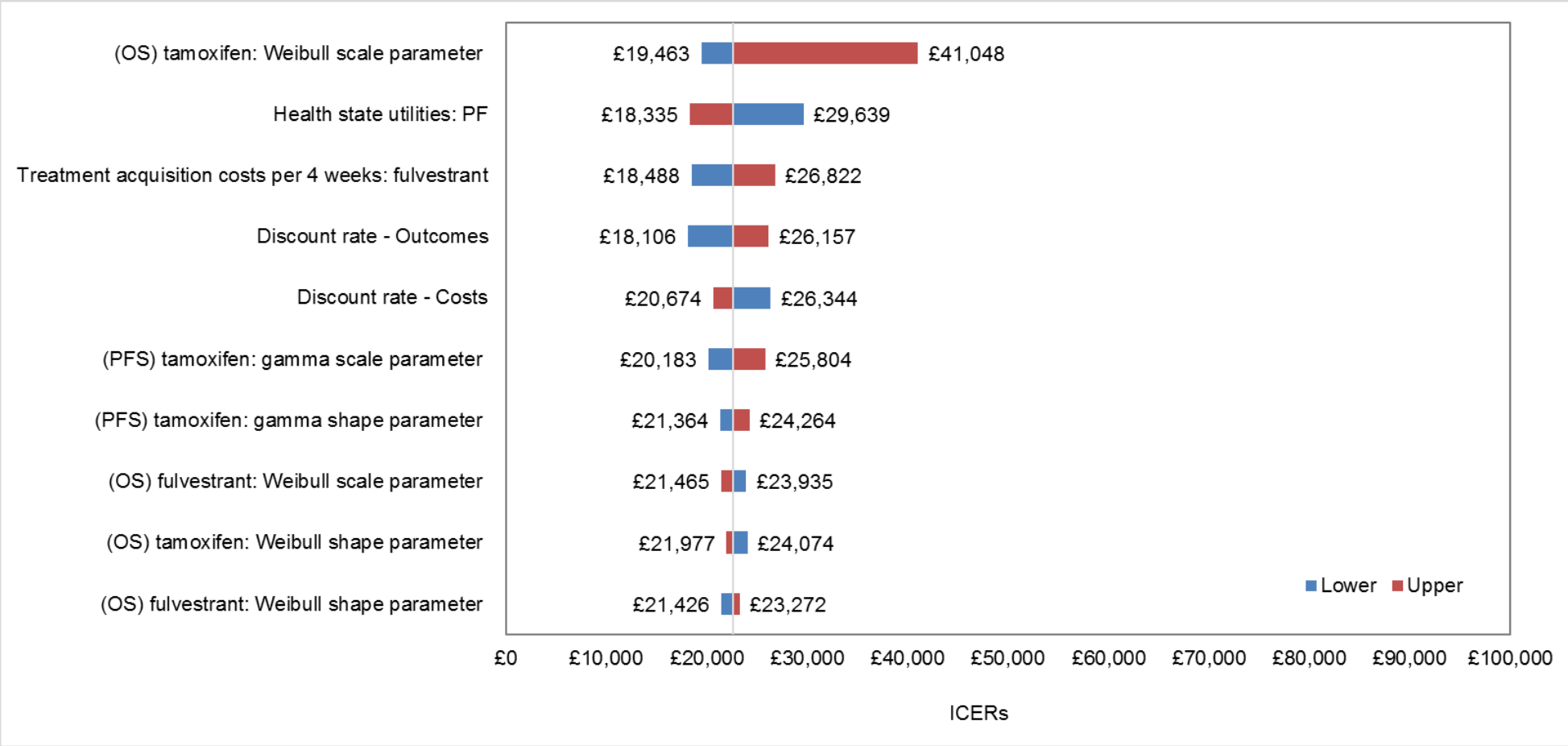
The results of the deterministic sensitivity analysis for fulvestrant vs. tamoxifen are presented in Table 96 and Figure 53, respectively. The results show that the ICER is most sensitive to OS survival curve parameters, health state utility values for the PF health state and the discount rate applied to the QALY outcomes.

Table 96: Results of deterministic sensitivity analysis – fulvestrant vs. tamoxifen

Parameter	Parameter value			Lower value (ICER)	Upper value (ICER)
	Lower value	Base case value	Upper value		
(OS) tamoxifen: Weibull scale parameter	[redacted]	[redacted]	[redacted]	£19,463	£41,048
Health state utilities: PF	0.6009	0.7511	0.9014	£29,639	£18,335
Treatment acquisition costs per 4 weeks: fulvestrant	£417.93	£522.41	£626.89	£18,488	£26,822
Discount rate - Outcomes	0.0%	3.5%	6.0%	£18,106	£26,157
Discount rate - Costs	0.0%	3.5%	6.0%	£26,344	£20,674
(PFS) tamoxifen: gamma scale parameter	[redacted]	[redacted]	[redacted]	£20,183	£25,804
(PFS) tamoxifen: gamma shape parameter	[redacted]	[redacted]	[redacted]	£21,364	£24,264
(OS) fulvestrant: Weibull scale parameter	[redacted]	[redacted]	[redacted]	£23,935	£21,465

Abbreviations: ICER, incremental cost-effectiveness ratio; PF, progression-free; PFS, progression-free survival; OS, overall survival.

Figure 53: Tornado diagram – fulvestrant vs. tamoxifen



Abbreviations: ICER, incremental cost-effectiveness ratio; PF, progression-free; PFS, progression-free survival; OS, overall survival.

5.8.3 Scenario analysis

As list of scenario analyses is presented in Table 97. Results of the scenario analyses are presented in Table 98, Table 99, Table 102, Table 103, Table 104, Table 105, Table 106 and Table 107.

Table 97: List of scenario analyses conducted

Parameter	Base case	Scenario	Comment
Survival extrapolations (OS)	'All shapes' NMA model OS - Weibull	'All shapes' NMA model plausible extrapolations: OS - generalised gamma	Assess the impact of more and/or less conservative survival estimates
Survival extrapolations (PFS)	'All shapes' NMA model PFS - generalised gamma	'All shapes' NMA model: PFS - log-logistic PFS - lognormal PFS - Weibull PFS - Gompertz	Assess the impact of more and/or less conservative survival estimates
Survival extrapolations (OS and PFS)	'All shapes' NMA model: OS - Weibull PFS - generalised gamma	'No shape arm' NMA model: OS - Weibull PFS - Weibull PFS - Gompertz	Assess the impact of not adjusted for differences in shapes between treatment arms
Survival extrapolations (OS and PFS)	'All shapes' NMA model: OS - Weibull PFS - generalised gamma	Assume equivalent efficacy between AIs 'All shapes' NMA model (anastrozole curves used for letrozole): OS - Weibull PFS - generalised gamma	Assess the impact of commonly held clinical opinion that AIs have equal efficacy
Utility values	FALCON MMRM (1)	FALCON summary statistics; FALCON MMRM (1) and Lloyd (2006); Lloyd (2006)	Assess the impact of using alternative data sources for health state utility values
Time horizon	30	5; 10; 15; 20; 25; 35	30 years was of sufficient duration to capture the differences in costs and QALYs for first line breast cancer; scenario analyses assess the impact of varying the time horizon.
Discount rate	3.5% for both costs and outcomes	1.5% for both costs and outcomes	According to NICE reference case(94)

Parameter	Base case	Scenario	Comment
AEs	AE costs and disutilities	No AE costs and disutilities	To assess the impact of inclusion of AE costs and disutilities on cost-effectiveness results
Treatment administration costs	Inclusion of administration costs for oral treatments	Exclusion of administration costs for all comparator therapies	To assess the impact that oral treatments are self-administered by the patient
Subsequent treatment costs and end of life care	Exclusion of fulvestrant as a subsequent treatment option for patients on first-line fulvestrant	Same subsequent treatment costs for all patients Exclusion of subsequent treatment costs altogether	Assess the impact of subsequent treatment overall and whether patients initially treated with fulvestrant will receive it again as a subsequent therapy

Abbreviation: AE; adverse event; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life-years.

5.8.3.1 Scenario analyses results

The base case analysis employs a Weibull distribution estimated from the fixed effects NMA to extrapolate OS. Scenarios varying the distribution used to provide plausible extrapolations for OS are summarized in Table 98. Across these scenarios, PFS was modelled using generalized gamma models estimated from the fixed effects NMA; differences in costs and outcomes relative to the base case are associated with different time on post-progression survival, and resulting OS. The ICERs for fulvestrant versus anastrozole, letrozole and tamoxifen when the generalized gamma distribution is used are £28,665, £33,387 and £22,183.

Table 98: Results of scenario analysis exploring the use of parametric survival models for OS estimated using the fixed effects NMA 'all shapes' model

Technologies	Discounted total cost	Discounted total QALY	Inc. costs	Inc. QALYs	ICER (fulvestrant vs. comparator)
[Base case] OS: Weibull; PFS: generalised gamma					
Letrozole	£25,928	2.455	£23,237	0.774	£30,025
Anastrozole	£30,261	2.676	£18,904	0.553	£34,179
Tamoxifen	£31,941	2.469	£17,223	0.760	£22,655
Fulvestrant	£49,165	3.229	-	-	-
OS: generalised gamma; PFS: generalised gamma					
Letrozole	£27,237	2.543	£23,724	0.828	£28,665
Anastrozole	£31,794	2.796	£19,167	0.574	£33,387
Tamoxifen	£33,302	2.574	£17,659	0.796	£22,183
Fulvestrant	£50,961	3.370	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

Table 99 presents scenario analyses when using alternative distributions for extrapolating PFS. OS was modelled using the Weibull distribution; differences in costs and outcomes relative to the base case are associated with different time pre- and post-progression. The ICERs for fulvestrant versus each comparator range from £22,402 to £35,340.

Table 99: Results of scenario analysis exploring the use of alternative parametric survival models for PFS estimated using the fixed effects NMA 'all shapes' model

Technologies	Discounted total cost	Discounted total QALY	Inc. costs	Inc. QALYs	ICER (fulvestrant vs. comparator)
[Base case] PFS: generalised gamma; OS: Weibull					
Letrozole	£25,928	2.455	£23,237	0.774	£30,025
Anastrozole	£30,261	2.676	£18,904	0.553	£34,179
Tamoxifen	£31,941	2.469	£17,223	0.760	£22,655
Fulvestrant	£49,165	3.229	-	-	-
PFS: Weibull; OS: Weibull					
Letrozole	£27,011	2.439	£21,856	0.767	£28,512
Anastrozole	£31,069	2.669	£17,799	0.537	£33,140
Tamoxifen	£31,802	2.469	£17,066	0.736	£23,174
Fulvestrant	£48,867	3.206	-	-	-
PFS: Gompertz; OS: Weibull					
Letrozole	£26,090	2.445	£22,702	0.751	£30,219
Anastrozole	£31,054	2.668	£17,739	0.529	£33,563
Tamoxifen	£31,082	2.473	£17,711	0.723	£24,489
Fulvestrant	£48,793	3.196	-	-	-
PFS: log-logistic; OS: Weibull					
Letrozole	£25,763	2.541	£24,644	0.782	£31,512
Anastrozole	£29,170	2.722	£21,237	0.601	£35,340
Tamoxifen	£31,263	2.482	£19,145	0.841	£22,772
Fulvestrant	£50,407	3.323	-	-	-
PFS: lognormal; OS: Weibull					
Letrozole	£25,132	2.507	£24,638	0.768	£32,091
Anastrozole	£29,684	2.685	£20,086	0.589	£34,086
Tamoxifen	£31,770	2.471	£18,001	0.804	£22,402
Fulvestrant	£49,770	3.274	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

As mentioned in section 4.10.1, the assumption of a proportional treatment effect (proportional hazards/ proportional acceleration factor) was judged to be unreasonable across the trials included in the NMA, based on a visual inspection of the log-cumulative hazard plots. For completeness, a side-by-side comparison of the scenarios presented in Table 99 using the 'all shapes' and 'no shape arm' models are presented in Table 100. As mentioned in section 4.10.1, the generalised gamma distribution was not included in the 'no shape arm' models; therefore, given this exclusion, and in conjunction with visual inspection of the extrapolated survival curves (see Figure 60; Appendix D) and comparison with expert clinical opinion, it

was judged that plausible extrapolations of OS were limited to the Weibull distribution.

Table 100: Results of scenario analysis exploring the use of parametric survival models for OS and PFS estimated using the fixed effects NMA 'no shapes arm' model

Technologies	ICER (fulvestrant vs. comparator)		
	'All shapes'	'No shape arm'	Difference
[Base case] PFS: generalised gamma; OS: Weibull			
Letrozole	£30,025	£30,025	-
Anastrozole	£34,179	£34,179	-
Tamoxifen	£22,655	£22,655	-
Fulvestrant	-	-	-
PFS: Weibull; OS: Weibull			
Letrozole	£28,512	£37,308	£8,796
Anastrozole	£33,140	£33,757	£617
Tamoxifen	£23,174	£25,135	£1,961
Fulvestrant	-	-	-
PFS: Gompertz; OS: Weibull			
Letrozole	£30,219	£36,246	£6,027
Anastrozole	£33,563	£33,720	£157
Tamoxifen	£24,489	£25,291	£802
Fulvestrant	-	-	-
PFS: Log-logistic; OS: Weibull			
Letrozole	£31,512	£46,164	£14,652
Anastrozole	£35,340	£39,748	£4,408
Tamoxifen	£22,772	£29,106	£6,334
Fulvestrant	-	-	-
PFS: Lognormal; OS: Weibull			
Letrozole	£32,091	£45,286	£13,195
Anastrozole	£34,086	£38,784	£4,698
Tamoxifen	£22,402	£29,367	£6,965
Fulvestrant	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

Results of the comparison between 'all shapes' and 'no shape arm' models show that the ICERs for fulvestrant versus each of the comparators increase to various degrees. The largest impact is seen in the comparison between fulvestrant and letrozole. Visual inspection of the projected OS curves (see Figure 60; Appendix D) shows that the OS curves for letrozole and anastrozole are more comparable under the assumption of fixed shapes; however as noted previously the 'no shape arm' models provide a poor representation of the crossing curves observed in the PO25 trial (see Figure 64; Appendix D).

Given the widely held clinical belief that anastrozole and letrozole have equivalent efficacy, a subsequent scenario was run to this effect. This was achieved by using the anastrozole PFS and OS curves estimated using the 'no shape arm' models for letrozole. The results of this scenario are presented in Table 101. The ICERs for fulvestrant versus letrozole range from £33,151 to £35,342; the base case ICER is £30,025.

Table 101: Results of scenario analysis exploring equal efficacy between AIs using the anastrozole parametric survival models, estimated using the fixed effects NMA 'all shapes' model, for PFS and OS for letrozole

Technologies	Discounted total cost	Discounted total QALY	Inc. costs	Inc. QALYs	ICER (fulvestrant vs. comparator)
[Base case] PFS: generalised gamma; OS: Weibull					
Letrozole	£25,928	2.455	£23,237	0.774	£30,025
Anastrozole	£30,261	2.676	£18,904	0.553	£34,179
Tamoxifen	£31,941	2.469	£17,223	0.760	£22,655
Fulvestrant	£49,165	3.229	-	-	-
PFS: generalised gamma; OS: Weibull					
Letrozole	£30,259	2.676	£18,906	0.553	£34,188
Anastrozole	£30,261	2.676	£18,904	0.553	£34,179
Tamoxifen	£31,941	2.469	£17,223	0.760	£22,655
Fulvestrant	£49,165	3.229	-	-	-
PFS: Weibull; OS: Weibull					
Letrozole	£31,065	2.669	£17,802	0.537	£33,151
Anastrozole	£31,069	2.669	£17,799	0.537	£33,140
Tamoxifen	£31,802	2.469	£17,066	0.736	£23,174
Fulvestrant	£48,867	3.206	-	-	-
PFS: Gompertz; OS: Weibull					
Letrozole	£31,050	2.668	£17,743	0.528	£33,575
Anastrozole	£31,054	2.668	£17,739	0.529	£33,563
Tamoxifen	£31,082	2.473	£17,711	0.723	£24,489
Fulvestrant	£48,793	3.196	-	-	-
PFS: log-logistic; OS: Weibull					
Letrozole	£29,172	2.722	£21,235	0.601	£35,342
Anastrozole	£29,170	2.722	£21,237	0.601	£35,340
Tamoxifen	£31,263	2.482	£19,145	0.841	£22,772
Fulvestrant	£50,407	3.323	-	-	-
PFS: lognormal; OS: Weibull					
Letrozole	£29,682	2.685	£20,088	0.589	£34,094
Anastrozole	£29,684	2.685	£20,086	0.589	£34,086
Tamoxifen	£31,770	2.471	£18,001	0.804	£22,402
Fulvestrant	£49,770	3.274	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

Table 102 presents the scenario analyses results that explore alternative utility values. Use of the FALCON summary statistics, the FALCON study MMRM model for the PF health state and the Lloyd model for the PD health state, or the Lloyd model, results in an increase in the ICER for fulvestrant versus all comparators ranging from £33 to £5,226. Use of the combination of the MMRM (1) model and Lloyd (2006) mixed model resulted in the highest ICERs for fulvestrant versus the AIs - £35,251 (vs. anastrozole) and £34,597 (vs. letrozole).

Table 102: Results of scenario analyses exploring alternative utility values

Technologies	Discounted total cost	Discounted total QALY	Inc. costs	Inc. QALYs	ICER (fulvestrant vs. comparator)
[Base case] FALCON MMRM (1)					
Letrozole	£25,928	2.455	£23,237	0.774	£30,025
Anastrozole	£30,261	2.676	£18,904	0.553	£34,179
Tamoxifen	£31,941	2.469	£17,223	0.760	£22,655
Fulvestrant	£49,165	3.229	-	-	-
FALCON summary statistics					
Letrozole	£25,928	2.451	£23,237	0.773	£30,077
Anastrozole	£30,261	2.672	£18,904	0.552	£34,232
Tamoxifen	£31,941	2.465	£17,223	0.759	£22,688
Fulvestrant	£49,165	3.224	-	-	-
FALCON study MMRM model (1) and Lloyd (2006)					
Letrozole	£25,928	2.129	£23,237	0.659	£35,251
Anastrozole	£30,261	2.242	£18,904	0.546	£34,597
Tamoxifen	£31,941	1.989	£17,223	0.800	£21,539
Fulvestrant	£49,165	2.788	-	-	-
Lloyd (2006)					
Letrozole	£25,928	2.146	£23,237	0.665	£34,962
Anastrozole	£30,261	2.261	£18,904	0.550	£34,362
Tamoxifen	£31,941	2.006	£17,223	0.805	£21,404
Fulvestrant	£49,165	2.811	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; MMRM, mixed models with repeated measurements; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

Six scenarios exploring different time horizons are presented in Table 103. As the time horizon increases, the incremental cost per QALY decreased as the benefits of additional survival on fulvestrant (in terms of QALYs) are realised. Using a time horizon of 35 years the ICERs are similar to the base case, which is expected as few patients are still alive.

Table 103: Results of scenario analyses exploring different time horizons

Technologies	Discounted total cost	Discounted total QALY	Inc. costs	Inc. QALYs	ICER (fulvestrant vs. comparator)
[Base case] 30 years					
Letrozole	£25,928	2.455	£23,237	0.774	£30,025
Anastrozole	£30,261	2.676	£18,904	0.553	£34,179
Tamoxifen	£31,941	2.469	£17,223	0.760	£22,655
Fulvestrant	£49,165	3.229	-	-	-
5 years					
Letrozole	£22,985	2.229	£14,170	0.176	£80,702
Anastrozole	£23,486	2.183	£13,669	0.221	£61,787
Tamoxifen	£26,431	2.106	£10,723	0.298	£36,032
Fulvestrant	£37,155	2.404	-	-	-
10 years					
Letrozole	£25,872	2.445	£20,854	0.616	£33,881
Anastrozole	£29,372	2.612	£17,354	0.449	£38,637
Tamoxifen	£31,456	2.438	£15,270	0.623	£24,513
Fulvestrant	£46,726	3.061	-	-	-
15 years					
Letrozole	£25,918	2.454	£22,836	0.744	£30,683
Anastrozole	£30,191	2.670	£18,564	0.528	£35,139
Tamoxifen	£31,919	2.467	£16,836	0.731	£23,044
Fulvestrant	£48,754	3.198	-	-	-
20 years					
Letrozole	£25,926	2.455	£23,141	0.767	£30,176
Anastrozole	£30,256	2.676	£18,810	0.546	£34,435
Tamoxifen	£31,940	2.469	£17,126	0.753	£22,747
Fulvestrant	£49,067	3.222	-	-	-
25 years					
Letrozole	£25,927	2.455	£23,210	0.772	£30,068
Anastrozole	£30,261	2.676	£18,877	0.551	£34,255
Tamoxifen	£31,941	2.469	£17,196	0.758	£22,681
Fulvestrant	£49,137	3.227	-	-	-
35 years					
Letrozole	£25,928	2.455	£23,249	0.775	£30,006
Anastrozole	£30,261	2.676	£18,916	0.554	£34,146
Tamoxifen	£31,941	2.469	£17,236	0.761	£22,644
Fulvestrant	£49,177	3.230	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

Table 104 presents the results of the scenario using a 1.5% discount rate for both costs and outcomes. The results were insensitive to changes in the discount rate: this scenario decreased the base-case ICERs for fulvestrant versus letrozole, anastrozole and tamoxifen by £1,797, £1,953 and £929 per QALY, respectively.

Table 104: Results of scenario analyses exploring the discount rate

Technologies	Discounted total cost	Discounted total QALY	Inc. costs	Inc. QALYs	ICER (fulvestrant vs. comparator)
[Base case] 3.5% for both costs and outcomes					
Letrozole	£25,928	2.455	£23,237	0.774	£30,025
Anastrozole	£30,261	2.676	£18,904	0.553	£34,179
Tamoxifen	£31,941	2.469	£17,223	0.760	£22,655
Fulvestrant	£49,165	3.229	-	-	-
1.5% for both costs and outcomes					
Letrozole	£27,060	2.547	£25,215	0.893	£28,228
Anastrozole	£32,069	2.813	£20,206	0.627	£32,227
Tamoxifen	£33,569	2.579	£18,706	0.861	£21,725
Fulvestrant	£52,275	3.440	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

Table 105 presents a scenario exploring the exclusion of AE costs and disutilities from the model. The results are insensitive to the removal AE costs and disutilities: the ICER for fulvestrant versus letrozole decreased by £136; the ICER for fulvestrant versus anastrozole decreased by £115, and the ICER for fulvestrant versus tamoxifen increased by £271.

Table 105: Results of scenario analyses exploring AEs

Technologies	Discounted total cost	Discounted total QALY	Inc. costs	Inc. QALYs	ICER (fulvestrant vs. comparator)
[Base case] inclusion of AE costs and disutilities					
Letrozole	£25,928	2.455	£23,237	0.774	£30,025
Anastrozole	£30,261	2.676	£18,904	0.553	£34,179
Tamoxifen	£31,941	2.469	£17,223	0.760	£22,655
Fulvestrant	£49,165	3.229	-	-	-
No AE costs and disutilities					
Letrozole	£25,916	2.456	£23,137	0.774	£29,889
Anastrozole	£30,209	2.676	£18,844	0.553	£34,065
Tamoxifen	£31,633	2.470	£17,420	0.760	£22,926
Fulvestrant	£49,053	3.230	-	-	-

Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; Inc., incremental; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

The results of the scenario exploring no administration costs for oral treatments self-administered by the patient are presented in Table 106. This scenario increased the base-case ICERs for fulvestrant versus letrozole, anastrozole and tamoxifen by £1,048, £1,325 and £738 per QALY, respectively.

Table 106: Results of scenario analysis exploring zero administration costs for comparator (oral) treatments

Technologies	Discounted total cost	Discounted total QALY	Inc. costs	Inc. QALYs	ICER (fulvestrant vs. comparator)
[Base case] administration costs included for all comparators					
Letrozole	£25,928	2.455	£23,237	0.774	£30,025
Anastrozole	£30,261	2.676	£18,904	0.553	£34,179
Tamoxifen	£31,941	2.469	£17,223	0.760	£22,655
Fulvestrant	£49,165	3.229	-	-	-
Zero administration costs for comparator (oral) treatments					
Letrozole	£25,117	2.455	£24,048	0.774	£31,073
Anastrozole	£29,528	2.676	£19,637	0.553	£35,504
Tamoxifen	£31,381	2.469	£17,784	0.760	£23,392
Fulvestrant	£49,165	3.229	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

The results of the scenario including fulvestrant as a subsequent treatment option for patients initiating treatment with fulvestrant (first line) and of the scenario excluding subsequent treatment costs altogether are presented in Table 107. Both scenarios had a minimal impact on the base case results.

Table 107: Results of scenario analyses exploring different assumptions regarding subsequent treatment costs

Technologies	Discounted total cost	Discounted total QALY	Inc. costs	Inc. QALYs	ICER (fulvestrant vs. comparator)
[Base case] exclusion of fulvestrant for those patients starting fulvestrant 1st line					
Letrozole	£25,928	2.455	£23,237	0.774	£30,025
Anastrozole	£30,261	2.676	£18,904	0.553	£34,179
Tamoxifen	£31,941	2.469	£17,223	0.760	£22,655
Fulvestrant	£49,165	3.229	-	-	-
Same subsequent treatment costs for all treatments					
Letrozole	£25,928	2.455	£23,496	0.774	£30,360
Anastrozole	£30,261	2.676	£19,163	0.553	£34,648
Tamoxifen	£31,941	2.469	£17,483	0.760	£22,996
Fulvestrant	£49,424	3.229	-	-	-
Exclusion of subsequent treatment costs					
Letrozole	£23,934	2.455	£23,782	0.774	£30,729
Anastrozole	£28,266	2.676	£19,450	0.553	£35,166
Tamoxifen	£29,354	2.469	£18,362	0.760	£24,153
Fulvestrant	£47,716	3.229	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

5.8.4 Summary of sensitivity analyses results

The results of the deterministic sensitivity analyses are presented in Table 94 and Figure 51 for fulvestrant vs. anastrozole; Table 95 and Figure 52 for fulvestrant vs. letrozole and Table 96 and Figure 53 for fulvestrant vs. tamoxifen. For each analysis, the key parameter groups were varied and the top ten drivers of the ICER identified. For anastrozole, the top driver is curtailed on the tornado diagram (Figure 51) for optimal presentation.

The deterministic sensitivity analysis showed that the largest drivers across each of the comparisons was the shape and scale parameters (for anastrozole) and differences in shape and scale (for fulvestrant, letrozole and tamoxifen) for PFS and OS. Other key parameters highlighted as being key drivers of changes in costs or QALYs included the health state utility values for progression-free and progressed disease, the discount rate for costs and outcomes, and the treatment acquisition costs for fulvestrant.

In the comparison with anastrozole, varying the change in the Weibull scale parameter for OS for the fulvestrant arm resulted in ICERs of £23,173 and £341,924

(the use of the upper bound of the 95% confidence interval for the change in Weibull scale parameter for fulvestrant led to a mean survival gain of 25.16 months, whilst the lower bound resulted in a marginal mean survival gain of 0.06 months). Other parameters did not have a large effect on the results, with ICERs ranging from £27,257 to £42,285; the base case ICER was £34,179.

In the comparison with letrozole, varying the change in the Weibull scale parameter for OS for the letrozole arm resulted in ICERs of £23,888 and £94,389. Varying the change in Weibull OS scale parameter for letrozole between the lower and upper bound of the 95% confidence interval results in a difference in mean OS between fulvestrant and letrozole of 26.08 months to 4.02 months, driving the decrease and increase in ICER, respectively. When the upper bound of the 95% confidence interval is used, the projected OS curve for letrozole sits above the projected OS curve for fulvestrant for the first 5 years of the analysis, thereafter the letrozole curve crosses the fulvestrant curve and remains below it for the remaining time horizon of the analysis. Varying the change in Weibull OS scale parameter for fulvestrant between the lower and upper bound of the 95% confidence interval results in the difference in mean OS varying between 5.59 and 16.66 months, causing the ICER to vary between £63,522 and £22,609. Other parameters did not have a large effect on the results, with ICERs ranging from £23,239 to £37,888; the base case ICER was £30,025.

In comparison with tamoxifen, varying the change in the Weibull scale parameter for OS for the fulvestrant arm resulted in ICERs of £19,463 and £41,048. The use of the upper bound of the 95% confidence interval for the change in Weibull scale parameter for fulvestrant led to a mean survival gain of 29.06 months, whilst the lower bound resulted in a marginal mean survival gain of 3.96 months. Other parameters did not have a large effect on the results, with ICERs ranging from £18,106 to £29,639; the base case ICER was £22,655.

5.8.5 Summary of scenario analyses results

The results of the scenario analyses are presented in Table 98 through to Table 107. Using the generalized gamma distribution to extrapolate OS produced a reduction in the deterministic ICERs for fulvestrant versus letrozole, anastrozole and tamoxifen of

£1,360, £792 and £472, respectively. Varying the choice of distribution for PFS caused the ICER for fulvestrant versus the comparators to vary between £22,402 and £35,340.

As discussed in section 4.10.1, there is a risk that the results of the OS analysis presented in the PO25 trial is confounded due to the optional cross-over study design (12). Given this and the belief the letrozole is considered to be of equal efficacy to other AIs, the assumption of clinical equivalency between AIs was explored in a subsequent scenario analysis. This was achieved by substituting the anastrozole PFS and OS survival curves estimated via the 'all shapes' NMA models for letrozole. Assuming equivalent efficacy between AIs caused the ICER for fulvestrant versus letrozole to increase to range between £33,151 and £35,342, using a range of different distributions. The ICERs for fulvestrant versus letrozole were similar to those observed for fulvestrant versus anastrozole, differing only by a maximum of £12 across the distributions tested.

The use of the FALCON summary statistics to estimate EQ-5D health state utilities had a minimal impact on the base case deterministic ICERs. The use of the combination of FALCON study MMRM (1) and Lloyd 2006, and the sole use of the Lloyd 2006 model to provide utility values for the progression-free and progressed disease health states increased the ICERs for fulvestrant versus anastrozole and letrozole (the largest ICERs observed were £34,597 and £35,251 for fulvestrant versus anastrozole and letrozole respectively when the combination option is chosen), and had a proportionately bigger effect on the comparison with letrozole due to the difference in projected OS between anastrozole and letrozole and the corresponding difference in the proportion of patients estimated to be in the progressed disease health state over time; the ICER for fulvestrant versus tamoxifen was decreased marginally using either approach. The tamoxifen result is intuitive given that the post-progression survival estimate for tamoxifen is marginally higher than that for fulvestrant (31.89 versus 30.51 months).

Changing the time horizon of the analysis indicated that the results were relatively stable from 15 years onwards with only minor differences from the base case ICERs. A time horizon of 10 years the ICERs for fulvestrant vs letrozole, anastrozole and

tamoxifen increase by £3,856, £4,458 and £1,858, respectively. Time horizons of less than 10 years cause the ICERs to rise significantly.

Simultaneous changes in the discount rates for costs and outcomes; the exclusion of costs and disutilities associated with adverse events; the assumption of zero administration costs for oral treatments and changes in the assumptions regarding the subsequent (post-progression) treatment costs had minimal impacts on the base case ICERs.

5.9 Subgroup analysis

Subgroup analysis in the pivotal phase III study, FALCON, failed to demonstrate any statistically or clinically significant differences in efficacy for fulvestrant compared to anastrozole (see Section 4.8.2). Therefore subgroup analyses are not considered in either the NMA or the economic evaluation.

5.10 Validation

5.10.1 Validation of de novo cost-effectiveness analysis

The economic analysis uses methods that have be used in numerous NICE oncology appraisals. The partitioned survival approach makes the best use of the available evidence without introducing additional assumptions commonly employed in other approaches. The three health states in the model (PF, PD and death) have been used extensively and validated in previous technology assessments of advanced breast cancer therapies, and captures the clinically important aspects of the disease.

An extensive review of existing NICE technology appraisals in advanced breast cancer was undertaken to aid decision making around modelling approaches, healthcare resource use; sources of costs, utility and disutility. Unit costs were sourced from the most recent PSSRU, eMIT database, BNF and NHS Reference Costs to ensure that the results of the economic analysis are appropriate to the UK setting. Extrapolated PFS and OS estimates were validated with UK clinical expert opinion to determine plausibility.

The economic model was reviewed by health economists within AstraZeneca; the review included an assessment of the face validity of the model, and third-party validation of the calculations and data sources within the model. A range of extreme value and logic tests were conducted to test the behavior of the model and ensure that the results were logical based on the test conducted.

5.11 Interpretation and conclusions of economic evidence

A de novo economic analysis was developed to evaluate the incremental cost-effectiveness of fulvestrant compared to alternative therapeutic options in the treatment of post-menopausal, endocrine naïve metastatic breast cancer.

- *Are the results from this economic evaluation consistent with the published literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?*

This is the first economic evaluation undertaken for fulvestrant in postmenopausal women with ER+, HER2-, locally advanced or metastatic breast cancer who have not received hormonal therapy. Therefore, it is not possible to compare the economic results presented here with previously published analyses.

Table 108 and Table 109 present a comparison between the long-term predicted model outcomes and corresponding clinical expert opinion for progression-free and overall survival for anastrozole, respectively; the long-term model outcomes for letrozole are also included for comparison. Final survival outputted from the economic model showed good consistency with clinical expert opinion in this disease area.

Table 108: Predicted proportion of patients progression-free

	1 year	2 years	5 years	10 years
KOL opinion (anastrozole)	50-60%	30-40%	5-10%	1-5%
Modelled PFS (anastrozole)	52.2%	25.7%	4.6%	0.6%
Modelled PFS (letrozole)	59.3%	30.8%	5.8%	0.7%

Abbreviations: KOL, key opinion leader; PFS, progression-free survival.

Table 109: Predicted proportion of patients alive

	1 year	2 years	5 years	10 years
KOL opinion (anastrozole)	75-85%	55-70%	20-30%	5-10%
Modelled OS (anastrozole)	86.0%	69.6%	30.7%	5.5%
Modelled OS (letrozole)	91.5%	74.5%	23.2%	0.7%

Abbreviations: KOL, key opinion leader; OS, overall survival.

- *Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem?*

The economic evaluation focusses on women with ER+, HER2-, locally advanced or metastatic breast cancer who have not received hormonal therapy. This covers all of patients who are likely to use the technology in clinical practice in England.

- *How relevant (generalisable) is the analysis to clinical practice in England?*

The age and race demographic in FALCON reflects the expected postmenopausal population within the UK. Patients presenting with de novo metastatic disease in whom chemotherapy is not indicated are expected to have a low symptom burden, and similarly good performance status as reflected by the FALCON trial population (7). The patient population in FALCON and the economic evaluation is judged to be reflective of patients with locally advanced or metastatic disease, and thus the clinical outcomes of PFS and OS are likely to be applicable to the patient population in England.

- *What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?*

Strengths

Health state utility values were derived from EQ-5D data collected in the FALCON study and are therefore directly applicable to the modelled population/ decision problem (7).

The model showed good consistency with clinical opinions from a panel of UK Breast cancer oncologists for projected progression-free and overall survival for anastrozole. A follow-up interview with a single UK clinician indicated that the extrapolated PFS estimates for fulvestrant, anastrozole, letrozole and tamoxifen

appeared appropriate; however, the clinician noted that there should be greater consistency for OS estimates between anastrozole and letrozole.

The highest percentage of absolute incremental QALY gain for fulvestrant versus anastrozole and tamoxifen was demonstrated in the progression-free health state, which is associated with a high level of maturity (67%) and can therefore be considered highly certain. The associated percentage gain of absolute incremental QALY gain for fulvestrant versus letrozole was 48.86%

When excluding changes to survival curve parameters, sensitivity analysis showed that uncertainty around the deterministic ICERs was manageable with ICERs ranging from £18,106 to £42,285. The major drivers of the model were OS, PFS, utility values, fulvestrant treatment acquisition costs and discount rates for costs and QALY outcomes.

Limitations

The FALCON OS data were immature at the time of the interim analysis (31%), to the extent that median OS could not be calculated (7). Whilst the available OS data numerically favour fulvestrant a significant difference between treatment arms was not demonstrated (HR: 0.875; p=0.4277). Given the immaturity in the OS data in FALCON, the expected separation in Kaplan-Meier curves, as observed in the FIRST study (9), has not yet occurred. At the time of data cut-off for the follow-up analysis in FIRST, 66.8% of patients had died; 61.8% in the fulvestrant 500 group, and 71.8% in the anastrozole group; fulvestrant significantly improved OS when compared with anastrozole (HR: 0.70; p=0.041) (9). It is therefore anticipated that the inclusion of FIRST in the network meta-analysis of parametric survival curves is a key driver of the OS improvement associated with fulvestrant.

The results of the fixed effects NMA for PFS are consistent with the belief that AIs have equivalent efficacy: letrozole did not demonstrate any statistically significant differences in shape and scale across the distributions used, when compared with anastrozole. The results of the fixed effects NMA for OS demonstrated a statistically significant difference in shape between letrozole and anastrozole across four of the five distributions used. It is anticipated that these results are influenced by the

reported cross-over in the PO25 trial (12), which was unable to be adjusted for given a lack of access to patient-level data, and caution is advised when interpreting the results. A scenario analysis examining the assumption of equal efficacy between AIs indicated that the pair-wise ICER for fulvestrant versus letrozole would sit between the range of £33,151 and £35,342, and would differ from the ICER for fulvestrant versus anastrozole by a maximum of £12.

- *What further analyses could be carried out to enhance the robustness or completeness of the results?*

A subsequent survival analysis from FALCON is planned at a maturity level of at least 50%. The data from this analysis will be able to reduce the uncertainty around the projected survival estimates for fulvestrant.

5.11.1 Summary of results

This economic evaluation estimated the cost-effectiveness of fulvestrant 500mg as positioned within this submission (Section 3).

Based on the results of this economic evaluation, using a time horizon of 30 years, the incremental analysis of fulvestrant versus the relevant AIs showed that letrozole was associated with the lowest total costs, followed by anastrozole and then fulvestrant. The estimated ICERs for each treatment versus the next least costly non-dominated option resulted in an ICER for anastrozole versus letrozole of £19,621, and for fulvestrant versus anastrozole of £34,179. The ICER for fulvestrant versus tamoxifen (in those patients in which AIs are not tolerated or are contraindicated) is £22,655. Therefore, at willingness to pay thresholds employed in England, fulvestrant 500mg can be considered a cost-effective use of NHS resources within this population.

In univariate sensitivity analysis, results were sensitive to OS, PFS, utility values, fulvestrant treatment acquisition costs and discount rates for costs and QALY outcomes. Probabilistic sensitivity analysis showed that the probability of fulvestrant being cost effective versus anastrozole and letrozole at willingness to pay thresholds of £20,000 and £30,000 was 0.9% and 26.8%, respectively; the corresponding probabilities for fulvestrant versus tamoxifen were 33.7% and 73.4%, respectively.

Scenario analysis showed that the ICERs were broadly consistent under differing assumptions: most scenarios showed a range of ICERs between £21,404 and £39,878; restriction of the time horizon of the analysis to 5 years increased the ICER for fulvestrant versus letrozole to £80,702.

6 Assessment of factors relevant to the NHS and other parties

6.1 Number of people eligible for treatment in England

The estimated number of eligible women in England with ER+, HER2-, locally advanced (not amenable to surgery or radiotherapy of curative intent) or metastatic breast cancer who have not received hormonal therapy. The total eligible population for fulvestrant in England is calculated in Table 110. The prevalent population is not considered due to the requirement that eligible patients be endocrine therapy naïve (de novo patients only).

The forecast uptake of fulvestrant over the next 5 years is presented in Table 111. These estimates increase year-on-year based on the England-population growth rate.

Table 110: Calculation of population in England eligible for fulvestrant

Description	Estimate	Assumptions and source	Number of women
Total population England 2015	54,786,300	ONS Population estimates summary for the UK, mid-1971 to mid-2015(128)	-
England population growth rate	0.86%		-
Total population England 2017	-	-	55,732,676
Breast cancer incidence in 2014 in postmenopausal women	0.0569%	ICD10 code C50 Malignant neoplasm of breast and D05 Carcinoma in situ of breast, postmenopausal assumed aged≥60/Total England population 2014=54,316,600/30,913=0.0569%. ONS Cancer Registration Statistics, England: 2014(129).	-
Estimated breast cancer diagnoses in postmenopausal women in 2017	-	-	31,992
Postmenopausal women diagnosed with invasive breast cancer	89.35%	ICD10 code C50/(ICD10 code C50 + D05) (postmenopausal assumed aged≥60)(129) =27,621/30,913	28,585
Postmenopausal women presenting with locally advanced or	10.05%	Incidence of stage IIIB/IV (5,397)/incidence of all stage (53,690)(130)	2,873

Description	Estimate	Assumptions and source	Number of women
metastatic breast cancer at diagnosis			
Postmenopausal women with HR+ breast cancer	83.8%	West Midlands Cancer Intelligence Unit(131)	2,408
Postmenopausal women with HER2- breast cancer	75%	Advanced Breast Cancer NICE Clinical Guideline(132)	1,806
Postmenopausal women with HR+ cancer for whom endocrine therapy is appropriate	70%	Advanced Breast Cancer NICE Clinical Guideline(132)	1,264

Abbreviations: NICE, National Institute for Health and Care Excellence; ONS, Office of National Statistics.

Table 111: Estimated number of patients eligible for first-line treatment with fulvestrant

	2018	2019	2020	2021	2022
Women eligible for treatment with fulvestrant	1,264	1,275	1,286	1,297	1,308

6.2 Acquisition and administration costs

Drug acquisition costs are calculated based on available formulations; pack sizes, unit costs and price per mg for each treatment included in the model. The dosing information is sourced from the BNF label for each treatment and the drug acquisition costs were sourced from eMIT. Treatment duration is assumed to be until objective disease progression. The treatment acquisition cost is multiplied by the overall compliance to treatment. The treatment dosing, pack size and costs, and compliance for each therapy is summarised in Table 63.

Treatment administration costs are calculated separately for the first 4-week cycle and subsequent cycles due to differences in resource use. Treatment administration costs are consistent with NICE TA239. Tamoxifen was not included in TA239 but, as an oral therapy, is assumed to have the same administration costs as anastrozole and letrozole. Treatment administration costs are summarised in Table 65.

An overview of the 4-weekly costs used in the budget impact calculations are given in Table 112.

Table 112: Acquisition and administration costs

	Acquisition costs		Administration costs	
	First 4 weeks	Subsequent 4-week cycle	First 4 weeks	Subsequent 4-week cycle
Fulvestrant	£1,044.82	£522.41	£370.35	£73.74
Anastrozole	£0.75	£0.75	£196.64	£27.93
Letrozole	£1.52	£1.52	£196.64	£27.93
Tamoxifen	£1.51	£1.51	£196.64	£27.93

6.3 Treatment duration

The average treatment duration was used to estimate the time on treatment for each new cohort considered in the calculations. This method assumes that all patients are treated for the same period, which can be shorter or longer than one year depending on the therapy considered. The duration of therapy for each therapy is presented in Table 113.

Table 113: Duration of treatment (months)

Treatment	Duration (months)	Source
Fulvestrant	29.58	Based on a simultaneous extrapolation and network meta-analysis of PFS and OS curves for all relevant comparators to be derived from available RCTs.
Anastrozole	19.56	
Letrozole	22.16	
Tamoxifen	13.16	

Abbreviations: PFS, progression-free survival; RCT, randomised controlled trial; OS, overall survival.

6.4 Market share in England

The current market share for hormone therapies in first-line breast cancer patients are presented in Table 114. The market share data was the moving annual total between July 2015 and June 2016. Based on internal projections, it is estimated that the uptake of fulvestrant will reach 80% by year 3 (Table 115).

The original values were recalculated to sum to 100% following the removal of:

- Fulvestrant (7% market share) due to the use being off-label
- Megestrol (2% market share) due to the very small market share and to maintain consistency with the scope of the cost-effectiveness model
- Exemestane (44% market share) to maintain consistency with the scope of the cost-effectiveness model.

In the scenario with fulvestrant, fulvestrant is assumed to take market share from all three comparators within the BIM in the same proportion as their respective market shares in the scenario without fulvestrant.

Table 114: Market share analysis – scenario without fulvestrant

	Y1 (2018)	Y2 (2019)	Y3 (2020)	Y4 (2021)	Y5 (2022)
Fulvestrant	0%	0%	0%	0%	0%
Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Y, year.

Table 115: Market share analysis – scenario with fulvestrant

	Y1 (2018)	Y2 (2019)	Y3 (2020)	Y4 (2021)	Y5 (2022)
Fulvestrant	30%	65%	80%	80%	80%
Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Y, year.

6.5 Estimated annual budget impact on the NHS in England

The budget impact is estimated as the number of patients and associated costs for treating those patients according to the assumed market share and expected uptake of fulvestrant in a scenario without (Table 116) and with fulvestrant (Table 117). The results of this analysis show that the net cumulative budget impact of introducing fulvestrant for postmenopausal women who are newly diagnosed with locally advanced (not amenable to surgery or radiotherapy of curative intent) or metastatic breast cancer from 2018-2022 is approximately £67.9 million (Table 118).

Table 116: Patient numbers and total costs in scenario without fulvestrant

	Y1 (2018)	Y2 (2019)	Y3 (2020)	Y4 (2021)	Y5 (2022)
Patients					
Fulvestrant	0	0	0	0	0
Anastrozole	323	326	328	331	334
Letrozole	861	868	875	883	891
Tamoxifen	81	81	82	83	84
Total costs					
Fulvestrant	£0	£0	£0	£0	£0
Anastrozole	£175,931	£254,220	£256,406	£258,611	£260,835
Letrozole	£477,758	£764,151	£770,723	£777,351	£784,036
Tamoxifen	£44,830	£48,246	£48,661	£49,080	£49,502

Abbreviations: Y, year.

Table 117: Patient numbers and total costs in scenario with fulvestrant

	Y1 (2018)	Y2 (2019)	Y3 (2020)	Y4 (2021)	Y5 (2022)
Patients					
Fulvestrant	383	836	1,038	1,047	1,056
Anastrozole	228	115	66	67	67
Letrozole	608	306	177	178	180
Tamoxifen	57	29	17	17	17
Total costs					
Fulvestrant	£3,296,747	£10,163,300	£16,784,013	£20,050,983	£20,922,646
Anastrozole	£123,152	£115,848	£62,897	£51,722	£52,167
Letrozole	£334,431	£366,252	£196,851	£155,470	£156,807
Tamoxifen	£31,381	£17,947	£10,191	£9,816	£9,900

Abbreviations: Y, year.

Table 118: Summary of budget impact

	Y1 (2018)	Y2 (2019)	Y3 (2020)	Y4 (2021)	Y5 (2022)
Scenario without fulvestrant	£698,520	£1,066,617	£1,075,790	£1,085,042	£1,094,373
Scenario with fulvestrant	£3,785,711	£10,663,347	£17,053,951	£20,267,991	£21,141,521
Change in costs	£3,087,191	£9,596,730	£15,978,161	£19,182,949	£20,047,148
Cumulative cost impact	£3,087,191	£12,683,921	£28,662,083	£47,845,032	£67,892,180

Abbreviations: Y, year.

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8 Appendices

Appendix A: Clinical search strategy

Table 119: Summary protocol

Objectives and research questions		
Primary objective	To assess the clinical efficacy, safety, and tolerability associated with pharmacological interventions as first-line treatment for postmenopausal women with hormone receptor-positive, locally advanced or metastatic breast cancer who had no prior hormonal treatment To conduct a feasibility assessment for network meta-analysis to assess the comparative efficacy and safety of Faslodex and relevant comparators	
Studies to include		
Study designs	Controlled clinical trials (RCTs irrespective of blinding status)	
Population	Age: adults (≥18 years) Gender: Female patients (in particular post-menopausal) Race: any Disease: HR positive, HER2 negative locally advanced or metastatic breast cancer	
Interventions	Fulvestrant Anastrozole Letrozole Tamoxifen Toremifene Exemestane Abiraterone acetate Megestrol acetate Atamestane Z-endoxifen Palbociclib Ribociclib Lapatinib	Everolimus Bevacizumab Docetaxel Paclitaxel Abemaciclib Temsirolimus Entinostat Alpelisib Taselisib Pictilisib Buparlisib Trastuzumab
Comparators	Any included intervention Any pharmacological intervention Placebo/best supportive care/observation	
Language	English language only (non-English studies will be highlighted to AZ)	
Publication timeframe	Database inception to present	
Line of therapy	First line (endocrine naïve HR+ (expressing ER and/or PR) locally advanced or metastatic breast cancer)	
Data sources		
Databases	Embase® MEDLINE® MEDLINE® In-Process	

	Cochrane central register of controlled trials (CENTRAL)
Information to extract*	
Study information	Study design (parallel group, cross-over, factorial, etc.) Analysis type (ITT/mITT/PP) Study objective Study setting Study methods including center and country Study phase Eligibility criteria (inclusion/exclusion) Details of study treatment Primary and secondary endpoints (including clinical, safety, and tolerability) Concomitant medications Study duration/trial length Method of randomization and concealment of allocation Blinding status Statistical method Author's conclusions and comments
Baseline data	Number of patients enrolled Number of patients randomized Number of patients analyzed Type of analysis Median age, range Disease duration Race (percent) Number of patients with ER+ and PR+ Number of patients HER2- Co-morbidities Metastatic sites Visceral metastases Line of therapy Eastern Cooperative Oncology Group (ECOG) performance status % of patients who are endocrine naïve % of patients who received prior chemotherapy Geographic region
Clinical efficacy outcomes	Overall Survival (OS) (median years; confidence intervals; hazard ratios). Progression-free survival (PFS) (median years; confidence intervals; hazard ratios). Time to progression Duration of response (DOR) (median years; confidence intervals; hazard ratios) Duration of clinical benefit (median years; confidence intervals; hazard ratios) Response rate (ORR) Clinical benefit rate (CBR) Overall survival rate Progression-free survival rate

Safety outcomes	Any adverse events Any grade 3/4 adverse events Any serious adverse events Any treatment-related adverse events
Tolerability outcomes	All withdrawals Withdrawal due to adverse events Withdrawal due to death
Feasibility assessment and analysis	
A detailed plan feasibility assessment for analysis along with the network diagrams will be prepared after the data extraction phase. Where possible, meta-analysis will be used to produce pooled estimates and confidence intervals of suitable effect sizes. Network diagrams will be constructed to inform possibility of indirect or mixed treatment comparisons. MTC will be conducted using the Bayesian approach in WinBUGS® software, version 14	
Reporting	
Data workbook in MS Excel format Feasibility assessment report in MS Word format Systematic review report including qualitative/quantitative analysis results in MS Word format	

Table 120: Search strategy for Embase® and MEDLINE® database searched via Embase.com platform (searched on 10 Jan 2017)

No.	Query	Results
1	'clinical trial'/exp OR 'randomization'/de OR 'controlled study'/de OR 'comparative study'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'clinical trial' OR 'clinical trials' OR 'controlled clinical trial' OR 'controlled clinical trials' OR 'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials' OR 'randomisation' OR 'randomization' OR rct OR 'random allocation' OR 'randomly allocated' OR 'allocated randomly' OR placebo* OR 'prospective study'/de OR allocated NEAR/2 random OR random* NEAR/1 assign* OR random* OR (single OR double OR triple OR treble) NEAR/1 (blind* OR mask*) NOT ('case study'/de OR 'case report' OR 'abstract report'/de OR 'letter'/de)	7,000,184
2	'breast tumor'/exp OR 'breast tumour' OR 'breast tumor'	412,660
3	'breast'/exp OR 'breast'	595,348
4	'breast neoplasms'/exp OR 'breast neoplasm' OR breast NEAR/5 carcinoma OR breast NEAR/5 cancer OR breast NEAR/5 malignan*	460,171
5	#2 OR #3 OR #4	596,979
6	advanced OR metastat* OR 'late' NEXT/2 'stage' OR 'stage iii' OR (stage AND iii*) OR 'stage iv' OR 'stage 3' OR 'stage 4' OR 'breast metastasis'/exp OR 'metastasis'/exp	1,153,786
7	#5 AND #6	131,951
8	metastatic NEAR/6 breast AND (tumor* OR tumour* OR carcinoma* OR neoplasm* OR cancer*)	25,563
9	advance* NEAR/6 breast AND (tumor* OR tumour* OR carcinoma* OR neoplasm* OR cancer*)	18,440
10	#7 OR #8 OR #9	132,889
11	'fulvestrant'/syn OR 'faslodex' OR 'ici 182 780' OR 'ici 182, 780' OR 'ici 182780' OR 'ici182780' OR 'zd 182780' OR 'zd 9238' OR 'zd182780' OR 'zd9238' OR 'zm 182780' OR 'zm182780'	6,923
12	'anastrozole'/syn OR 'anastrazole' OR 'arimidex' OR 'ici d1033' OR 'icid1033' OR 'trozolet' OR 'zd 1033' OR 'zd1033'	7,683
13	'letrozole'/syn OR 'cgs 20267' OR 'cgs20267' OR 'femar' OR 'femara'	8,519
14	'tamoxifen'/syn OR 'kessar' OR 'nsc 180973' OR 'tamoplac' OR 'tamoxasta' OR 'tamoxifene'	54,404
15	'toremifene'/syn OR 'estrimex' OR 'fareston' OR 'fc 1157 a' OR 'fc 1157a' OR 'fc1157a' OR 'toremifene citrate'	1,959
16	'exemestane'/syn OR 'aromasin' OR 'aromasine' OR 'fce 24304' OR 'fce24304' OR 'nikidess' OR 'pnu 155971' OR 'pnu155971'	4,723

No.	Query	Results
17	'abiraterone'/syn OR abretone OR 'cb 7630' OR 'cb7630' OR zytiga	2,893
18	'megestrol acetate'/syn OR endace OR maygace OR megace OR 'megacees' OR 'megaceos' OR 'megaplex' OR 'megase' OR megastrol OR megejohn OR megestat OR megestil OR 'megestranol acetate' OR 'megestrinol acetate' OR 'megestrolacetate' OR 'megestrole acetate' OR 'megostat' OR 'mergestrol acetate' OR mestrel OR niagestin OR niagestine OR ovaban OR ovarid OR pallace OR 'sc 10363' OR 'sc10363'	29,486
19	'atamestane'/syn OR 'sh 489' OR 'sh489'	146
20	'endoxifen'/syn OR 'z-endoxifen' OR '4 hydroxy n desmethyltamoxifen' OR '4 hydroxynortamoxifen' OR 'endoxifen hydrochloride' OR 'endoxifen hydrochloride hydrate'	563
21	'palbociclib'/syn OR 'ibrance' OR 'palbociclib isethionate' OR 'pd 0332991' OR 'pd 0332991 0054' OR 'pd 0332991-0054' OR 'pd 332991' OR 'pd0332991' OR 'pd0332991 0054' OR 'pd0332991-0054' OR 'pd332991' OR 'pf 00080665 73' OR 'pf 00080665-73' OR 'pf00080665 73' OR 'pf00080665-73'	782
22	'ribociclib'/syn or ‘lee 011’ or ‘lee011’	123
23	'lapatinib'/syn OR 'gw 2016' OR 'gw 572016' OR 'gw 572016f' OR 'gw2016' OR 'gw572016' OR 'gw572016f' OR 'lapatinibditosylate' OR 'lapatinibditosylate monohydrate' OR 'lapatinibtosylate' OR 'ykerb' OR 'tyverb'	8,847
24	'everolimus'/syn OR 'affinitor' OR 'afinitor' OR 'afinitordisperz' OR 'certican' OR 'nvp rad 001' OR 'nvp rad001' OR 'rad 001' OR 'rad 001a' OR 'rad001' OR 'rad001a' OR 'sdz rad' OR 'votubia' OR 'xience' OR 'xience v' OR 'zortress'	18,909
25	‘bevacizumab’/syn OR ‘altuzan’ OR ‘avastin’ OR ‘nsc 704865’ OR ‘nsc704865’	39,741
26	'docetaxel'/syn OR 'daxotel' OR 'dexotel' OR 'docefrez' OR 'docetaxel accord' OR 'lit 976' OR 'lit976' OR 'nsc 628503' OR 'nsc628503' OR 'oncodocel' OR 'rp 56976' OR 'rp56976' OR 'taxoter' OR 'taxotere' OR 'texot'	42,260
27	'paclitaxel'/syn OR 'abi 007' OR 'abi007' OR 'abraxane' OR 'albumin bound paclitaxel' OR 'albumin-bound paclitaxel' OR 'anzatax' OR 'asotax' OR 'biotax' OR 'bms 181339' OR 'bms181339' OR 'bristaxol' OR 'britaxol' OR 'coroxane' OR 'formoxol' OR 'genexol' OR 'genexol pm' OR 'hunxol' OR 'ifaxol' OR 'infinnium' OR 'intaxel' OR 'mbt 0206' OR 'mbt0206' OR 'medixel' OR 'mitotax' OR 'nab paclitaxel' OR 'nanoparticle albumin bound paclitaxel' OR 'nsc 125973' OR 'nsc125973' OR 'oncogel' OR 'onxol' OR 'pacitaxel' OR 'paclitaxel nab' OR 'pacxel' OR 'padexol' OR 'parexel' OR 'paxceed' OR 'paxene' OR 'paxus' OR 'praxel' OR 'taxocris' OR 'taxol' OR 'taxus' OR 'taycovit' OR 'yewtaxan'	83,677

No.	Query	Results
28	'abemaciclib'/syn OR 'bemaciclib' OR 'ly 2835219' OR 'ly2835219'	96
29	'temsirolimus'/syn OR 'cci 779' OR 'cci779' OR 'cell cycle inhibitor 779' OR 'nsc 683864' OR 'nsc683864' OR 'torisel' OR 'way-cci 779'	6,481
30	'entinostat'/syn or 'entinostat'/syn OR 'ms 27 275' OR 'ms 275' OR 'ms27 275' OR 'ms275' OR 'sndx 275' OR 'sndx275'	1,936
31	'alpelisib'/syn OR 'nvpbyl 719' OR 'nvp byl719'	298
32	'taselisib'/syn OR 'gdc 0032' OR 'gdc0032' OR 'rg 7604' OR 'rg7604'	82
33	'pictilisib'/syn OR 'gdc 0941' OR 'gdc0941' OR 'pictrelisib'	841
34	'buparlisib'/syn OR 'bkm 120' OR 'bkm 120 aaa' OR 'bkm 120 nx' OR 'bkm 120aaa' OR 'bkm 120nx' OR 'bkm120' OR 'bkm120 aaa' OR 'bkm120 nx' OR 'bkm120aaa' OR 'bkm120nx' OR 'buparlisib hydrochloride' OR 'nvpbkm 120' OR 'nvp bkm120'	924
35	'trastuzumab'/syn OR 'herceptin'	28,268
36	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35	256,792
37	#1 AND #10 AND #37	18,779
38	#37 AND ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [review]/lim)	6,077
39	#37 AND [animals]/lim NOT ([humans]/lim AND [animals]/lim)	253
40	#37 AND ([animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim)	735
41	#37 AND ([embryo]/lim OR [fetus]/lim OR [newborn]/lim OR [infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim)	97
42	#38 OR #39 OR #40 OR #41	6,856
43	#37 NOT #42	11,923
44	#43 AND ([conference abstract]/lim OR [conference review]/lim)	2,526
45	#43 NOT #44	9,397

Table 121: Search strategy for Cochrane database (searched on 10 Jan 2017**)**

No.	Query	Results
1	MeSH descriptor: [Breast Neoplasms] explode all trees	9,746
2	metastatic near/6 breast and (tumor* or tumour* or carcinoma* or neoplasm* or cancer*)	3,003
3	advance* near/6 breast and (tumor* or tumour* or carcinoma* or neoplasm* or cancer*)	2,721
4	#1 or #2 or #3	12,803

No.	Query	Results
5	“fulvestrant” OR “faslodex” OR “ici 182 780” OR “ici 182, 780” OR “ici 182780” OR “ici182780” OR “zd 182780” OR “zd 9238” OR “zd182780” OR “zd9238” OR “zm 182780” OR “zm182780”	208
6	“anastrozole” OR “anastrazole” OR “arimidex” OR “ici d1033” OR “icid1033” OR “trozolet” OR “zd 1033” OR “zd1033”	766
7	“letrozole” OR “cgs 20267” OR “cgs20267” OR “femar” OR “femara”	867
8	“tamoxifen” OR “kessar” OR “nsc 180973” OR “tamoplac” OR “tamoxasta” OR “tamoxifene”	3962
9	“toremifene” OR “estrimex” OR “fareston” OR “fc 1157 a” OR “fc 1157a” OR “fc1157a” OR “toremifene citrate”	148
10	“exemestane” OR “aromasin” OR “aromasine” OR “fce 24304” OR “fce24304” OR “nikidess” OR “pnu 155971” OR “pnu155971”	489
11	“abiraterone” OR abretone OR “cb 7630” OR “cb7630” OR zytiga	116
12	“megestrol acetate” OR endace OR maygace OR megace OR “megacees” OR “megaceos” OR “megaplex” OR “megase” OR megastrol OR megejohn OR megestat OR megestil OR “megestranol acetate” OR “megestrinol acetate” OR “megestrolacetate” OR “megestrole acetate” OR “megostat” OR “mergestrol acetate” OR mestrel OR niagestin OR niagestine OR ovaban OR ovarid OR pallace OR “sc 10363” OR “sc10363”	438
13	“Atamestane” OR “sh 489” OR “sh489”	11
14	“endoxifen” OR “z-endoxifen” OR “4 hydroxy n desmethyltamoxifen” OR “4 hydroxynortamoxifen” OR “endoxifen hydrochloride” OR “endoxifen hydrochloride hydrate”	16
15	“palbociclib” OR “ibrance” OR “palbociclib isethionate” OR “pd 0332991” OR “pd 0332991 0054” OR “pd 0332991-0054” OR “pd 332991” OR “pd0332991” OR “pd0332991 0054” OR “pd0332991-0054” OR “pd332991” OR “pf 00080665 73” OR “pf 00080665-73” OR “pf00080665 73” OR “pf00080665-73”	16
16	“ribociclib” or “lee 011” or “lee011”	1
17	“Lapatinib” OR “gw 2016” OR “gw 572016” OR “gw 572016f” OR “gw2016” OR “gw572016” OR “gw572016f” OR “lapatinibditosylate” OR “lapatinibditosylate monohydrate” OR “lapatinibtosylate” OR “ykerb” OR “tyverb”	358
18	“everolimus” OR “affinitor” OR “afinitor” OR “afinitordisperz” OR “certican” OR “nvp rad 001” OR “nvp rad001” OR “rad 001” OR “rad 001a” OR “rad001” OR “rad001a” OR “sdz rad” OR “votubia” OR “xience” OR “xience v” OR “zortress”	1,403
19	“bevacizumab” OR “altuzan” OR “avastin” OR “nsc 704865” OR “nsc704865”	2005
20	“docetaxel” OR “daxotel” OR “dexotel” OR “docefrez” OR “docetaxel accord” OR “lit 976” OR “lit976” OR “nsc 628503” OR “nsc628503” OR “oncodocel” OR “rp 56976” OR “rp56976” OR “taxoter” OR “taxotere” OR “texot”	3149

No.	Query	Results
21	“paclitaxel” OR “abi 007” OR “abi007” OR “abraxane” OR “albumin bound paclitaxel” OR “albumin-bound paclitaxel” OR “anzatax” OR “asotax” OR “biotax” OR “bms 181339” OR “bms181339” OR “bristaxol” OR “britaxol” OR “coroxane” OR “formoxol” OR “genexol” OR “genexol pm” OR “hunxol” OR “ifaxol” OR “infinnium” OR “intaxel” OR “mbt 0206” OR “mbt0206” OR “medixel” OR “mitotax” OR “nab paclitaxel” OR “nanoparticle albumin bound paclitaxel” OR “nsc 125973” OR “nsc125973” OR “oncogel” OR “onxol” OR “pacitaxel” OR “paclitaxel nab” OR “pacxel” OR “padexol” OR “parexel” OR “paxceed” OR “paxene” OR “paxus” OR “praxel” OR “taxocris” OR “taxol” OR “taxus” OR “taycovit” OR “yewtaxan”	4,693
22	“abemaciclib” OR “bemaciclib” OR “ly 2835219” OR “ly2835219”	1
23	“Temsirolimus” OR “cci 779” OR “cci779” OR “cell cycle inhibitor 779” OR “nsc 683864” OR “nsc683864” OR “torisel” OR “way-cci 779”	131
24	“entinostat” OR “ms 27 275” OR “ms 275” OR “ms27 275” OR “ms275” OR “sndx 275” OR “sndx275”	17
25	“Alpelisib” OR “nvpbyl 719” OR “nvp byl719”	282
26	“taselisib” OR “gdc 0032” OR “gdc0032” OR “rg 7604” OR “rg7604”	2
27	“pictilisib” OR “gdc 0941” OR “gdc0941” OR “pictrelisib”	8
28	“buparlisib” OR “bkm 120” OR “bkm 120 aaa” OR “bkm 120 nx” OR “bkm 120aaa” OR “bkm 120nx” OR “bkm120” OR “bkm120 aaa” OR “bkm120 nx” OR “bkm120aaa” OR “bkm120nx” OR “buparlisib hydrochloride” OR “nvpbkm 120” OR “nvp bkm120”	8
29	“trastuzumab”/syn OR “herceptin”	1,030
30	MeSH descriptor: [Tamoxifen] explode all trees	1,973
31	MeSH descriptor: [Megestrol Acetate] explode all trees	165
32	MeSH descriptor: [Everolimus] explode all trees	387
33	MeSH descriptor: [Bevacizumab] explode all trees	563
34	MeSH descriptor: [Paclitaxel] explode all trees	1,693
35	MeSH descriptor: [Trastuzumab] explode all trees	185
36	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35	16,005
37	#7 and #36 (in Trials and Methods Studies)	3,815

Table 122: Search strategy for MEDLINE® In-Process searched via PubMed® platform (searched on 10 Jan 2017**)**

No.	Query	Results
1	Search "breast neoplasms"	234,500
2	Search ("breast cancer" or ‘‘breast tumor’‘ OR ‘‘breast tumour’‘ OR ‘‘breast neoplasms’‘ OR ‘‘breast neoplasm’‘ OR “breast carcinoma” OR "breast malignan*")	230,819
3	Search Breast cancers[tiab]	17,591
4	Search Breast neoplasm[tiab]	414
5	Search Breast neoplasms[tiab]	7,650
6	Search Breast tumour[tiab]	1,319
7	Search Breast tumor[tiab]	7,385
8	Search Breast tumors[tiab]	9,099
9	Search Mammary carcinoma[tiab]	5,956
10	Search Mammary carcinomas[tiab]	2,039
11	Search Mammary neoplasm[tiab]	38
12	“Search Mammary neoplasms[tiab]	599
13	Search Breast tumours[tiab]	2,008
14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	303,828
15	Search Advanced	379,719
16	Search Metastatic	800,252
17	Search "Stage 3"	7,375
18	Search "Stage 4"	4,378
19	Search "Stage III"	26,019
20	Search "Stage IIIB"	3,560
21	Search "Stage IIIC"	902
22	Search "Stage IV"	16,651
23	Search Metastasis	279,276
24	Search Metastases	280,469
25	Search Unresectable	13,833
26	Search Inoperable	10,707
27	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	1,355,596
28	#14 AND #27	84,180
29	Search (“fulvestrant” OR “faslodex” OR “ici 182 780” OR “ici 182, 780”OR “ici 182780” OR “ici182780” OR “zd 182780” OR “zd 9238” OR“zd182780” OR “zd9238” OR “zm 182780” OR “zm182780”)	3,642
30	Search (“anastrozole” OR “anastrazole” OR “arimidex” OR “ici d1033”OR “icid1033” OR “trozolet” OR “zd 1033” OR “zd1033”)	1,876
31	Search (“letrozole” OR “cgs 20267” OR “cgs20267” OR “femar” OR“femara”)	2,298
32	Search (“tamoxifen” OR “kessar” OR “nsc 180973” OR “tamoplac” OR“tamoxasta” OR “tamoxifene”)	23,591
33	Search (“toremifene” OR “estrimex” OR “fareston” OR “fc 1157 a” OR “fc1157a” OR “fc1157a” OR “toremifene citrate”)	698

No.	Query	Results
34	Search (“exemestane” OR “aromasin” OR “aromasine” OR “fce 24304”OR “fce24304” OR “nikidess” OR “pnu 155971” OR “pnu155971”)	1,104
35	Search (“abiraterone” OR abretone OR “cb 7630” OR “cb7630” OR zytiga)	929
36	Search (“megestrol acetate” OR endace OR maygace OR megace OR “megacees” OR “megaceos” OR “megaplex” OR “megase” OR megastrol OR megejohn OR megestat OR megestil OR “megestranol acetate” OR “megestrinol acetate” OR “megestrolacetate” OR “megestrole acetate” OR “megostat” OR “mergestrol acetate” OR mestrel OR niagestin OR niagestine OR ovaban OR ovarid OR pallace OR “sc 10363” OR “sc10363”)	147,573
37	Search (“Atamestane” OR “sh 489” OR “sh489”)	50
38	Search (“endoxifen” OR “z-endoxifen” OR “4 hydroxy n desmethyltamoxifen” OR “4 hydroxynortamoxifen” OR “endoxifen hydrochloride” OR “endoxifen hydrochloride hydrate”)	240
39	Search (“palbociclib” OR “ibrance” OR “palbociclib isethionate” OR “pd0332991”	155
40	Search (“ribociclib” or “lee 011” or “lee011”)	1117
41	Search (“Lapatinib” OR “gw 2016” OR “gw 572016” OR “gw 572016f” OR“gw2016” OR “gw572016” OR “gw572016f” OR “lapatinibditosylate” OR“lapatinibditosylate monohydrate” OR “lapatinibtosylate” OR “ykerb”OR “tyverb”)	7,665
42	Search (“everolimus” OR “affinitor” OR “afinitor” OR “afinitordisperz”OR “certican” OR “nvp rad 001” OR “nvp rad001” OR “rad 001” OR “rad001a” OR “rad001” OR “rad001a” OR “sdz rad” OR “votubia” OR“xience” OR “xience v” OR “zortress”)	4,503
43	Search (“bevacizumab” OR “altuzan” OR “avastin” OR “nsc 704865” OR“nsc704865”)	12,208
44	Search (“docetaxel” OR “daxotel” OR “dexotel” OR “docefrez” OR“docetaxel accord” OR “lit 976” OR “lit976” OR “nsc 628503” OR“nsc628503” OR “oncodocel” OR “rp 56976” OR “rp56976” OR “taxoter”OR “taxotere” OR “texot”)	12,084
45	Search (“paclitaxel” OR “abi 007” OR “abi007” OR “abraxane” OR“albumin bound paclitaxel” OR “albumin-bound paclitaxel” OR “anzatax”OR “asotax” OR “biotax” OR “bms 181339” OR “bms181339” OR“bristaxol” OR “britaxol” OR “coroxane” OR “formoxol” OR “genexol”OR “genexol pm” OR “hunxol” OR “ifaxol” OR “infinnium” OR “intaxel”OR “mbt 0206” OR “mbt0206” OR “medixel” OR “mitotax” OR “nabpaclitaxel” OR “nanoparticle albumin bound paclitaxel” OR “nsc 125973”OR “nsc125973” OR “oncogel” OR “onxol” OR “pacitaxel” OR “paclitaxelnab” OR “pacxel” OR “padexol” OR “parexel” OR “paxceed” OR“paxene” OR “paxus” OR “praxel” OR “taxocris” OR “taxol” OR “taxus”OR “taycovit” OR “yewtaxan”)	31,127

No.	Query	Results
46	Search (“abemaciclib” OR “bemaciclib” OR “ly 2835219” OR “ly2835219”)	13,250
47	Search (“Temsirolimus” OR “cci 779” OR “cci779” OR “cell cycle inhibitor779” OR “nsc 683864” OR “nsc683864” OR “torisel” OR “way-cci 779”)	1,262
48	Search (“entinostat” OR “ms 27 275” OR “ms 275” OR “ms27 275” OR“ms275” OR “sndx 275” OR “sndx275”)	464
49	Search (“Alpelisib” OR “nvpbyl 719” OR “nvp byl719”)	23
50	Search (“taselisib” OR “gdc 0032” OR “gdc0032” OR “rg 7604” OR“rg7604”)	6
51	Search (“pictilisib” OR “gdc 0941” OR “gdc0941” OR “pictrelisib”)	133
52	Search (“buparlisib” OR “bkm 120” OR “bkm 120 aaa” OR “bkm 120 nx”OR “bkm 120aaa” OR “bkm 120nx” OR “bkm120” OR “bkm120 aaa” OR“bkm120 nx” OR “bkm120aaa” OR “bkm120nx” OR “Buparlisibhydrochloride” OR “nvpbkm 120” OR “nvp bkm120”)	291
53	Search (“trastuzumab” OR “herceptin”)	7,990
54	#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53	5,593,083
55	#28 AND #54 AND ((inprocess[sb] OR pubstatusaheadofprint))	642

Table 123: Total number of citations retrieved from all databases

Database	Numbers retrieved
Embase® and MEDLINE®	9,397
CENTRAL	3,815
MEDLINE® In-Process	642
Total	**13,854**

Appendix B: Included and Excluded studies

Table 124: List of included studies in the review

Study Name	Publication type	Sample size	Treatment
FALCON trial	CSR	462	Fulvestrant
			Anastrozole
FIRST study	CSR	205	Fulvestrant
			Anastrozole
Milla-Santos 2003	Journal article	238	Anastrozole
			Tamoxifen
North American trial	Journal article	353	Anastrozole
			Tamoxifen
Howell 2004	Journal article	587	Fulvestrant
			Tamoxifen

Study Name	Publication type	Sample size	Treatment
Paridaens 2008	Journal article	382	Exemestane
			Tamoxifen
PALOMA-1 study	Journal article	165 (110)*	Palbociclib + letrozole
			Letrozole
PALOMA-2 study	ASCO conference presentation	666 (291)*	Palbociclib + letrozole
			Letrozole
Pyrhonen 1997	Journal article	415 (238)*	Toremifene
			Tamoxifen
PO25 trial	Journal article	916 (599)*	Letrozole
			Tamoxifen
TARGET trial	Journal article	668 (298)*	Anastrozole
			Tamoxifen
SWOG 0226 study	Journal article	695 (414)*	Anastrozole
			Anastrozole + Fulvestrant
De 1990	Journal article	60	Tamoxifen
			Tamoxifen + Medroxyprogesterone acetate
Ingle 1991	Journal article	249	Tamoxifen
			Tamoxifen + Fluoxymesterone
Van 1986	Journal article	138 (52)*	Medroxyprogesterone acetate
			Tamoxifen
Mouridsen 1979	Journal article	101 (41)*	Tamoxifen
			Tamoxifen + Medroxyprogesterone acetate
Allegra 1985	Journal article	131	Megestrol Acetate
			Tamoxifen
Ettinger 1986	Journal article	197	Megestrol Acetate
			Tamoxifen
Morgan 1985	Journal article	106 (30)*	Tamoxifen
			Megestrol Acetate
Beex 1981	Journal article	63 (24)*	Ethinyl estradiol
			Tamoxifen
Thurlimann 1996	Journal article	212	Tamoxifen
			Fadrozole
Rose 2000	Journal article	313 (53)*	Tamoxifen
			Tamoxifen + Aminoglutethimide + Hydrocortisone
			Tamoxifen + Fluoxymesterone

*Data in brackets represents sample size of subgroup of interest.

ASCO: American Society of Clinical Oncology; CSR: Clinical Study Report

Table 125: List of excluded studies from the review

Study name	Intervention	Comparator 1	Comparator 2	Reason of exclusion
Ibrahim 2011	AS1402 + Letrozole	Letrozole	-	This study was terminated and further development of AS1402 for breast cancer was stopped
MINT trial	Anastrozole + Placebo	AZD8931 40 mg bid + Anastrozole	AZD893120 mg bid + Anastrozole	This study was terminated and further development of AZD8931 for breast cancer was stopped
Arpino 2003	Tamoxifen	Idoxifene	-	The trial was stopped due to economic considerations and limited potential for future profitability of the drug. Development of idoxifene was discontinued as this study was unable to demonstrate superiority of idoxifene over tamoxifen
Buzdar 2002	Tamoxifen	Droloxifene	-	Droloxifene proved to be significantly less effective than tamoxifen and in light of the results, no further development of droloxifene was undertaken
Deshmane 2007	Tamoxifen	Arzoxifene	-	This study comparing arzoxifene with tamoxifen for breast cancer treatment was stopped when a planned interim analysis suggested a minimal possibility of arzoxifene demonstrating superiority to tamoxifen, if the trial was completed
HORIZONE trial	Letrozole	Letrozole + Temsirolimus	-	This study was terminated after second interim analyses as it was unlikely to reach its primary endpoint of PFS
Osborne 2011	Tamoxifen	Tamoxifen + Gefitinib	-	• Development of gefitinib discontinued for breast cancer
Cristofanilli 2010	Anastrozole	Anastrozole + Gefitinib	-	• Development of gefitinib discontinued for breast cancer
Mouridsen 1980	Tamoxifen	Tamoxifen + Diethylstilboestrol	-	• Marketing of diethylstilbestrol discontinued
Ingle 1981	Tamoxifen	Tamoxifen + Diethylstilboestrol	-	• Marketing of diethylstilbestrol discontinued
Ingle 1999	Tamoxifen	Tamoxifen + Octreotide	-	• Octreotide not indicated for breast cancer
Bajetta 2002	Tamoxifen	Octreotidepamoate + Tamoxifen	-	• Octreotide not indicated for breast cancer
Ingle 1986	Tamoxifen	Tamoxifen + Aminoglutethimide + Hydrocortisone	-	• Marketing of aminoglutethimide discontinued; hydrocortisone added to regimen to prevent symptomatic adrenal insufficiency
Coombes 1984	Tamoxifen	Tamoxifen + Aminoglutethimide + Danazol + Hydrocortisone	-	• Marketing of aminoglutethimide discontinued; hydrocortisone added to regimen to prevent symptomatic adrenal insufficiency • Marketing of danazol discontinued
Bezwoda 1982	Tamoxifen	Tamoxifen + CMF	-	• Chemotherapy not of interest to the review as used after endocrine therapy in regular practice
Taylor 1986	Tamoxifen	Cyclophosphamide + Methotrexate + Fluorouracil	-	• Chemotherapy not of interest to the review as used after endocrine therapy in regular practice
Rubens 1988	Tamoxifen	Tamoxifen + prednisolone	-	• Tamoxifen + prednisolone combination not recommended by treatment guidelines in the indication of breast cancer
Ingle 1991	Tamoxifen	Tamoxifen + prednisolone	-	• Tamoxifen + prednisolone combination not recommended by treatment guidelines in the indication of breast cancer

Study name	Intervention	Comparator 1	Comparator 2	Reason of exclusion
Stewart 1982	Tamoxifen	Tamoxifen + prednisolone	-	• Tamoxifen + prednisolone combination not recommended by treatment guidelines in the indication of breast cancer
Blanchett 2007	Atamestane + Toremifene	Letrozole	-	• Development of atamestane for breast cancer has been discontinued
Bergh 2012	-	-	-	• Bergh 2012 reported graphical data for subgroup of interest (endocrine naïve patients) as hazard ratio for PFS; however the data was reported in a disproportionate manner and hence confidence intervals could not be calculated (Bergh 2012)
Perry 1987	-	-	-	• Perry 1987 evaluated cyclophosphamide + doxorubicin + 5-fluoro uracil with or without tamoxifen. This trial was excluded as it had no common comparator to be linked in the network diagram (Perry 1987)

MPA: Medroxy-progesterone acetate; CMF: Cyclophosphamide + Methotrexate + 5-Fluoro uracil; US-FDA: United States Food and Drug Administration; SEOM: Sociedad Española de OncologíaMédica; EMA: European Medicines Agency; ESMO: European Society of Medical Oncology

Table 126: Studies assessing comparators not of interest

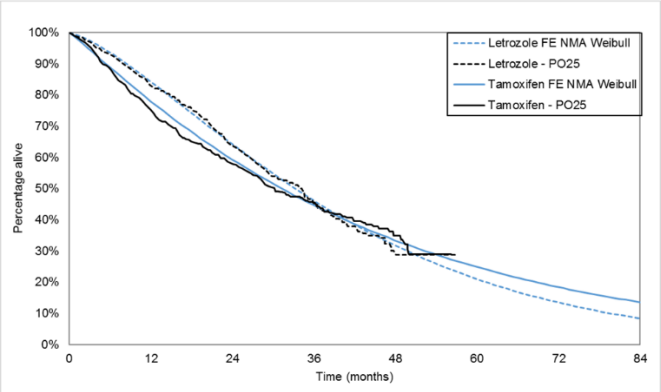
Study name	Comparator 1	Comment
Rose 2000	Tamoxifen versus Tamoxifen + Aminoglutethimide + Hydrocortisone and Tamoxifen + Fluoxymesterone	• Marketing of aminoglutethimide discontinued; hydrocortisone added to regimen to prevent symptomatic adrenal insufficiency • Marketing of fluoxymesterone discontinued • Androgens recommended by SEOM guidelines in second-line therapy
Ingle 1991	Tamoxifen versus Tamoxifen + Fluoxymesterone	• Marketing of fluoxymesterone discontinued • Androgens recommended by SEOM guidelines in second-line therapy
De 1990	Tamoxifen versus Tamoxifen + MPA	• MPA or other progestins recommended in second-line by SEOM and ESMO guidelines
Van 1986	Tamoxifen versus MPA	• MPA or other progestins recommended in second-line by SEOM and ESMO guidelines
Mouridsen 1979	Tamoxifen versus Tamoxifen + MPA	• MPA or other progestins recommended in second-line by SEOM and ESMO guidelines
Allegra 1985	Tamoxifen versus Megestrol Acetate	• Megestrol acetate or other progestins recommended in second-line by SEOM and ESMO guidelines
Ettinger 1986	Tamoxifen versus Megestrol Acetate	• Megestrol acetate or other progestins recommended in second-line by SEOM and ESMO guidelines
Morgan 1985	Tamoxifen versus Megestrol Acetate	• Megestrol acetate or other progestins recommended in second-line by SEOM and ESMO guidelines
Beex 1981	Tamoxifen versus Ethinyl estradiol	• Androgens and estrogens recommended in second-line by SEOM guidelines
Thurlimann 1996	Tamoxifen versus Fadrozole	• Fadrozole only available in Japan. Not approved by US-FDA or EMA
Howell 2004	Tamoxifen versus Fulvestrant	• The study by Howell and colleagues compared fulvestrant 250 mg monthly with tamoxifen 20 mg od. However, in 2010, EMA had approved 500 mg dose of fulvestrant based on the results of CONFIRM trial. Results of CONFIRM trial showed that fulvestrant 500 mg showed better efficacy compared to fulvestrant 250 mg, without compromising on safety.

EMA: European Medicines Agency; ESMO: European Society of Medical Oncology; MPA: Medroxyprogesterone Acetate; SEOM: Sociedad Española de OncologíaMédica; US-FDA: United States-Food and Drug Administration

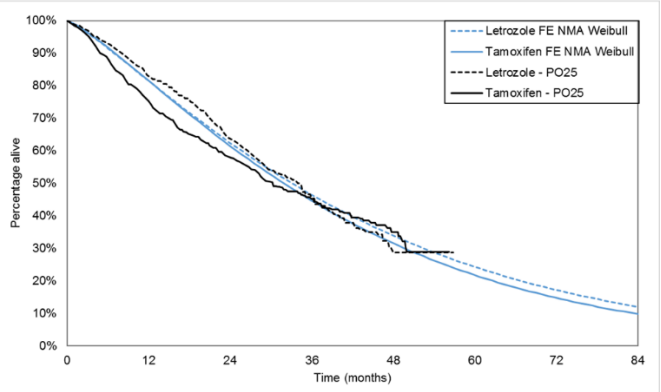
Appendix C: Visual comparison of fixed effects network meta-analysis 'all shapes' and 'no shape arm' curve fits

Figure 54: Comparison of fixed effects network meta-analysis 'all shapes' and 'no shape arm' curve fits to PO25 trial OS data

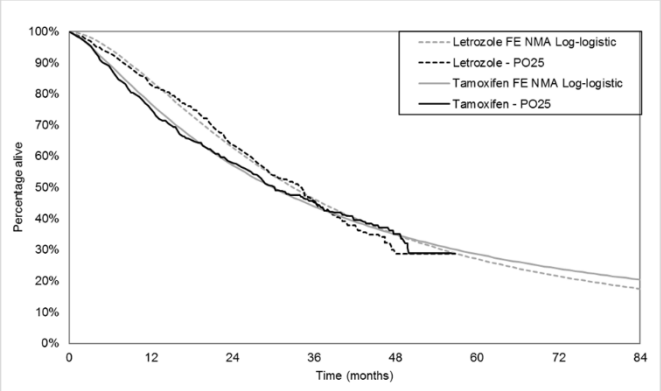
'All shapes' Weibull model



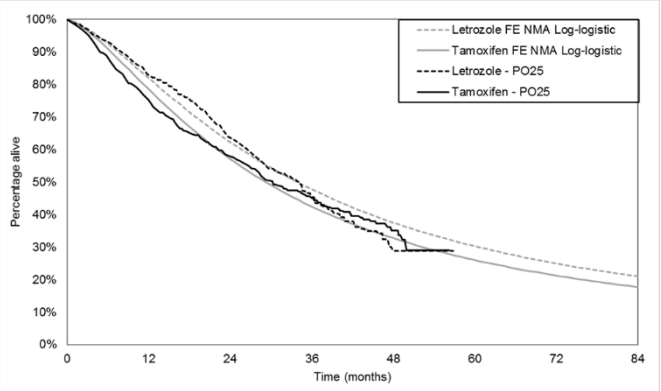
'No shape arm' Weibull model



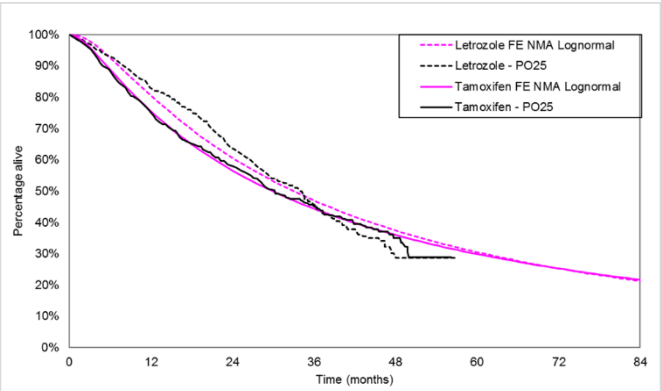
'All shapes' log-logistic model



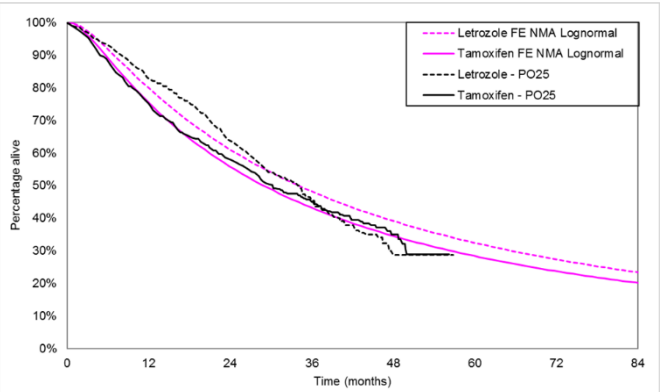
'No shape arm' log-logistic model



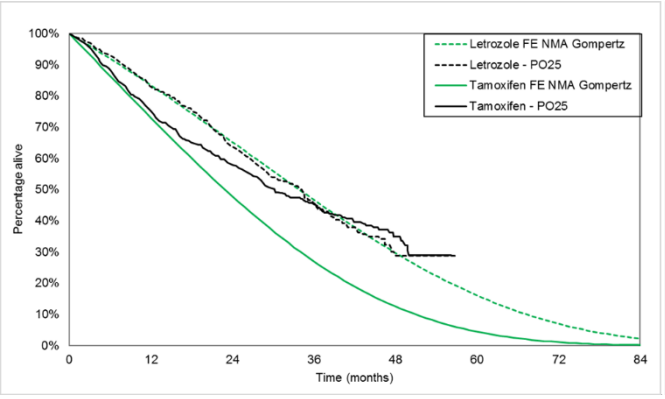
'All shapes' lognormal model



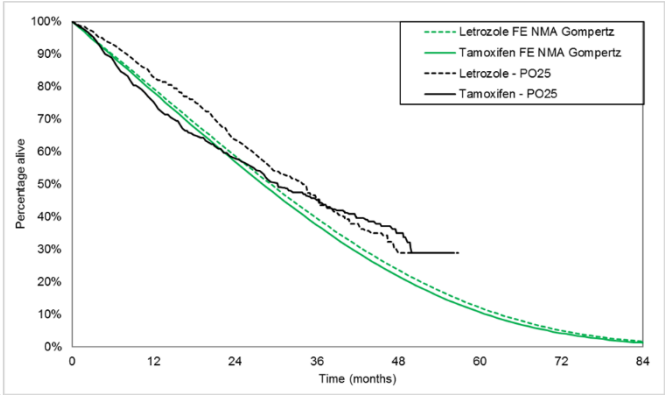
'No shape arm' lognormal model



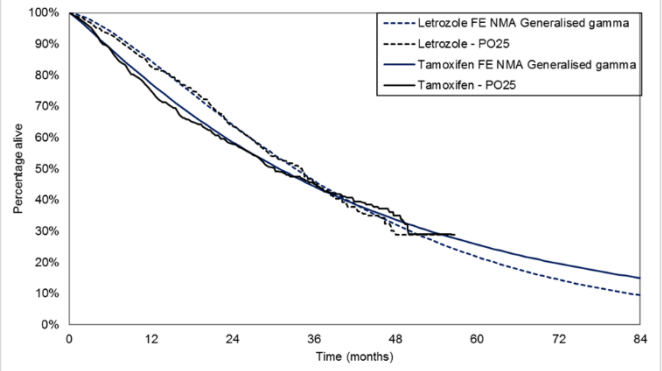
'All shapes' Gompertz model



'No shape arm' Gompertz model



[redacted]



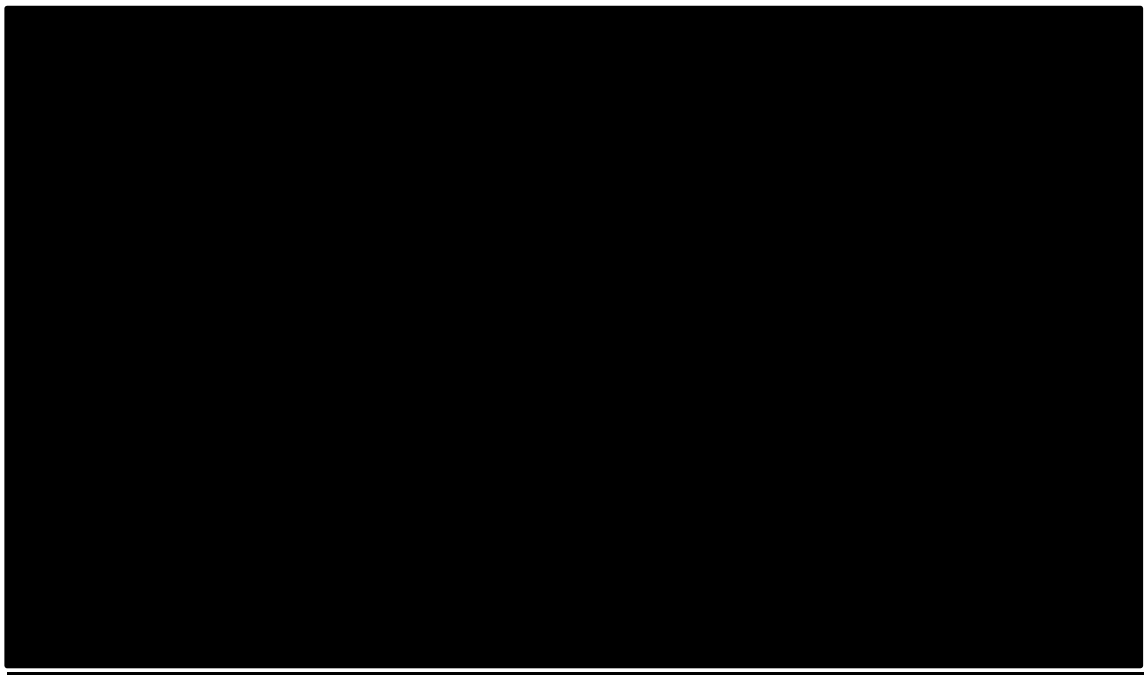
Due to the complexity in the interpretation of setting two of the generalised gamma distributions' three parameters equal, this distribution was not included in the 'no shape arm' models.

Appendix D: Fixed effects network meta-analysis 'no shape arm' models

This appendix presents the results for the network meta-analyses for PFS and OS using the 'no shape arm' models. Table 127 presents the results of the PFS NMA: baseline shape and scale and difference from baseline for each of the treatment alternatives versus (FALCON) anastrozole. The corresponding results for the OS NMA are presented in Table 128. Figure 55 presents the survival curves estimated from the fixed effects network meta-analysis 'no shape arm' models. The corresponding plots for OS are presented in Figure 60.

Due to the complexity in the interpretation of setting two of the generalised gamma distributions' three parameters equal, this distribution was not included in the 'no shape arm' models.

Figure 55: PFS as estimated from fixed effects network meta-analysis models



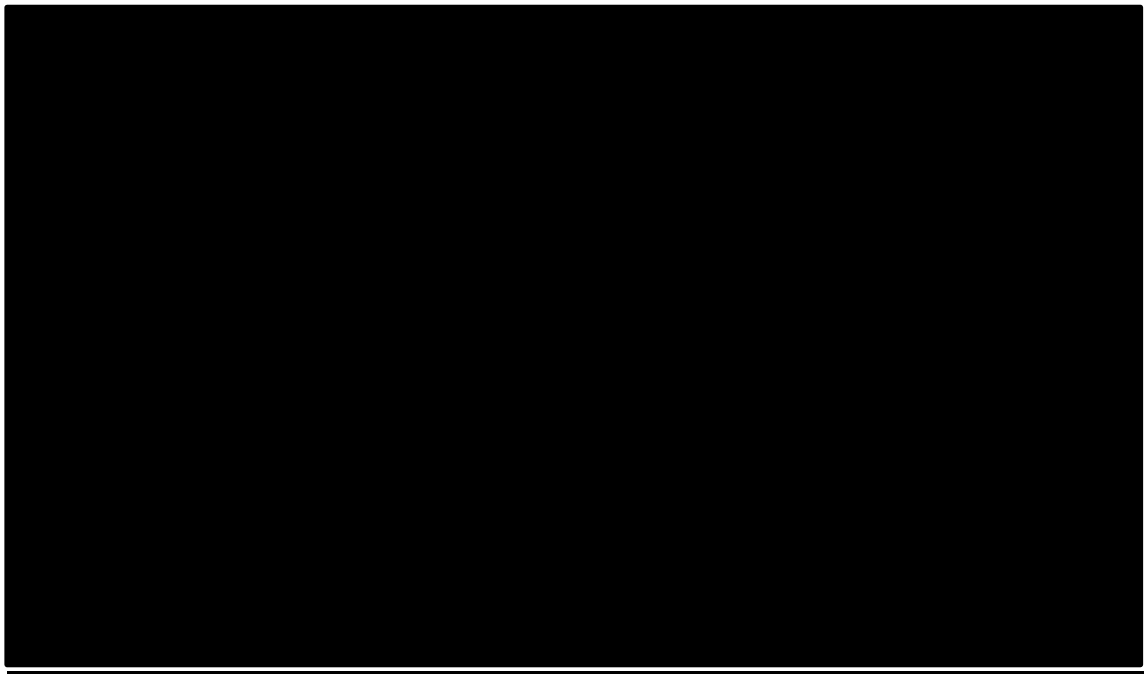


Figure 56 to Figure 58, present the study fits for PFS when the results are adjusted for between-study differences in the shape parameter. The between study differences are included for validation purposes only; that is, to assess whether estimated models provide a reasonable fit to the individual trial data. The corresponding plots for OS are presented in Figure 61 to Figure 64.

Table 127: Fixed effect network meta-analysis PFS results: baseline parametric distribution parameters and difference from baseline for treatment alternatives versus (FALCON) anastrozole

Weibull	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Gompertz	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Log-logistic	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Lognormal	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					

Abbreviations: L, lower; OS, overall survival; U, upper.

Figure 56: FALCON PFS study fit with fixed effects 'no shape arm' network meta-analysis models

[redacted]

Figure 57: FIRST PFS study fit with fixed effects 'no shape arm' network meta-analysis models adjusted for between-study differences

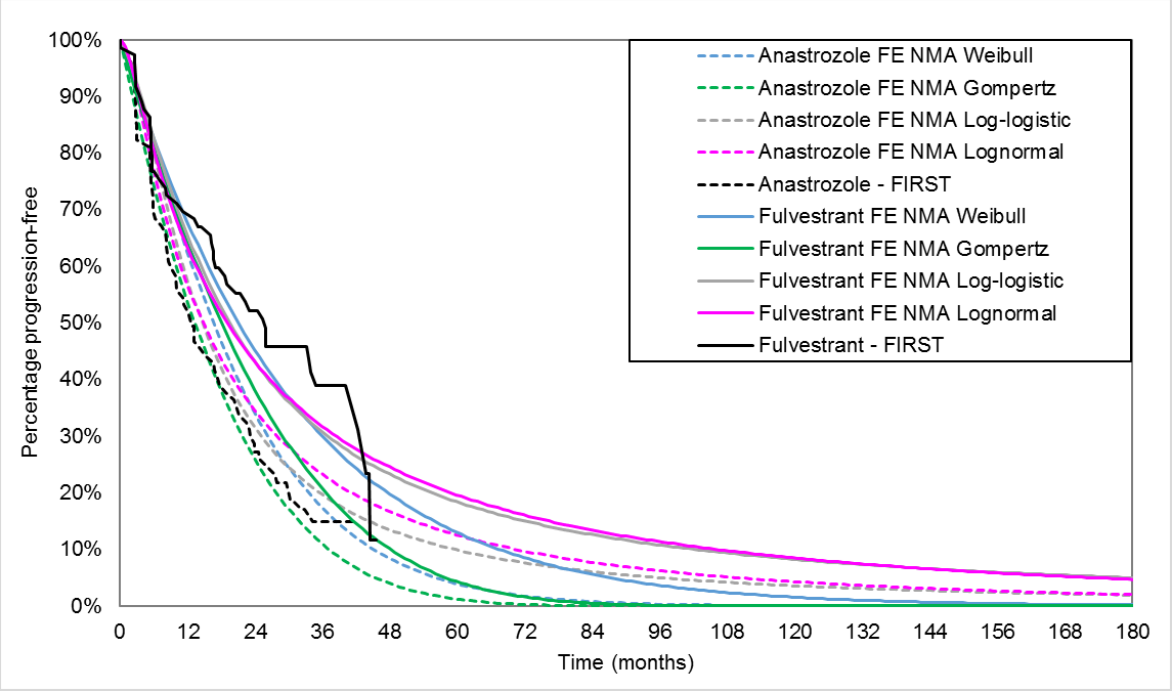


Figure 58: NorthAmTarget PFS study fit with fixed effects 'no shape arm' network meta-analysis models adjusted for between-study differences

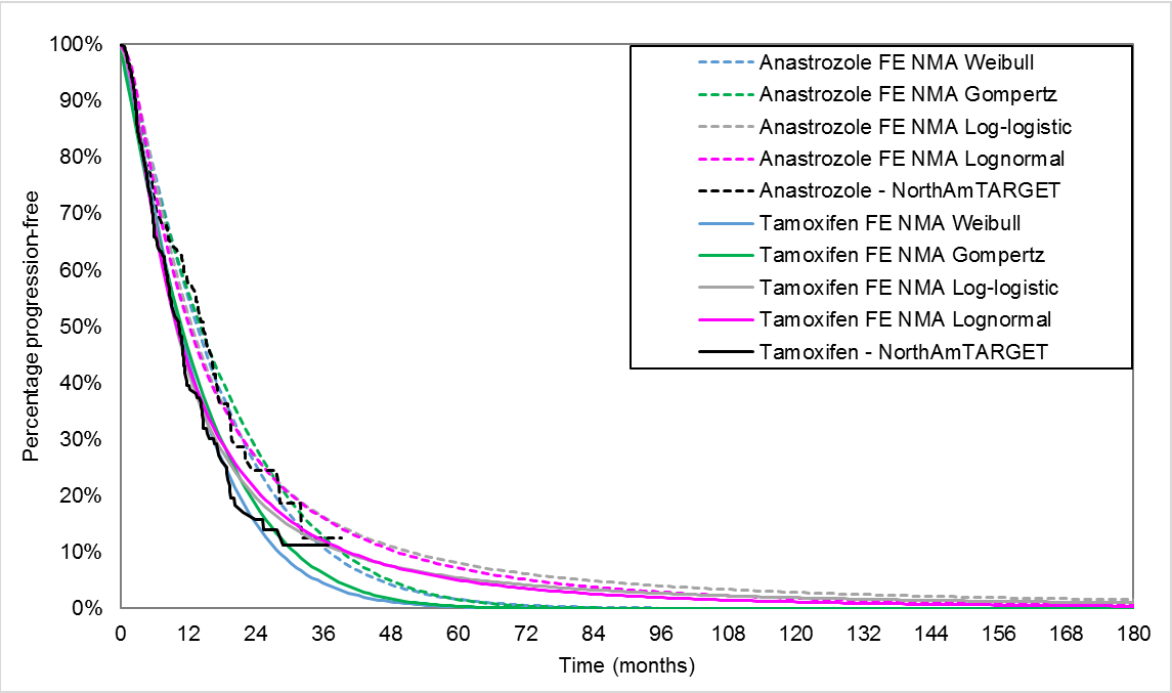


Figure 59: PO25 PFS study fit with fixed effects 'no shape arm' network meta-analysis models adjusted for between-study differences

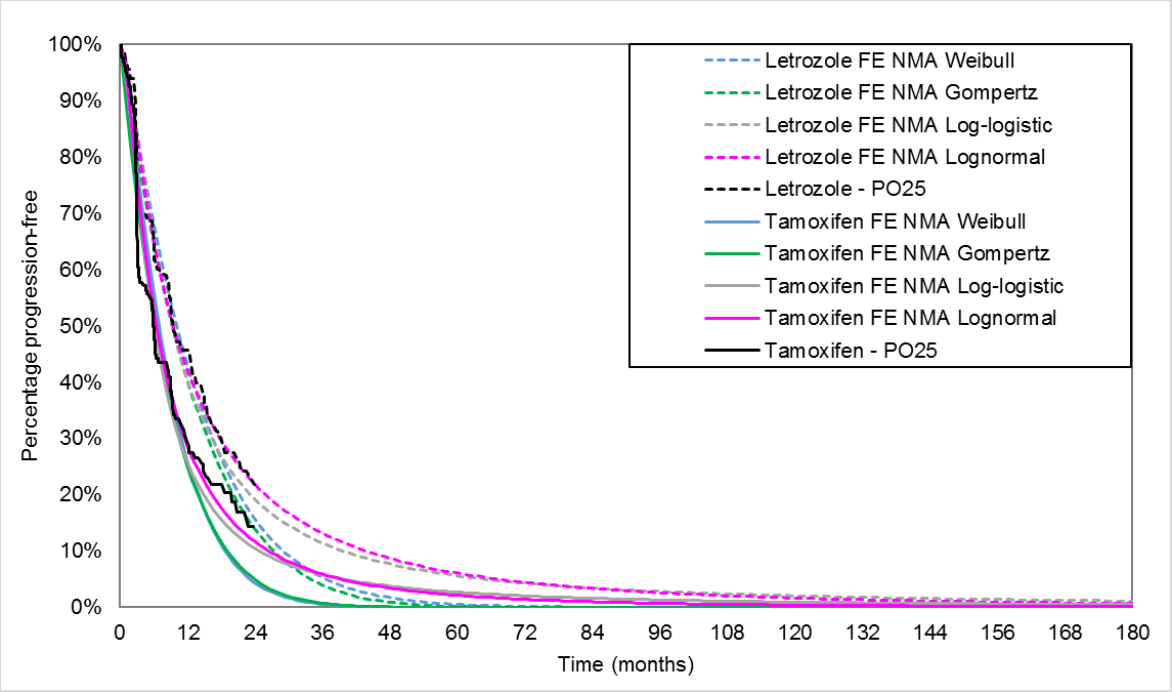
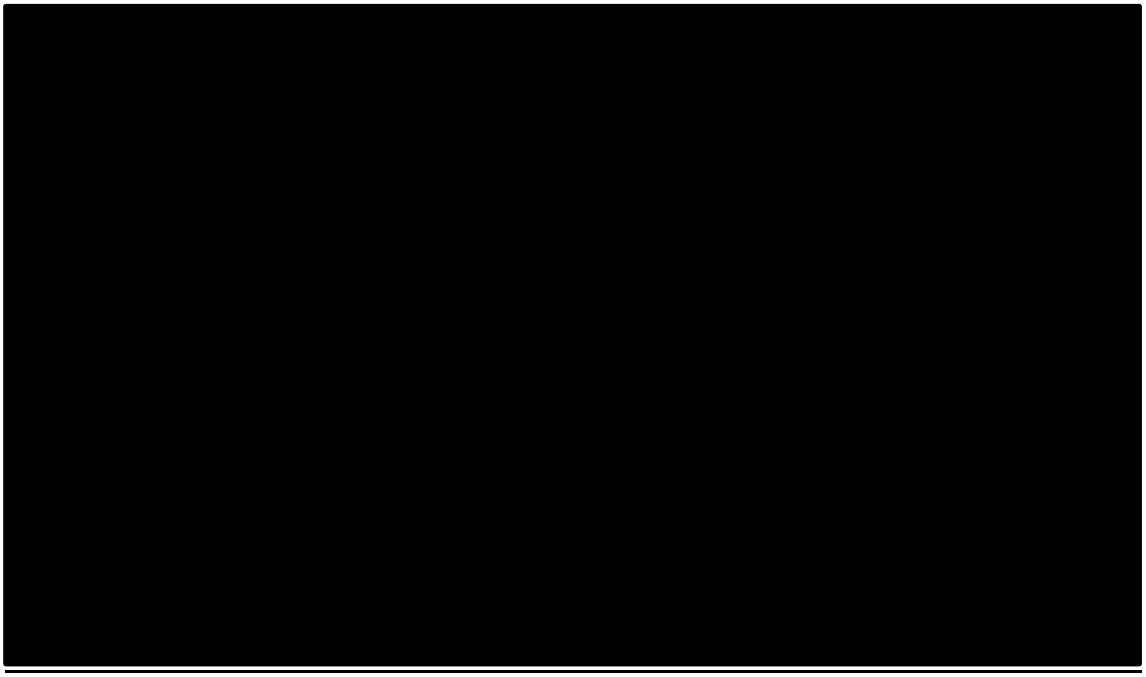


Table 128: Fixed effect network meta-analysis OS results: baseline parametric distribution parameters and difference from baseline for treatment alternatives versus (FALCON) anastrozole

Weibull	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Gompertz	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Log-logistic	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Lognormal	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					

Abbreviations: L, lower; OS, overall survival; U, upper.

Figure 60: OS as estimated from fixed effects network meta-analysis models



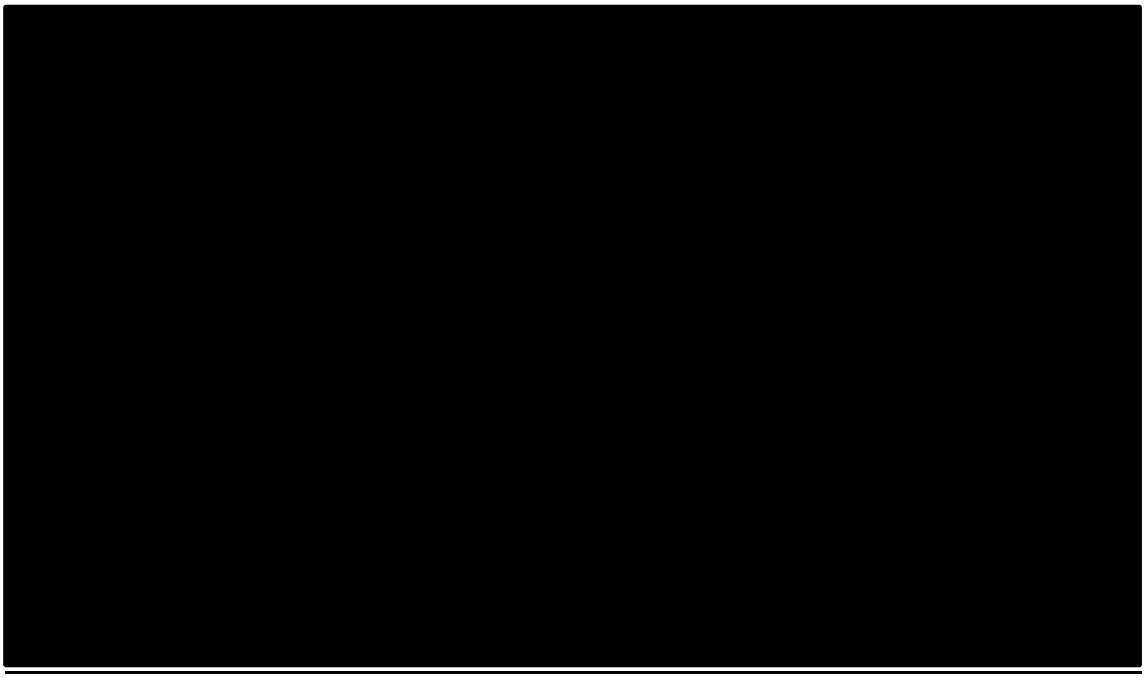


Figure 61: FALCON OS study fit with fixed effects 'no shape arm' network meta-analysis models

[redacted]

Figure 62: FIRST OS study fit with fixed effects 'no shape arm' network meta-analysis models adjusted for between-study differences

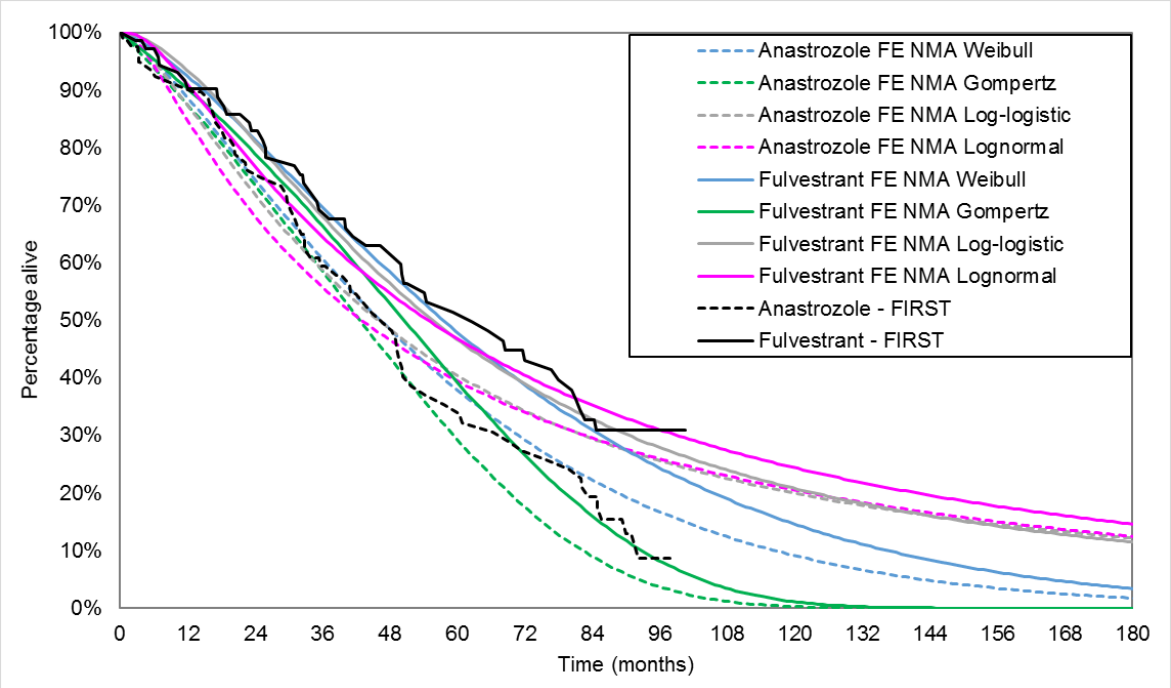


Figure 63: NorthAmTarget OS study fit with fixed effects 'no shape arm' network meta-analysis models adjusted for between-study differences

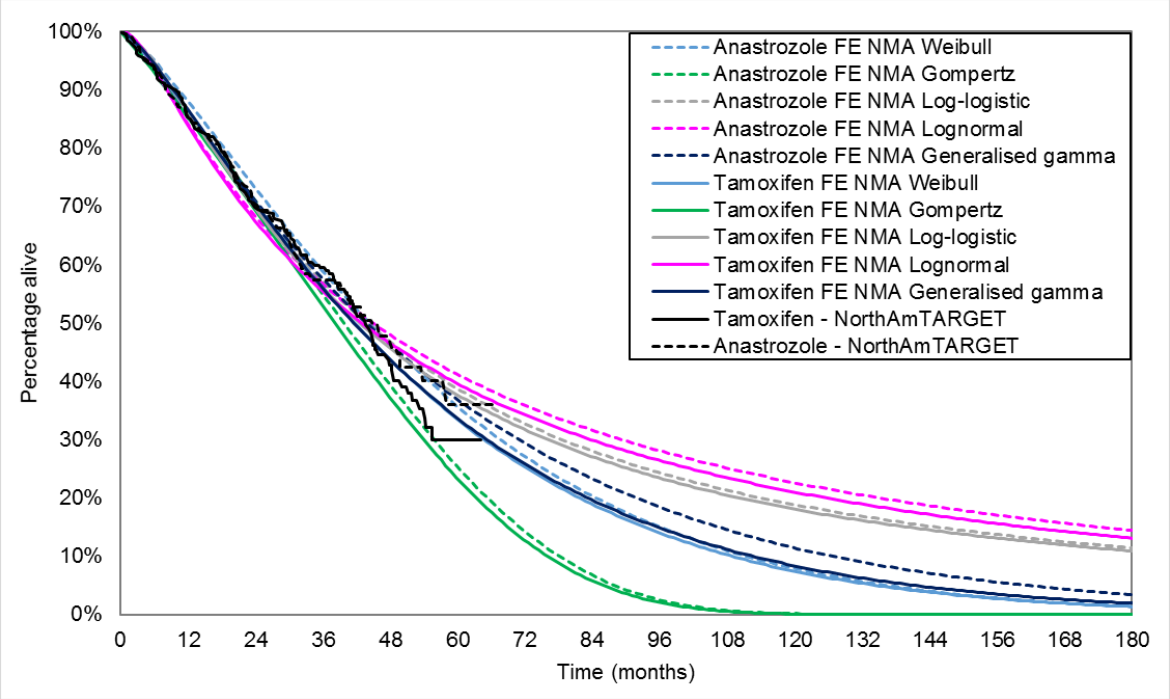
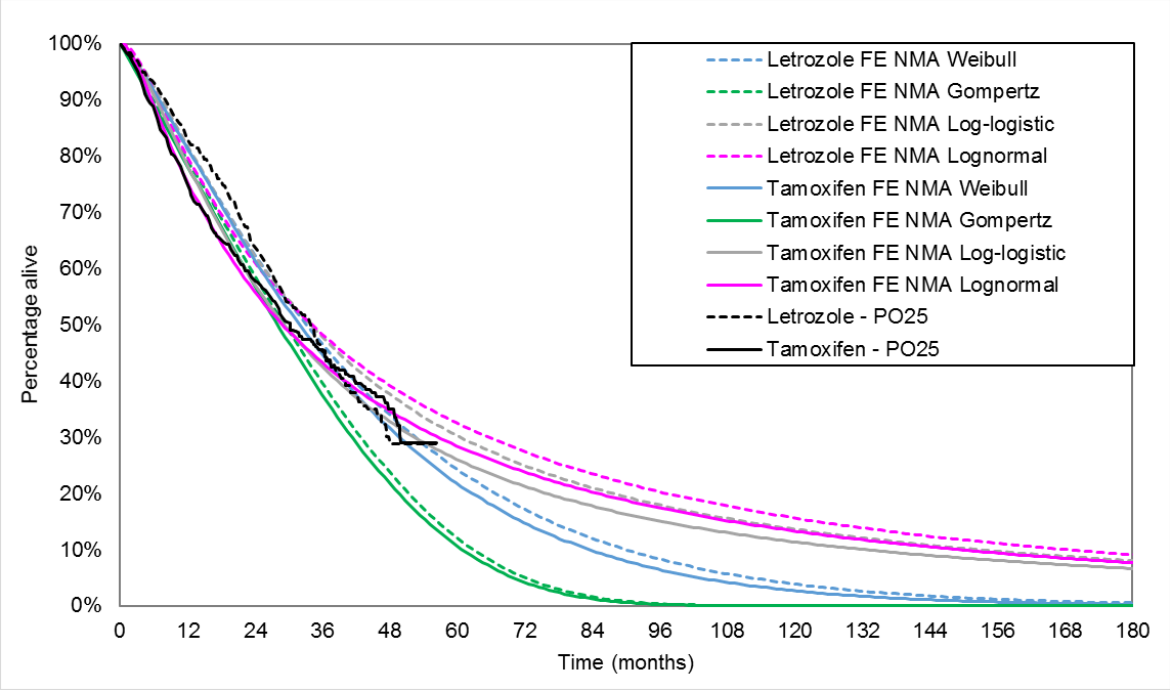


Figure 64: PO25 OS study fit with fixed effects 'no shape arm' network meta-analysis models adjusted for between-study differences



Appendix E: Overview of identified HTA submissions

Table 129 provides an overview of previous HTA submissions, including a description of the licensed indication.

Table 129: Overview of HTA submissions

Intervention	NICE	SMC	PBAC	CADTH
Trastuzumab	In combination with paclitaxel for HER2 scored at levels of 3+ who have not received chemotherapy for metastatic breast cancer and in whom anthracycline treatment is inappropriate(87)	HER2+ metastatic breast cancer in which tumours have either HER2 overexpression or HER2 gene amplification(133)	HER2+ locally advanced breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant trastuzumab(134)	-
	As monotherapy for HER2 scored at levels of 3+ who have received at least two chemotherapy regimens for metastatic breast cancer(87)			
	In combination with an AI for first-line treatment in postmenopausal women with metastatic HR+ breast cancer that overexpresses HER2(82)			
Bevacizumab	In combination with a taxane for first-line treatment of metastatic breast cancer(85)	In combination with capecitabine for first-line treatment of metastatic breast cancer when treatment with other chemotherapy options including taxanes or	-	-

Intervention	NICE	SMC	PBAC	CADTH
		anthracyclines is not considered appropriate(135)		
	In combination with capecitabine for first-line treatment of metastatic breast cancer when treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate, or when taxanes or anthracyclines have been used as part of adjuvant treatment within the past 12 months(81)		-	-
Gemcitabine	In combination with paclitaxel for metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate(86)	In combination with paclitaxel for metastatic breast cancer after relapse following adjuvant/neoadjuvant chemotherapy; prior chemotherapy should have included an anthracycline unless clinically contraindicated(136)	-	-
Fulvestrant	Postmenopausal women with ER+, locally advanced or metastatic breast cancer that has relapsed on or after adjuvant anti-ooestrogen therapy, or progressed on therapy with an anti-ooestrogen(84)	Postmenopausal women with ER+, locally advanced or metastatic breast cancer that has relapsed on or after adjuvant anti-ooestrogen therapy, or progressed on therapy with an anti-ooestrogen(137)	-	-

Intervention	NICE	SMC	PBAC	CADTH
Eribulin	Locally advanced or metastatic breast cancer that has progressed after at least two chemotherapy regimens for advanced disease; provided with a discount agreed in the PAS(83)	Locally advanced or metastatic breast cancer that has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine if indicated(138)	Locally advanced or metastatic breast cancer that has progressed after at least two chemotherapy regimens for advanced disease(139)	Metastatic or incurable locally advanced breast cancer previously treated with a taxane and an anthracycline, has had at least two chemotherapy regimens for metastatic or locally recurrent disease, and has progressed after the last therapy(140)
Lapatinib	In combination with an AI for first-line treatment in postmenopausal women with metastatic HR+ breast cancer that overexpresses HER2(82)	In combination with capecitabine, for the treatment of advanced or metastatic breast cancer in which tumours overexpress HER2 and the disease has progressed following prior therapy including anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting(141)	In combination with capecitabine, for the treatment of advanced or metastatic breast cancer in which tumours overexpress HER2 and the disease has progressed following prior therapy including trastuzumab(142)	In combination with letrozole in postmenopausal patients with HR+, HER2+ metastatic breast cancer(143)
Trastuzumab emtansine	HER2+, unresectable locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane(79)	HER2+, unresectable locally advanced or metastatic breast cancer, previously treated with trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for locally advanced or metastatic disease, or developed disease recurrence during or within 6	HER2+, unresectable locally advanced or metastatic breast cancer that received prior therapy with trastuzumab and a taxane and progressed despite treatment with trastuzumab for metastatic disease, or within 6 months of completing adjuvant therapy(145)	HER2+, unresectable locally advanced or metastatic breast cancer with prior treatment of trastuzumab plus chemotherapy in the metastatic setting or in which disease recurred during or within 6 months of completing adjuvant therapy with trastuzumab plus chemotherapy(146)

Intervention	NICE	SMC	PBAC	CADTH
		months of completing adjuvant therapy(144)		
Everolimus	In combination with exemestane, for postmenopausal women without symptomatic visceral disease and with advanced, HER2- HR+ breast cancer that has recurred or progressed following treatment with an NSAI; provided with a discount agreed in the PAS(80)	HR+, HER2- advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following an NSAI(147)	In combination with exemestane, of postmenopausal women with HR+, HER2- advanced breast cancer after failure of letrozole or anastrozole(139)	In combination with exemestane, for HR+, HER2- advanced breast cancer in postmenopausal women after recurrence or progression following an NSAI(148)
Pertuzumab	In combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adults with HER2+ locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence; provided with a discount agreed in the PAS(88)	In combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2+, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence(149) In combination with trastuzumab and docetaxel in adult patients with HER2+ metastatic or locally recurrent unresectable breast cancer, with no previous anti-HER2 therapy or chemotherapy for metastatic disease(150)	In combination with trastuzumab and docetaxel, for the treatment of HER2+ metastatic breast cancer with no prior anti-HER2 therapy or chemotherapy for metastatic disease(151)	In combination with trastuzumab and a taxane as neoadjuvant treatment for HER2+ primary operable or locally advanced/inflammatory breast cancer(152) In combination with trastuzumab and a taxane for the palliative treatment of HER2+ unresectable locally recurrent or metastatic breast cancer with no prior anti-HER2 therapy or chemotherapy for metastatic disease(153)
Vinorelbine	Second- or third-line treatment for advanced	Advanced breast cancer stage III and stage IV	Advanced breast cancer after failure of standard therapy,	-

Intervention	NICE	SMC	PBAC	CADTH
	breast cancer which is not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting)(132)	relapsing after, or refractory to, an anthracycline-containing regimen(154)	as a single agent or in combination(155)	

Abbreviations: AI: Aromatase inhibitor; CADTH, Canadian Agency for Drugs and Technologies in Health; ER, Ooestrogen receptor; HER2, Human epidermal growth factor; HR, Hormone receptor; HTA, Health Technology Assessment; NICE, National Institute of Health and Care Excellence; NSAI, Non-steroidal aromatase inhibitor; PSA, Patient Access Scheme; PBAC, Pharmaceutical Benefits Advisory Committee; SMC, Scottish Medicines Consortium.

Appendix F: EQ-5D-3L Index (UK) from FALCON

EQ-5D-3L: all patients and visits without progression

The means per visit of the EQ-5D-3L index (UK) do not indicate and systematic differences between the fulvestrant and anastrozole group between week 0 (baseline) and week 56 (end of study) with overlapping 95% confidence intervals at all visits (Figure 65). The proportions of missing values of the EQ-5D-3L index (UK) do not indicate and systematic differences between treatment groups over the study time and show overlapping 95% confidence intervals at all visits (Figure 66).

Figure 65: EQ-5D-3L index (UK) per treatment and visit without progression

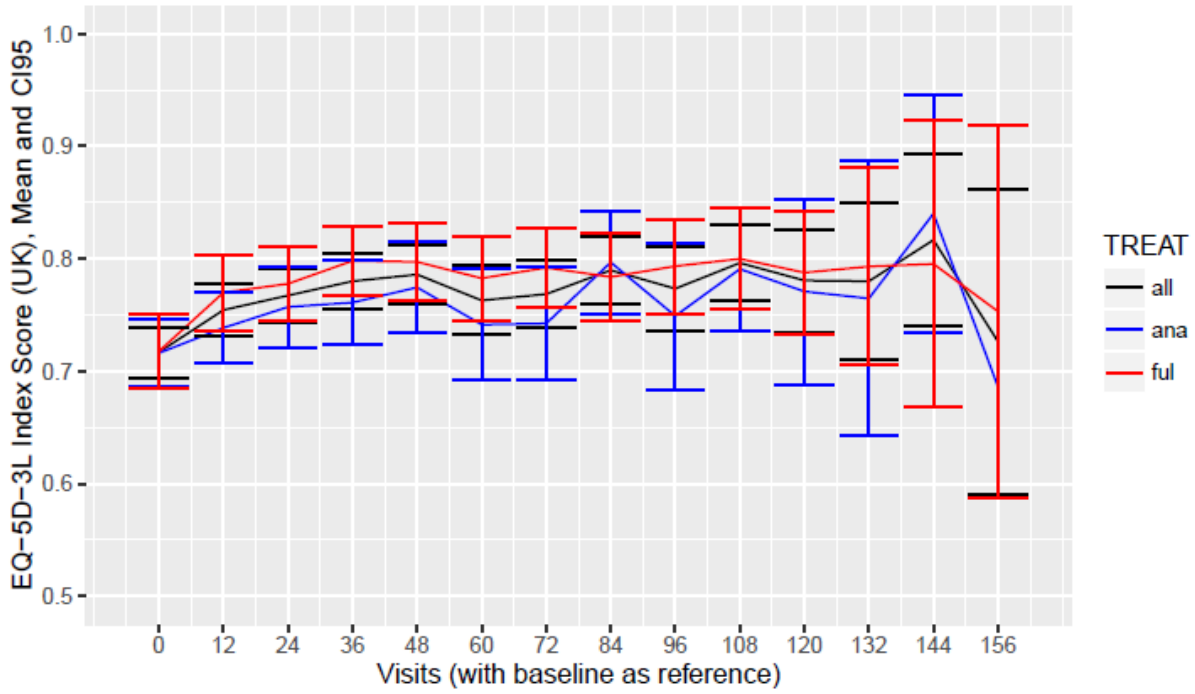
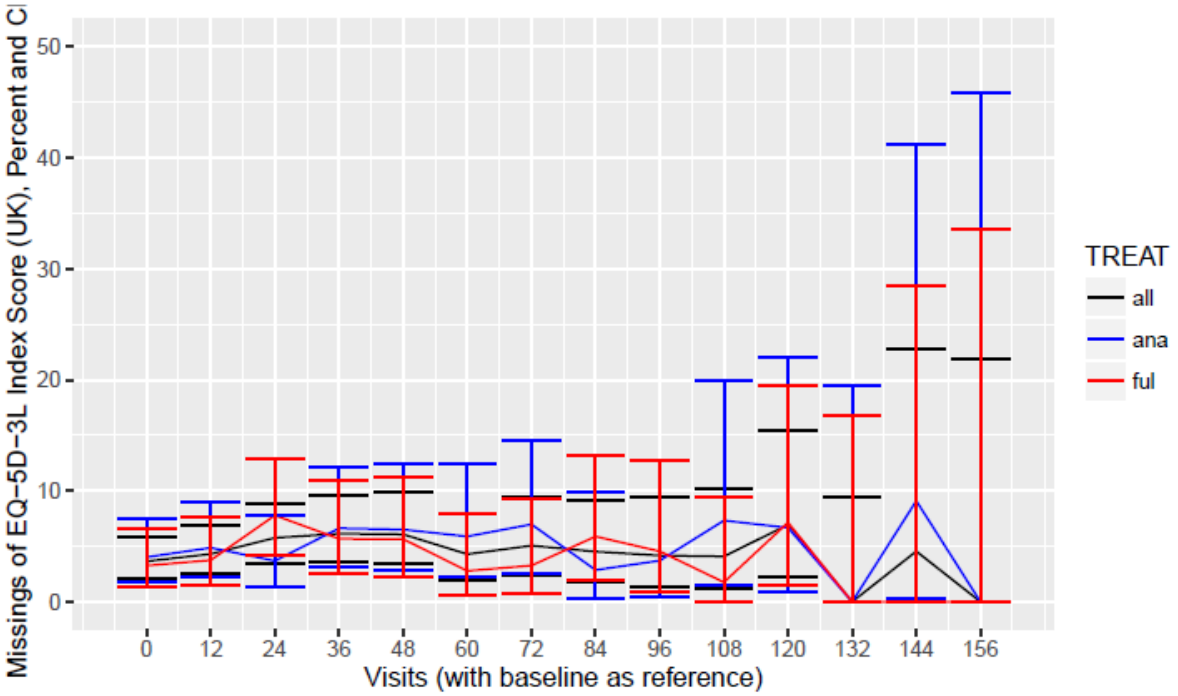


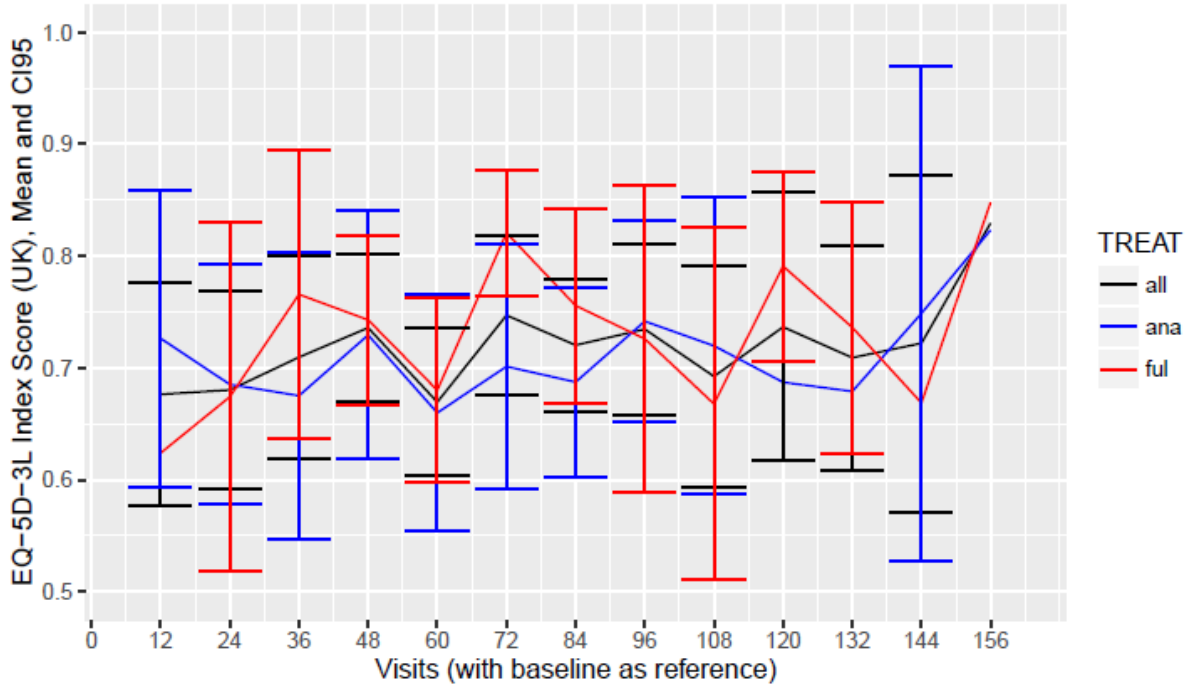
Figure 66: Missing EQ-5D-3L index (UK) per treatment and visit without progression



EQ-5D-3L: patients and visits with progression

The means per visit of the EQ-5D-3L index (UK) in the fulvestrant and anastrozole group do not show any systematic differences with overlapping 95% confidence intervals at all visits (Figure 67).

Figure 67: EQ-5D-3L index (UK) per treatment and visit with progression



The proportions of missing values of the EQ-5D-3L index (UK) do not indicate any systematic differences between treatment groups over the study time and show overlapping 95% confidence intervals at all visits (Figure 68).

Figure 68: Missing EQ-5D-3L index (UK) per treatment and visit with progression

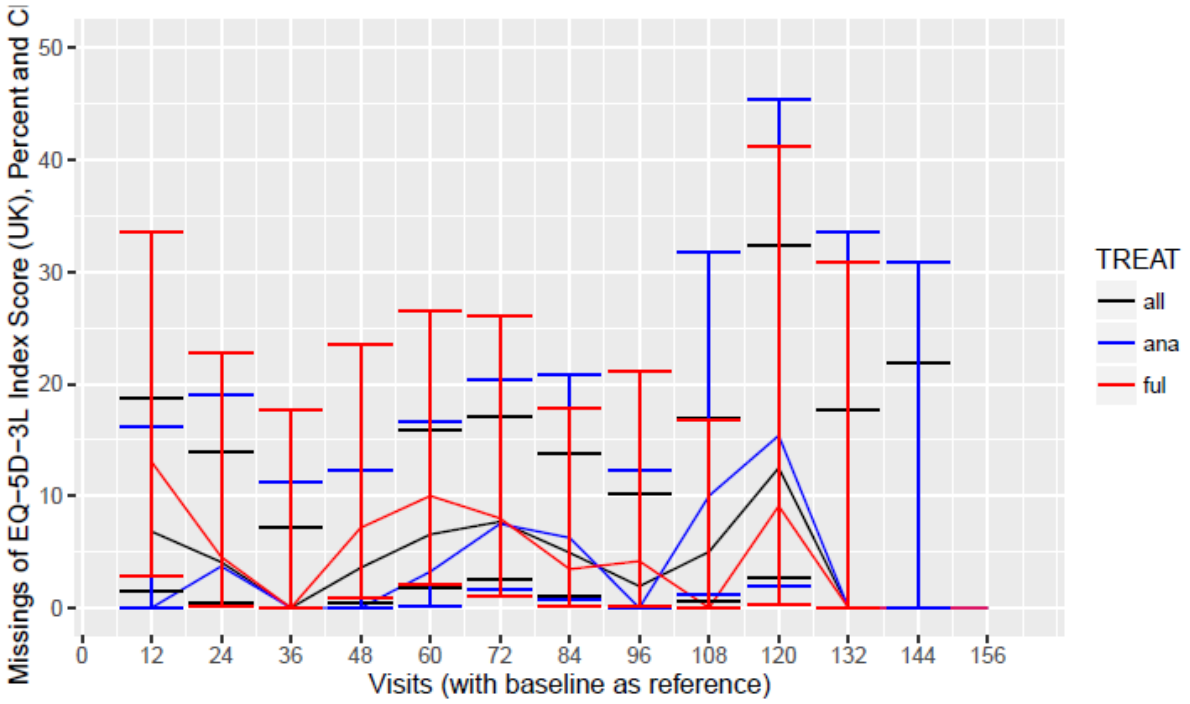
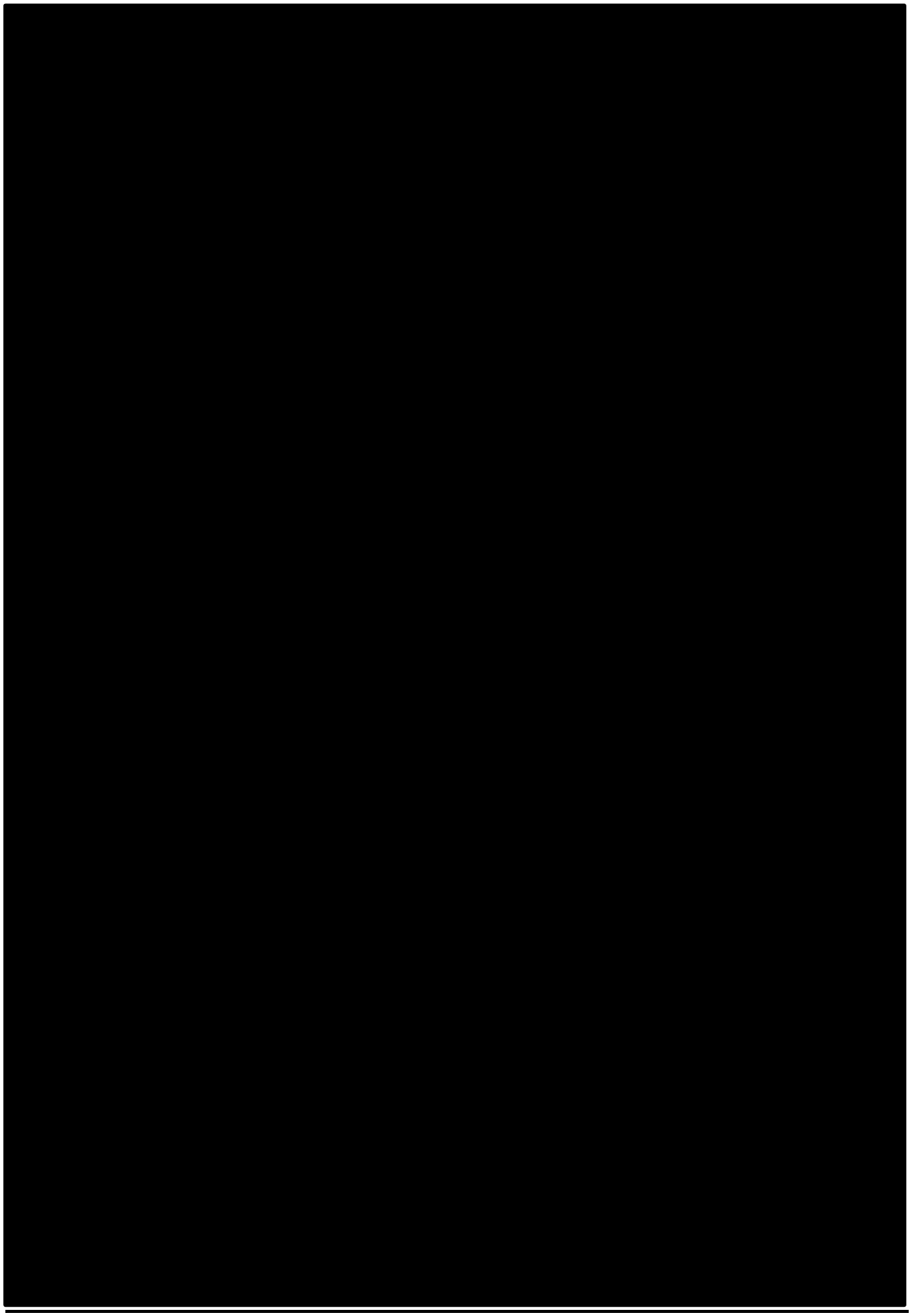
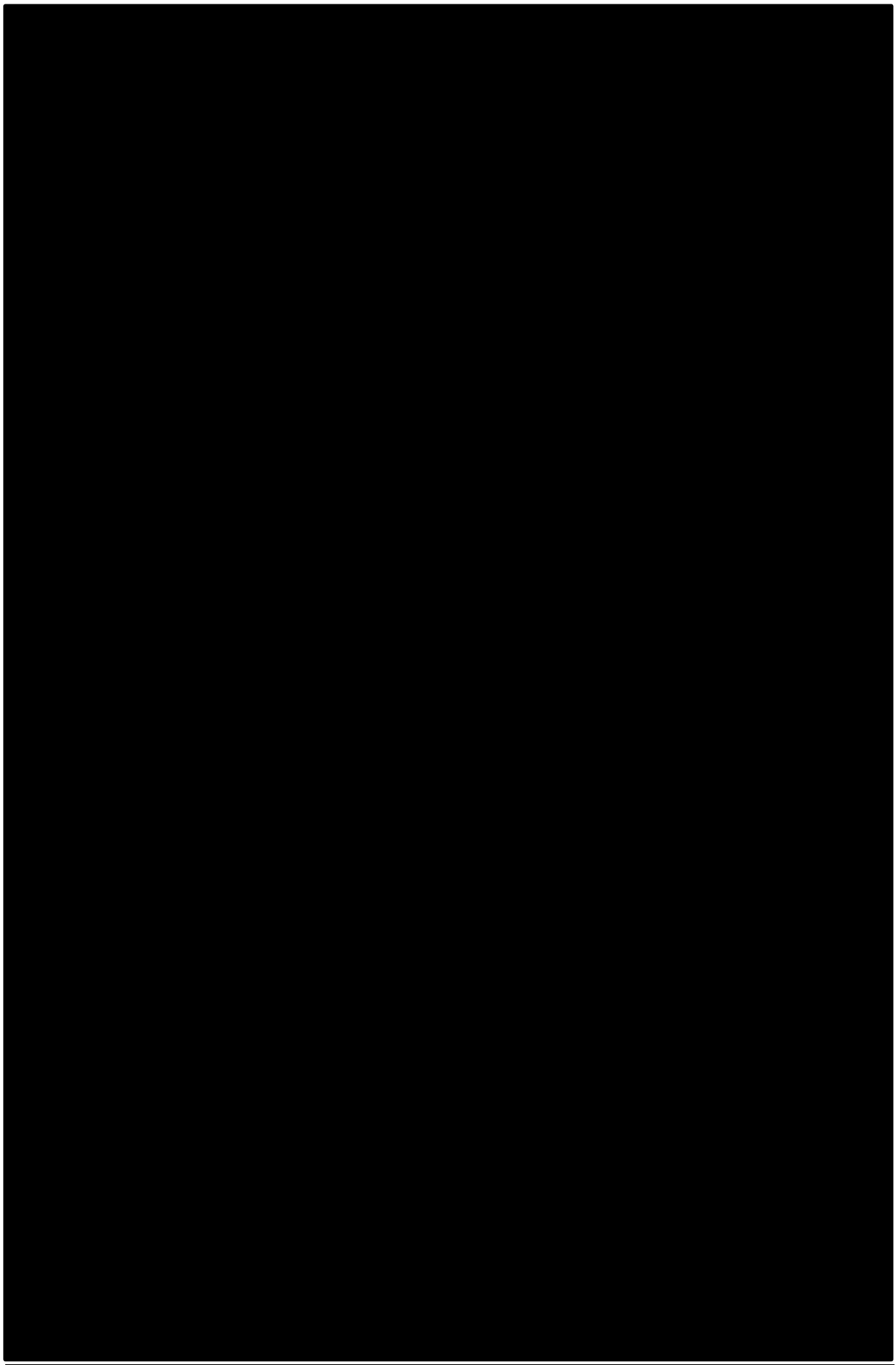
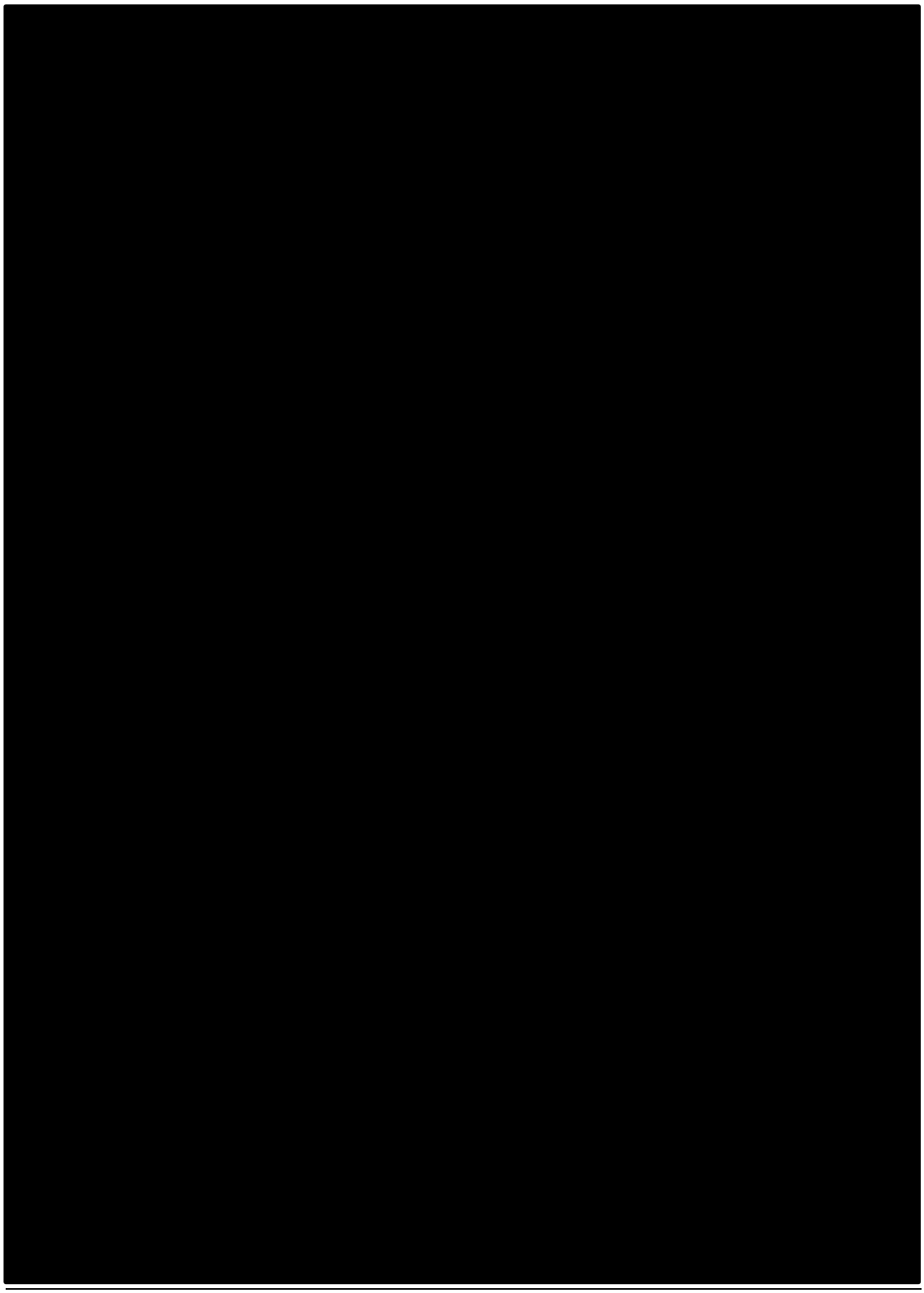


Table 130: Logistic regression of missing EQ-5D-3L index (UK) on patient characteristics







Appendix G: Utility studies included for review

Table 131: Study excluded after title and abstract (13 studies – 3 included)

Study	Reason for exclusion
Dranitsaris et al. 2015(156)	Early breast cancer patients interviewed using time-trade off
Fehlings et al. 2013(157)	Focus on metastatic epidural spinal cord compression with only a small proportion of patients having breast cancer
Kuchuk et al. 2013(158)	Patient with all stages of breast cancer interviewed using standard gamble
Simons et al. 2012(159)	Advanced breast cancer patients interviewed using standard gamble and visual analogue scale
Jones et al. 2009(160)	Summary of ERG report for lapatinib. The model for lapatinib plus letrozole directly estimated the utility value for the 'alive and no disease progression' state using data from the Functional Assessment of Cancer Therapy – Breast cancer (FACT-B) questionnaire that was administered during a clinical trial, although the methods used to map from FACT-B to EQ-5D are not clear
Jones et al. 2009(161)	Summary of ERG for gemcitabine shows values but does not present sources. A survey of 100 members of the general public who completed valuation tasks using visual analogue scales and the SG technique was used, but further details of the study source were not provided
Rodgers et al. 2011(162)	Summary of ERG report for bevacizumab. Values not presented. Submission used values from unsystematic search of the literature
Lee et al. 2014(163)	Mixed cancer population, EQ-5D logistic regression reported by domain, not utility values
Delea e al. 2013(164)	Mapped FACT-G to TTO
Delea e al. 2013b(165)	Mapped FACT-G to TTO
Slovacek et al. 2012(166)	Presented EQ-5D scores however abstract only and population was not clear (metastatic breast cancer survivors and sub-group of healthy females)

Abbreviations: EQ-5D, EuroQol-5 Dimension; ERG, Evidence Review Group; FACT-G, Functional Assessment of Cancer Therapy – Generic; NICE, National Institute of Health and Care Excellence; TTO, Time trade off

Table 132: Excluded review studies (10 studies – none included)

Study	Reason for exclusion
Dvortsin et al. 2016(167)	Reported utilities from Dutch submissions of trastuzumab, original source not in English
Pouwels et al. 2015(168)	Review of cost-effectiveness studies, abstract only so no utility values or sources were presented
Beauchemin et al. 2015(169)	Not specific to breast cancer and no utilities reported
Zikos et al. 2015(170)	Review of utilities in breast cancer but abstract only so no values or sources reported
Holmstrom et al. 2015(171)	Conceptual model of the impact of breast cancer on HRQoL, qualitative only
Huxley et al. 2015(172)	An economic evaluation for detecting lymph node metastases in breast cancer, utilities taken from a published source Tengs & Wallace (2000); source prior to 2013
de Andrade et al. 2015(173)	Review of trastuzumab cost-effectiveness studies in metastatic breast cancer, no values or source of utilities reported
Hughes et al. 2014(174)	Focused on EQ-5D in breast and prostate cancer however only utility ranges reported
Parkinson et al. 2014(175)	Review of trastuzumab cost-effectiveness studies in breast cancer, discuss five primary sources of utilities; 4 used SG on general population or oncology nurses and 1 used EQ-5D but was prior to 2013 and only had one utility value for PD/PFS
Rabbani et al. 2013(176)	Review of trastuzumab cost-effectiveness studies in breast cancer, no values or source of utilities reported

Abbreviations: EuroQol-5 Dimension; HRQoL: Health-related quality of life; PD, progressed disease; PFS, progression-free survival.

Table 133: Excluded studies identified in secondary sources (18 studies – no secondary sources included)

Study	Utility sources	Reason for exclusion
Durkee et al. 2016(177)	SD - 0.65 from Hedden (2012) Assessing the real-world cost-effectiveness of adjuvant trastuzumab in HER-2/neu positive breast cancer	Pre 2013
	Attard (2015) cost-effectiveness analysis of neoadjuvant perutuzumab and trastuzumab therapy for locally advanced, inflammatory, or early HER2+ BC in Canada	Already included
	PD - 0.29 from recent CEA of trastuzumab and pertuzumab	Pre 2013
Beauchemin et al. 2016(178)	Hannouf MB, Sehgal C, Cao JQ, et al Cost-effectiveness of adding cetuximab to platinum-based chemotherapy for first-line treatment of recurrent or metastatic head and neck cancer. PLoS One 2012	Pre 2013
	Muszbek N, Shah S, Carroll S, et al. Economic evaluation of sorafenib in the treatment of hepatocellular carcinoma in Canada. Curr Med Res Opin 2008;24:3559-69	Pre 2013
	Brown RE, Hutton J. Cost-utility model comparing docetaxel and paclitaxel in advanced breast cancer patients. Anticancer Drugs 1998;9:899-907	Pre 2013
	Brown RE, Hutton J, Burrell A. Cost effectiveness of treatment options in advanced breast cancer in the UK. Pharmacoeconomics 2001;19:1091-102	Pre 2013
	Delea TE, Sofrygin O, Amonkar MM. Patient preference-based utility weights from the Functional Assessment of Cancer Therapy–General (fact-G) in women with hormone receptor positive metastatic breast cancer receiving letrozole plus lapatinib or letrozole alone. Value Health 2010;3:PCN104	Pre 2013

Study	Utility sources	Reason for exclusion
	Dranitsaris G, Leung P, Mather J, et al. Cost-utility analysis of second-line hormonal therapy in advanced breast cancer: a comparison of two aromatase inhibitors to megestrol acetate. Anticancer Drugs 2000	Pre 2013
	Hauser R, Theriault R, Wilson J, et al. Utilities of metastatic breast cancer patients (pt) treated with taxanes compared to utilities of oncology nurses (nur). Value Health 2001	Pre 2013
	Hutton J, Brown R, Borowitz M, et al. A new decision model for cost-utility comparisons of chemotherapy in recurrent metastatic breast cancer. Pharmacoeconomics 1996	Pre 2013
	Kuchuk I, Bouganim N, Beusterien K, et al. Preference weights for chemotherapy side effects from the perspective of women with breast cancer. Breast Cancer Res Treat 2013	Already included
	Launois R, Reboul-Marty J, Henry B, et al. A cost-utility analysis of second-line chemotherapy in metastatic breast cancer. Docetaxel versus paclitaxel versus vinorelbine. Pharmacoeconomics1996	Pre 2013
	Leung PP, Tannock IF, Oza AM, et al. Cost-utility analysis of chemotherapy using paclitaxel, docetaxel, or vinorelbine for patients with anthracycline-resistant breast cancer. J Clin Oncol 1999	Pre 2013
	Lloyd A, Nafees B, Narewska J, et al. Health state utilities for metastatic breast cancer. Br J Cancer 2006	Pre 2013
	Bonomi AE, Boudreau DM, Fishman PA, et al. Quality of life valuations of mammography screening. Qual Life Res 2008	Pre 2013

Study	Utility sources	Reason for exclusion
	de Haes JC, de Koning HJ, van Oortmarssen GJ, et al. The impact of a breast cancer screening programme on quality-adjusted lifeyears. Int J Cancer 1991	Pre 2013
Squires et al. 2016(179)	Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer 2006; 95:683-90.	Pre 2013
Stein et al. 2016(180)	DF (chemo/ no chemo), recurrence local or distant - Campbell (2011) The cost-effectiveness of adjuvant chemotherapy for early breast cancer: a comparison of no chemotherapy and first, second, and third generation regimens for patients with differing prognoses	Pre 2013
	Age specific baselines - Kind (1998) Variations in population health status: results from a United Kingdom national questionnaire survey.	Pre 2013
Safonov et al. 2016(181)	de Koning HJ, van Ineveld BM, van Oortmarssen GJ, de Haes JC, Collette HJ, Hendriks JH, van der Maas PJ (1991) Breast cancer screening and cost-effectiveness; policy alternatives, quality of life considerations and the possible impact of uncertain factors Int J Cancer 49(4):531–537	Pre 2013
	Tengs TO, Wallace A (2000) One thousand health-related quality- of-life estimates. Med care 38:583–637	Pre 2013
	Fenwick E, Byford S (2005) A guide to cost-effectiveness acceptability curves. Brit J Psychiat 187:106–108.	Pre 2013
Majethia et al. 2015(182)	Not completely clear but mapped using Kaufman, et al., 2015 alogirthm	Mapping to EQ-5D
Attard et al. 2015(183)	Event-free, year 1 – 0.97; event-free, year 2 – 0.99; local recurrence – 0.75; metastatic disease – 0.65; weighted utility for relapsed – 0.68 from Heddon (2012) Assessing the real-world cost-effectiveness of adjuvant trastuzumab in HER-2/neu positive breast cancer	Pre 2013

Study	Utility sources	Reason for exclusion
Blank et al. 2015(184)	DFS - EQ-5D VAS 335 Swedish patients Lidgren M, Wilking N, Jonsson B, Rehnberg C. Health related quality of life in different states of breast cancer. Qual Life Res. 2007;16(6):1073–81	Pre 2013
	Chemotherapy decrement - 29 studies Peasgood T, Ward SE, Brazier J. Health-state utility values in breast cancer. Expert Rev Pharmacoecon Outcomes Res. 2010;10(5):553–66.	Pre 2013
De Souza et al. 2015(185)	DFS & PD - Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer 2006; 95:683-90.	Pre 2013
Romero & Gil 2015(186)	Utilities taken from NICE report trastuzumab emtansine	Pre 2013
Xie et al. 2015(187)	Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer 2006; 95:683-90.	Pre 2013
Djalalov et al. 2015(188)	DF - Sullivan (2005) national catalog of preference-based scores for chronic conditions in the United State	Pre 2013
	Mitmann (1999) Utility scores for chronic conditions in a community-dwelling population	Pre 2013
	Recurrence and distant metastaisis Peasgood (2010) Health-state utility values in breast cancer	Pre 2013
Fleeman et al. 2015(189)	Review of pertuzumab submission, used Lloyd et al. 2006	Already included from review of submissions
Hudgens et al. 2014(190)	Crott R, Versteegh M, Uyl-de-Groot C. An assessment of the external validity of mapping QLQ-C30 to EQ-5D preferences. Qual Life Res. 2013 Jun;22(5):1045-54.	Mapping QLQ-C30 to EQ-5D
	Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer 2006; 95:683-90.	Pre 2013

Study	Utility sources	Reason for exclusion
Diaby et al. 2014(191)	SD & multiple AEs - Lloyd A, Nafees B, Narewska J, et al. Health state utilities for metastatic breast cancer. Br J Cancer. 2006; 95:683–690. [PubMed: 16967055]	Pre 2013
	Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med. 2012; 366:520–529.	Pre 2013
Hannouf et al. 2014(192)	Baseline 0.824 from Hanmer (2006) Report of nationally representative values for the noninstitutionalized US adult population for 7 health-related quality-of life scores then multiplied by utility estimates for women with BC from	Pre 2013
	Wolowacz (2008) Docetaxel in combination with doxorubicin and cyclophosphamide as adjuvant treatment for early node-positive breast cancer: a cost-effectiveness and cost-utility analysis	Pre 2013
	Smith (1993) The efficacy and cost-effectiveness of adjuvant therapy of early breast cancer in premenopausal women	Pre 2013
	Earle (2000) Systematic overview of cost-utility assessments in oncology	Pre 2013
	Thornton (2005) The impact of a second breast cancer diagnosis on health-related quality of life	Pre 2013
	Fryback (1997) Dollars may not buy as many QALYs as we think: a problem with defining quality-of-life adjustments	Pre 2013
Sen et al. 2014(193)	Treatment, recurrence and age -Hayman JA, Fairclough DL, Harris JR, et al. Patient preferences concerning the trade-off between the risks and benefits of routine radiation therapy after conservative surgery for early-stage breast cancer. J Clin Oncol. 1997;15(3):1252–1260.	Pre 2013

Study	Utility sources	Reason for exclusion
	Stout NK, Rosenberg MA, Trentham-Dietz A, et al. Retrospective cost-effectiveness analysis of screening mammography. J Natl Cancer Inst. 2006;98(11):774–782.	Pre 2013
Habib et al. 2013(194)	Utility inputs were based on a time trade-off study. (Matza LS et al. Eur J Health Econ 2013)	Described as time trade off study but cannot find original source

Appendix H: Summary of base case de novo analysis inputs and assumptions

Table 134 provides a summary of all parameters used in the model, along with the variation of the parameters used in the PSA.

Table 134: Summary of model parameters and parameters used in PSA

Reference to section in Main Submission	Parameter		Model input	Variation in PSA	Comment
Model Settings and Patient Characteristics	Time horizon		30 years	NA	
	Discount rate, costs		3.5%	None	Only in DSA
	Discount rate, outcomes		3.5%	None	Only in DSA
	Cohort size		1	NA	
	Starting age		63.8 years	None	
Clinical data	Fulvestrant	OS	[redacted]	Cholesky decomposition	Used in base case analysis
		PFS	[redacted]	Cholesky decomposition	Used in base case analysis
	Anastrozole	OS	[redacted]	Cholesky decomposition	Used in base case analysis
		PFS	[redacted]	Cholesky decomposition	Used in base case analysis

Reference to section in Main Submission	Parameter		Model input	Variation in PSA	Comment
	Letrozole	OS	[redacted]	Cholesky decomposition	Used in base case analysis
		PFS	[redacted]	Cholesky decomposition	Used in base case analysis
	Tamoxifen	OS	[redacted]	Cholesky decomposition	Used in base case analysis
		PFS	[redacted]	Cholesky decomposition	Used in base case analysis
Safety data	Fulvestrant	ALT	Mean: 0.013157895	SE: 0.007546570	
		AST	Mean: 0.013158000	SE: 0.007546570	
		Hypertension	Mean: 0.017543860	SE: 0.008694643	
		Pleural effusion	Mean: 0.021929825	SE: 0.009699183	
		Pain, bone	Mean: 0.004385965	SE: 0.004376336	
		Pain, other	Mean: 0.013157895	SE: 0.007546570	
		Dyspnoea	Mean: 0.0	SE: 0.0	
		Bilirubin increased	Mean: 0.0	SE: 0.0	
	Anastrozole	ALT	Mean: 0.0	SE: 0.0	
		AST	Mean: 0.004310345	SE: 0.004301045	
		Hypertension	Mean: 0.017241379	SE: 0.008546050	
		Pleural effusion	Mean: 0.004310345	SE: 0.004301045	

Reference to section in Main Submission	Parameter		Model input	Variation in PSA	Comment
		Pain, bone	Mean: 0.004310345	SE: 0.004301045	
		Pain, other	Mean: 0.008620690	SE: 0.006069416	
		Dyspnoea	Mean: 0.008620690	SE: 0.006069416	
		Bilirubin increased	Mean: 0.004310345	SE: 0.004301045	
	Letrozole	ALT	Mean: 0.0	SE: 0.0	
		AST	Mean: 0.0	SE: 0.0	
		Hypertension	Mean: 0.0	SE: 0.0	
		Pleural effusion	Mean: 0.0	SE: 0.0	
		Pain, bone	Mean: 0.0	SE: 0.0	
		Pain, other	Mean: 0.013513514	SE: 0.007749135	
		Dyspnoea	Mean: 0.004504505	SE: 0.004494348	
		Bilirubin increased	Mean: 0.0	SE: 0.0	
	Tamoxifen	ALT	Mean: 0.042328042	SE: 0.014645074	
		AST	Mean: 0.047619048	SE: 0.015490477	
		Hypertension	Mean: 0.031746032	SE: 0.012752886	
		Pleural effusion	Mean: 0.0	SE: 0.0	
		Pain, bone	Mean: 0.058201058	SE: 0.017029960	
		Pain, other	Mean: 0.031746032	SE: 0.012752886	
		Dyspnoea	Mean: 0.026455026	SE: 0.011673503	
		Bilirubin increased	Mean: 0.015873016	SE: 0.009091267	
Disease management costs	PF, resource use	Community nurse (20 minutes) – resource usage per 4 weeks	2	Gamma Alpha: 25 Beta: 0.08	Assumed 20% SE
		Consultation with a GP (in surgery) – resource usage per 4 weeks	1	Gamma Alpha: 25 Beta: 0.04	Assumed 20% SE
		Clinical nurse specialist (1 hour)	1	Gamma Alpha: 25 Beta: 0.04	Assumed 20% SE

Reference to section in Main Submission	Parameter		Model input	Variation in PSA	Comment
		– resource usage per 4 weeks			
	PF, unit cost (£)	Community nurse visit	£14.67	None	
		GP surgery consultation	£46.02	None	
		Clinical nurse specialist visit	£108.00	None	
	PD, resource use	Community nurse (20 minutes) – resource usage per 4 weeks	4	Gamma Alpha: 25 Beta: 0.16	Assumed 20% SE
		Consultation with a GP (home visit) – resource usage per 4 weeks	2	Gamma Alpha: 25 Beta: 0.08	Assumed 20% SE
		Clinical nurse specialist (1 hour) – resource usage per 4 weeks	4	Gamma Alpha: 25 Beta: 0.16	Assumed 20% SE
		NHS community occupational therapist – resource usage per 4 weeks	2	Gamma Alpha: 25 Beta: 0.08	Assumed 20% SE
	PD, unit cost (£)	Community nurse visit	£14.67	None	
		GP home visit	£65.00	None	
		Clinical nurse specialist visit	£108.00	None	

Reference to section in Main Submission	Parameter		Model input	Variation in PSA	Comment
		NHS community occupational therapist visit	£42.00	None	
	Terminal care usage	Hospital	0.40	Gamma Alpha: 25 Beta: 0.016	Assumed 20% SE
		Hospice	0.10	Gamma Alpha: 25 Beta: 0.004	Assumed 20% SE
		Home	0.50	Gamma Alpha: 25 Beta: 0.02	Assumed 20% SE
	Terminal care, unit cost (£)	Hospital	£5595.20	None	
		Hospice	£6975.58	None	
		Home	£2886.77	None	
Treatment costs	Acquisition, cost per pack (£)	Fulvestrant – first 4 weeks	£1044.82	None	
		Fulvestrant – subsequent weeks	£522.41	None	
		Anastrozole	£0.75	None	
		Letrozole	£1.52	None	
		Tamoxifen	£1.51	None	
	Administration, cost per first 4 weeks (£)	Fulvestrant	£370.35	Gamma Alpha: 25 Beta: 14.814	Assumed 20% SE
		Anastrozole	£196.64	Gamma Alpha: 25 Beta: 7.86556	Assumed 20% SE
		Letrozole	£196.64	Gamma Alpha: 25 Beta: 7.86556	Assumed 20% SE

Reference to section in Main Submission	Parameter		Model input	Variation in PSA	Comment
		Tamoxifen	£196.64	Gamma Alpha: 25 Beta: 7.86556	Assumed 20% SE
	Administration, cost per subsequent 4-week period (£)	Fulvestrant	£73.74	Gamma Alpha: 25 Beta: 2.94944	Assumed 20% SE
		Anastrozole	£27.93	Gamma Alpha: 25 Beta: 1.11707	Assumed 20% SE
		Letrozole	£27.93	Gamma Alpha: 25 Beta: 1.11707	Assumed 20% SE
		Tamoxifen	£27.93	Gamma Alpha: 25 Beta: 1.11707	Assumed 20% SE
	Relative dose intensity/ compliance	Fulvestrant (first 4 weeks)	1.00	None	
		Fulvestrant (subsequent 4 weeks)	0.99	None	
		Anastrozole	0.99	None	
		Letrozole	1.00	None	
		Tamoxifen	1.00	None	
Subsequent treatment following progression	Average treatment duration (weeks) – first 4 weeks	Endocrine 2nd line	4.00	None	
		Chemotherapy 2nd line	4.00	None	
		Targeted 2nd line	4.00	None	
		Endocrine 3rd line	4.00	None	
		Chemotherapy 3rd line	4.00	None	
		Targeted 3rd line	0.00	None	

Reference to section in Main Submission	Parameter		Model input	Variation in PSA	Comment
	Average treatment duration (weeks) – subsequent 4-week period	Endocrine 2nd line	29.82	None	
		Chemotherapy 2nd line	21.52	None	
		Targeted 2nd line	29.82	None	
		Endocrine 3rd line	18.78	None	
		Chemotherapy 3rd line	18.52	None	
		Targeted 3rd line	0.00	None	
	Total cost of subsequent treatments (first 4 weeks)	Endocrine 2nd line	£344.85	Gamma Alpha: 25 Beta: 9.0924	Assumed 20% SE
		Chemotherapy 2nd line	£343.86	Gamma Alpha: 25 Beta: 12.3856	Assumed 20% SE
		Targeted 2nd line	£2697.00	Gamma Alpha: 25 Beta: 7.8656	Assumed 20% SE
		Endocrine 3rd line	£676.50	Gamma Alpha: 25 Beta: 11.8976	Assumed 20% SE
		Chemotherapy 3rd line	£849.38	Gamma Alpha: 25 Beta: 11.3616	Assumed 20% SE
		Targeted 3rd line	£0.00		
	Total cost of subsequent treatments (subsequent 4-week period)	Endocrine 2nd line	£97.77	Gamma Alpha: 25 Beta: 1.5056	Assumed 20% SE
		Chemotherapy 2nd line	£262.87	Gamma Alpha: 25 Beta: 9.146	Assumed 20% SE
		Targeted 2nd line	£2528.29	Gamma	Assumed 20% SE

Reference to section in Main Submission	Parameter		Model input	Variation in PSA	Comment
				Alpha: 25 Beta: 1.1172	
		Endocrine 3rd line	£250.25	Gamma Alpha: 25 Beta: 2.3936	Assumed 20% SE
		Chemotherapy 3rd line	£711.74	Gamma Alpha: 25 Beta: 5.856	Assumed 20% SE
		Targeted 3rd line	£0.00		
	Proportion of patients using subsequent treatments	Fulvestrant to endocrine 2nd line	0.54	Beta Alpha: 10.869 Beta: 9.12916	Assumed 20% SE
		Fulvestrant to chemotherapy 2nd line	0.38	Beta Alpha: 15.2318 Beta: 25.3107	Assumed 20% SE
		Fulvestrant to targeted 2nd line	0.08	Beta Alpha: 22.8992 Beta: 260.507	Assumed 20% SE
		Fulvestrant to endocrine 3rd line	0.24	Beta Alpha: 18.7548 Beta: 59.3251	Assumed 20% SE
		Fulvestrant to chemotherapy 3rd line	0.30	Beta Alpha: 17.0986 Beta: 39.1653	Assumed 20% SE
		Fulvestrant to targeted 3rd line	0.00		
		Anastrozole to endocrine 2nd line	0.54	Beta Alpha: 10.869 Beta: 9.12916	Assumed 20% SE

Reference to section in Main Submission	Parameter		Model input	Variation in PSA	Comment
		Anastrozole to chemotherapy 2nd line	0.38	Beta Alpha: 15.2318 Beta: 25.3107	Assumed 20% SE
		Anastrozole to targeted 2nd line	0.08	Beta Alpha: 22.8992 Beta: 260.507	Assumed 20% SE
		Anastrozole to endocrine 3rd line	0.24	Beta Alpha: 18.7548 Beta: 59.3251	Assumed 20% SE
		Anastrozole to chemotherapy 3rd line	0.30	Beta Alpha: 17.0986 Beta: 39.1653	Assumed 20% SE
		Anastrozole to targeted 3rd line			
		Letrozole to endocrine 2nd line	0.54	Beta Alpha: 10.869 Beta: 9.12916	Assumed 20% SE
		Letrozole to chemotherapy 2nd line	0.38	Beta Alpha: 15.2318 Beta: 25.3107	Assumed 20% SE
		Letrozole to targeted 2nd line	0.08	Beta Alpha: 22.8992 Beta: 260.507	Assumed 20% SE
		Letrozole to endocrine 3rd line	0.24	Beta Alpha: 18.7548 Beta: 59.3251	Assumed 20% SE
		Letrozole to chemotherapy 3rd line	0.30	Beta Alpha: 17.0986 Beta: 39.1653	Assumed 20% SE
		Letrozole to targeted 3rd line			

Reference to section in Main Submission	Parameter		Model input	Variation in PSA	Comment
		Tamoxifen to endocrine 2nd line	0.54	Beta Alpha: 10.869 Beta: 9.12916	Assumed 20% SE
		Tamoxifen to chemotherapy 2nd line	0.38	Beta Alpha: 15.2318 Beta: 25.3107	Assumed 20% SE
		Tamoxifen to targeted 2nd line	0.08	Beta Alpha: 22.8992 Beta: 260.507	Assumed 20% SE
		Tamoxifen to endocrine 3rd line	0.24	Beta Alpha: 18.7548 Beta: 59.3251	Assumed 20% SE
		Tamoxifen to chemotherapy 3rd line	0.30	Beta Alpha: 17.0986 Beta: 39.1653	Assumed 20% SE
		Tamoxifen to targeted 3rd line			
Adverse event costs (£)	Resource use	ALT	1	Gamma Alpha: 25 Beta: 0.04	Assumed 20% SE
		AST	1	Gamma Alpha: 25 Beta: 0.04	Assumed 20% SE
		Hypertension	1	Gamma Alpha: 25 Beta: 0.04	Assumed 20% SE
		Pleural effusion	1	Gamma Alpha: 25 Beta: 0.04	Assumed 20% SE
		Pain, bone	1	Gamma Alpha: 25	Assumed 20% SE

Reference to section in Main Submission	Parameter		Model input	Variation in PSA	Comment
				Beta: 0.04	
		Pain, other	1	Gamma Alpha: 25 Beta: 0.04	Assumed 20% SE
		Dyspnoea	1	Gamma Alpha: 25 Beta: 0.04	Assumed 20% SE
		Bilirubin increased	1	Gamma Alpha: 25 Beta: 0.04	Assumed 20% SE
	Unit cost (£)	ALT	£1757.79	None	
		AST	£1757.79	None	
		Hypertension	£729.87	None	
		Pleural effusion	£1830.68	None	
		Pain, bone	£1038.08	None	
		Pain, other	£626.97	None	
		Dyspnoea	£718.76	None	
		Bilirubin increased	£1757.79	None	
Utilities	Health states	Progression-free	0.75114	Beta SE: 0.00867	
		Progressed disease	0.69131	Beta SE: 0.01348621	
		Death	0.0	N/A	
QALY loss due to adverse events	QALY loss	ALT	0.003832991	Lognormal Alpha: -5.58372 Beta: -1451.17	Assumed 20% SE
		AST	0		
		Hypertension	0.003351129	Lognormal Alpha: -5.71807 Beta: -1700.59	Assumed 20% SE
		Pleural effusion	0.003047228	Lognormal	Assumed 20% SE

Reference to section in Main Submission	Parameter		Model input	Variation in PSA	Comment
				Alpha: -5.81313 Beta: -1901.87	
		Pain, bone	0.003211499	Lognormal Alpha: -5.76063 Beta: -1787.99	Assumed 20% SE
		Pain, other	0.003211499	Lognormal Alpha: -5.76063 Beta: -1787.99	Assumed 20% SE
		Dyspnoea	0.003581383	Lognormal Alpha: -5.65162 Beta: -1572.40	Assumed 20% SE
		Bilirubin increased	0		

Abbreviation: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DSA, deterministic sensitivity analysis; GP, General Practitioner; NA, not applicable; OS, overall survival; PF, progression-free; PFS, progression-free survival; SE, standard error.

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Single technology appraisal

Fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer [ID951]

Dear Kevin

The Evidence Review Group, Southampton Health Technology Assessments Centre (SHTAC) and the technical team at NICE have looked at the submission received on **Friday 5 May 2017** from AstraZeneca. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Thursday 15 June 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals https://appraisals.nice.org.uk/request/29227 on 'NICE Docs/Appraisals'].

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact [redacted], Technical Lead [redacted]. Any procedural questions should be addressed to the Project Team at TACommA@nice.org.uk

Yours sincerely

Janet Robertson
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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. **Priority question** CS Figure 5 and Figure 6 p. 42-43 and Table 124 Appendix B. Figure 5 indicates 44 studies identified and Figure 6 indicates 6 studies of relevance to the evidence network. Therefore 38 identified studies were excluded from the evidence network of which 16 appear to be listed in Appendix B Table 124 (for 11 of these an exclusion reason is provided) and the remaining 22 are listed in Appendix B Table 125 with exclusion reasons given. There are therefore 5 excluded studies for which no exclusion reason is provided. Please provide exclusion reasons for these five studies: Paridaens 2008; PALOMA-1 study; PALOMA-2 study; Pyrhonen 1997; and SWOG 0226.

A2. **Priority question** In CS Table 19 (p.70) the numbers given for the two groups (n=193 and n=196) seem to be for the FALCON trial not the FIRST trial. Please confirm if this is an error. Should the values be fulvestrant n=89; anastrozole n=93 for this table? Please also provide the numbers of patients achieving ORR, CR, PR, SD and PD in both groups.

A3. **Priority question** CS Figure 16 (p. 73) presents mean trial outcome index score and Figure 17 the EQ-5D-3L scores. In Figure 16 the number of patients does not correspond to any of the patient analysis sets described, and no patient numbers are given for Figure 17 (p. 74). Please clarify why there are missing patient data from Figure 16 and provide data for the number of patients contributing data to each of the time points shown in Figure 17 (with reasons for any missing data). If possible please supply reference 70 which is cited in the Health Related Quality of Life section (CS p72 -74) but which does not appear to have been provided in the reference pack.

A4. **Priority question** Table 20 CS p. 76 reports expected duration of response (EDoR) and expected duration of clinical benefit (EDoCB). Are these mean or median values? CS p. 58 states that EDoCB and EDoR were calculated using the method described by Ellis and colleagues (citing reference 6 in the reference list) but the ERG has not found the method described in this reference. Please supply the method for calculating EDoCB and EDoR. Please also provide mean values alongside the medians reported in this table.

A5. **Priority question** Table 25 CS p. 85. The ERG believes the sample size of PO25 trial is 907, not 916 as reported (and as also reported in Table 11). Please confirm if the ERG is correct. Asterisk indicates study reports subgroup data for the population of interest but n for the subgroup is not reported. Appendix B Table 124 gives 916 with 599 sample size in brackets. Is the 599 the correct subgroup sample size (this would correspond to the ER and /or PgR positive subgroup n=294 +305 = 599)?

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A6. **Priority question**. Table 25 CS p. 85. Which TTP data were extracted from the PO25 study? TTP is reported for the receptor status positive subgroup in Table 4 of the Mouridsen et al 2001 paper but there is no separate Kaplan–Meier plot for this subgroup. Page 90 of the CS states that reported Kaplan-Meier curves were digitised and an algorithm run to reconstruct patient-level data so was the curve used for this for the whole PO25 study population and not the subgroup of interest? Furthermore there is no overall survival KM plot in the Mouridsen et al 2001 paper. Did overall survival data come from the KM plot presented as Figure 4 in Mouridsen et al 2003 (CS reference 76)?

A7. **Priority question** CS p.90 indicates that combined OS results were used from the North American and Target trials and cites reference 71 as the source of the combined data. However, reference 71 is the same as reference 10 which is the North American trial alone. Please supply the correct reference for the combined North American and Target trial data.

A8. **Priority question**. CS p. 90 Section 4.10.1 Method of network meta-analysis states that "For those trials identified in the systematic literature review and where patient-level data was available (FIRST and NorthAmTarget) the inclusion and exclusion criteria from the FALCON trial was applied to each treatment arm in both trials to better match the FALCON trial population (7)." Were all of the inclusion and exclusion criteria from the FALCON Trial applied? If so, how were criteria that were not reported by all trials matched e.g. an exclusion criterion of the FALCON trial was human epidermal growth factor receptor over-expression or gene amplification but data on this was not reported by the North American or Target studies? What methodology was used for the matching process?

A9. **Priority question** CS p. 90 section 4.10.1 please provide the numbers of participants whose data were retained after the matching process and a table summarizing the socio-demographic and clinical characteristics of the remaining participants from each trial after matching (i.e. the trial participants that contributed data to the NMA).

A10. **Priority question** Please provide results for fixed effect and random effects pairwise comparisons of interventions in the NMA (i.e. fulvestrant vs anastrozole; anastrozole vs tamoxifen 20mg; letrozole vs tamoxifen; fulvestrant vs tamoxifen 20mg; fulvestrant vs letrozole).

A11. **Priority question** NMA results section 4.10.2. Please also provide results from a random effects NMA for the outcomes of PFS and OS. Please report the model fit statistics for both the fixed effect and random effects models so that these can be compared.

A12. **Priority question** Please provide NMA and full cost-effectiveness results obtained using all study data from FIRST and NorthAmTarget, i.e. without undertaking the

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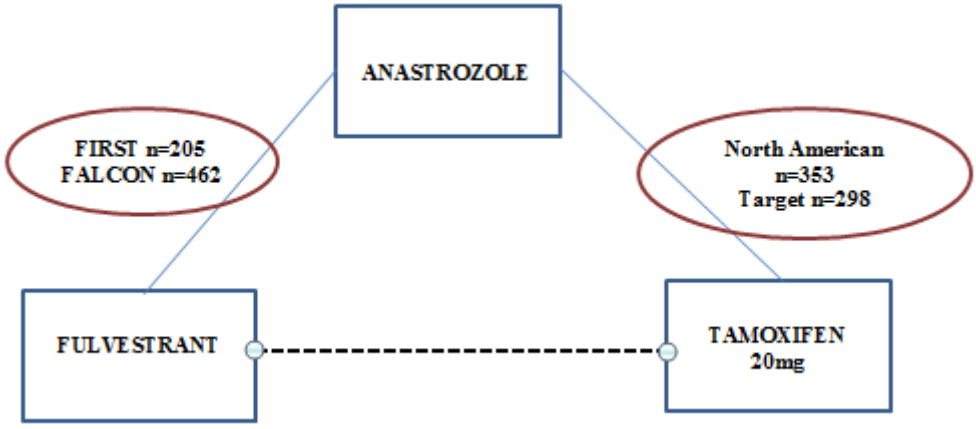
matching process. If the ITT populations are used is the assumption of proportional hazards for PFS and OS still violated?

A13. **Priority question** As noted in the CS (CS p. 96) study PO25 differs from the other studies included in the NMA in that individual patient data were not available so the data could not be matched to the FALCON trial, cross-overs between treatment arms took place and, as clarification question A6 indicates, it is not clear to the ERG whether data for TTP and OS came from the whole population or the hormone receptor positive subgroup (66%). Furthermore, as CS p97 indicates, the efficacy of letrozole is widely accepted to be equivalent to that of anastrozole. Therefore please also provide NMA and full cost-effectiveness results (pairwise fixed and random effects as well as fixed and random effects NMA) from a network omitting the PO25 study as well as the Milla-Santos study i.e. for the network shown in the diagram below:



A14. Were participants allowed to cross over between trial arms in either FIRST or FALCON?

A15. CS p. 67 states that concordance rates between local investigator and blinded independent review were high and similar between the two treatment arms "(88.4% [84/95] in the fulvestrant arm compared to 86.3% [82/95] in the anastrozole arm)". What do the numerator and denominator (the 84/95 and the 82/95) in this text represent?

A16. CS Table 18 p.67 presents data that the ERG assumes is numbers of patients with percentages in brackets, is this correct? Additionally, in this table the clinical benefit definition includes stable disease ≥24 weeks (i.e. stable disease greater than or equal to 24 weeks). The ERG therefore presumes that the patients included in the no clinical benefit group are those with stable disease of less than 24 weeks duration (<24 weeks) and not less than or equal to 24 weeks (≤ 24 weeks) as indicated in the

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table. Please would the company confirm whether our understanding is correct or not.

A17. CS Subgroup analysis for Falcon p.78. Please clarify which of the subgroup analyses were prespecified as there are differences between the subgroups reported in CS, those reported in the published paper, and those specified in the CSR.

A18. CS section 4.10.2 p.100 Network meta-analysis results. The text states that fulvestrant and tamoxifen demonstrated statistically significant differences in the scale parameter. Please indicate how statistical significance was determined (e.g. is this due to non-overlapping credible intervals of the two treatments?).

A19. CS section 4.10.2 p.101 Network meta-analysis results. Please confirm that the upper and lower 95% limits presented in Tables 29 and 30 represent the bounds of the credible interval.

Section B: Clarification on cost-effectiveness data

B1. **Priority Question.** CS Section 5.5 Cost and healthcare resource use identification, measurement and valuation (p. 163). Please comment on whether health care resources were collected for the FALCON trial. Where data are available, provide a summary of resource use for patients in the progression-free and progressed health states.

B2. CS p. 148 states that adverse events experienced by more than 2% of patients were included, however it seems adverse events with less than 2% have also been included (Table 49 and company model). Please comment on the reason for this discrepancy.

B3. CS Table 49 p. 149. The ERG has two queries about adverse events in this table. Firstly, the literature (Finn 2016) reports the frequency of dyspnoea as 1.4% but CS (Table 49) and the company model report 0.5% for letrozole, please explain this difference. Secondly please clarify for 'AST increased' why in the CS (Table 49) the frequency for Tamoxifen is 1.6% but in the model the frequency is 4.8%.

B4. In CS p152, the health utility search was restricted to new publications from October 2013, 'the date the last NICE Technology Appraisal search was conducted'. Please clarify which NICE submission this refers to and explain why more recent NICE Technology Appraisals have not been considered.

B5. CS Table 57 p. 162. The disutility for dyspnoea is cited to be derived from Lloyd et al. However, this parameter does not appear to be reported in this publication. Please clarify where this parameter has been derived from. Similarly the disutility for pleural effusion is cited to be derived from Swinburn et al (CS Table 57). However this

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parameter does not appear to be reported in this publication. Please clarify where this parameter has been derived from.

B6. CS Table 72 p.179. Please provide the NHS reference costs codes that have been used to calculate 'Pain, other'

B7. CS Table 73 p. 180. The Shape and Scale parameter values for PFS reported in Table 73 of the CS do not seem to have been used within the model. The ERG notes that PFS parameters reported in "Surv_calcs" Sheet are derivable from CS Table 47. Please confirm that these values in Table 73 are not used in the model.

B8. CS Table 79 and Table 80 p. 186. Please provide the references of the studies obtained from the systematic literature review which provide the data reported in column 3 of Table 79 and Table 80.

B9. CS Table 100 p.205. The base case results (ICERs) obtained from using the "All shapes model" and "No shape model" are the same in Table 100 whereas in the economic model, the results obtained are different. Please clarify the difference in the results reported in the CS and the model.

Section C: Textual clarifications and additional points

C1. Please supply an abbreviations list for the CS.

C2. CS p. 33 - Please confirm whether or not the experts on the panel are associated with Astra Zeneca, and whether or not they worked on Fulvestrant clinical trials?

C3. CS p. 78 Section 4.8.2 states "As discussed previously in XXX, "please would the company confirm the section/page being cross referenced here.

C4. References 68 and 97 seem to be duplicates of the same Clinical Study Protocol (FALCON CSR). Figure 15 and Table 49 cite reference 68 and 97, respectively, but the corresponding references do not contain these results. Please confirm this discrepancy and provide the correct reference source.

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Single technology appraisal

Fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer [ID951]

Dear Lesley

The Evidence Review Group, Southampton Health Technology Assessments Centre (SHTAC) and the technical team at NICE have looked at the submission received on **Friday 5 May 2017** from AstraZeneca. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Thursday 15 June 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals [embed NICE DOCS LINK on 'NICE Docs/Appraisals'].

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact XXXXXXXXX XXXXXXXX Technical Lead (XXXXXXXXXXXXXXXXXX). Any procedural questions should be addressed to the Project Team at TACommA@nice.org.uk

Yours sincerely

Janet Robertson
Associate Director – Appraisals
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Encl. checklist for confidential information

Economic model clarification
During additional validation work following the execution of supplementary analyses requested by the ERG, several calculation errors were identified in the electronic model used to generate the cost-effectiveness results in the submission document. The corrections, along with their impact on the submitted base case results, are presented in the Appendix. The cost-effectiveness results of the supplementary analyses requested by the ERG have been undertaken in the corrected model.

Section A: Clarification on effectiveness data

A1. **Priority question** CS Figure 5 and Figure 6 p. 42-43 and Table 124 Appendix B. Figure 5 indicates 44 studies identified and Figure 6 indicates 6 studies of relevance to the evidence network. Therefore 38 identified studies were excluded from the evidence network of which 16 appear to be listed in Appendix B Table 124 (for 11 of these an exclusion reason is provided) and the remaining 22 are listed in Appendix B Table 125 with exclusion reasons given. There are therefore 5 excluded studies for which no exclusion reason is provided. Please provide exclusion reasons for these five studies: Paridaens 2008; PALOMA-1 study; PALOMA-2 study; Pyrhonen 1997; and SWOG 0226.

These five studies were excluded as they included comparators not of interest to the evidence network (Table 1):

Table 1: Exclusion reasons for 5 studies

Study name	Comparators	Comment
Paridaens 2008 (1)	Exemestane Tamoxifen	Exemestane was not considered a relevant comparator
PALOMA-1 study (2)	Palbociclib + letrozole Letrozole	Palbociclib + letrozole is not currently recommended by NICE and not considered a relevant comparator
PALOMA-2 study (3)	Palbociclib + fulvestrant Fulvestrant	Palbociclib + fulvestrant is not currently recommended by NICE and not considered a relevant comparator
Pyrhonen 1997 (4)	Toremifene Tamoxifen	Toremifene was not considered a relevant comparator
SWOG 0226 study (5)	Anastrozole Anastrozole + fulvestrant	Anastrozole + fulvestrant is not approved by the EMA

A2. **Priority question** In CS Table 19 (p.70) the numbers given for the two groups (n=193 and n=196) seem to be for the FALCON trial not the FIRST trial. Please confirm if this is an error. Should the values be fulvestrant n=89; anastrozole n=93 for

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this table? Please also provide the numbers of patients achieving ORR, CR, PR, SD and PD in both groups.

We can confirm that the N presented in Table 19 (p70) should be 89 for fulvestrant and 93 for anastrozole (according to the FIRST CSR(6)). The patients in the Evaluable for Response analysis for FIRST with ORR, CR, PR, SD and PS is presented below.

Table 18 Summary of best objective response: Evaluable for Response analysis set

Objective Response classification	Best objective response (BOR)	Number (%) of patients	
		Fulvestrant 500 mg (N=89)	Anastrozole 1 mg (N=93)
Response	Complete Response	0	1 (1.1)
	Partial Response	32 (36.0)	32 (34.4)
	Total with Response	**32 (36.0)**	**33 (35.5)**
Non-response	Stable Disease	45 (50.6)	41 (44.1)
	Progression	9 (10.1)	18 (19.4)
	Not Evaluable	3 (3.4)	1 (1.1)
	Total with non-response	**57 (64.0)**	**60 (64.5)**

N: Number of patients.
Data derived from Table 11.2.2, Section 11.

A3. **Priority question** CS Figure 16 (p. 73) presents mean trial outcome index score and Figure 17 the EQ-5D-3L scores. In Figure 16 the number of patients does not correspond to any of the patient analysis sets described, and no patient numbers are given for Figure 17 (p. 74). Please clarify why there are missing patient data from Figure 16 and provide data for the number of patients contributing data to each of the time points shown in Figure 17 (with reasons for any missing data). If possible please supply reference 70 which is cited in the Health Related Quality of Life section (CS p72 -74) but which does not appear to have been provided in the reference pack.

*Summaries and analyses of the trial outcome index were performed in the intention-to-treat (ITT) analysis set. However, with the ITT population, only 209 and 219 patients in the fulvestrant and anastrozole treatment arms, respectively, provided evaluable forms at baseline from which Trial Outcome Index (TOI) could be derived (*Table 2*).*
Details of the number of patients contributing data to each of the time points shown in Figure 17 in the original submission (with reasons for any missing data) are provided in Reference 70 which was omitted from the Reference Pack in error.

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Table 2: Trial Outcome Index (TOI) score over time for patients in the FALCON study (Table 11.2.3.2 from CSR (7))

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Table 11.2.3.2 Trial outcome index (TOI) score over time
(Intention to treat analysis set)

Group	Time point	n	Result Mean	SD	Min	Q1	Median	Q3	Max
Fulvestrant 500 mg (N=230)	Baseline [a]	209	63.9	11.86	34	56	65.0	72	90
	Week 12	204	67.3	11.83	24	61	68.0	76	92
	Week 24	172	67.5	11.14	37	61	68.0	76	91
	Week 36	147	68.3	11.02	42	62	69.0	77	91
	Week 48	134	67.2	10.74	37	60	67.0	75	92
	Week 60	112	66.8	11.35	36	58	67.0	75	91
	Week 72	98	67.1	10.41	44	62	66.5	73	91
	Week 84	88	66.8	10.66	44	59	67.0	73	91
	Week 96	73	66.7	11.64	29	60	66.0	73	92
	Week 108	56	66.6	11.62	38	58	66.0	75	92
	Week 120	38	66.2	10.65	45	59	66.0	73	91
	Week 132	22	66.3	11.65	40	59	69.0	74	86
	Week 144	11	64.9	13.43	44	52	67.0	74	90
	Week 156	9	68.1	14.41	47	54	71.0	77	91
	Post Disc + 12 Weeks (With Prog)	57	59.8	14.29	25	49	63.0	70	89
	Post Disc + 24 Weeks (With Prog)	3	54.7	23.03	31	31	56.0	77	77
	Post Disc + 36 Weeks (With Prog)	31	65.9	12.31	37	59	68.0	75	89
	Post Disc + 48 Weeks (With Prog)	3	72.0	13.23	57	57	77.0	82	82
	Post Disc + 60 Weeks (With Prog)	22	61.6	14.45	27	51	63.5	73	84
	Post Disc + 72 Weeks (With Prog)	3	68.3	10.60	57	57	70.0	78	78
	Post Disc + 84 Weeks (With Prog)	12	66.8	8.68	51	60	67.0	72	80
	Post Disc + 96 Weeks (With Prog)	2	65.5	9.19	59	59	65.5	72	72
	Post Disc + 108 Weeks (With Prog)	4	58.3	9.43	46	53	59.0	64	69
	Post Disc + 12 Weeks (No Prog)	6	62.0	9.03	49	55	63.0	69	73
	Post Disc + 24 Weeks (No Prog)	6	62.3	11.50	46	56	62.0	70	78
	Post Disc + 36 Weeks (No Prog)	4	73.0	5.48	65	70	75.0	77	77
	Post Disc + 48 Weeks (No Prog)	4	75.3	7.80	64	70	78.0	81	81
Fulvestrant 500 mg (N=230)	Post Disc + 60 Weeks (No Prog)	3	76.0	4.00	72	72	76.0	80	80
	Post Disc + 72 Weeks (No Prog)	1	73.0	NC	73	73	73.0	73	73

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Final
Table 11.2.3.2 Trial outcome index (TOI) score over time
(Intention to treat analysis set)

Group	Time point	n	Result Mean	SD	Min	Q1	Median	Q3	Max
Anastrozole 1 mg (N=232)	Baseline [a]	219	63.2	11.89	23	55	64.0	72	91
	Week 12	195	65.0	11.66	34	56	66.0	74	90
	Week 24	176	66.7	11.15	36	58	67.5	75	91
	Week 36	146	66.5	11.46	23	58	68.0	75	91
	Week 48	127	65.8	12.25	36	57	66.0	74	92
	Week 60	110	64.2	12.11	18	56	64.0	72	89
	Week 72	101	64.5	12.39	33	55	66.0	73	91
	Week 84	77	66.6	11.20	42	59	66.0	75	91
	Week 96	62	64.6	11.43	35	57	63.0	74	87
	Week 108	47	64.2	10.64	39	56	62.0	71	85
	Week 120	30	65.4	11.49	39	57	66.5	73	87
	Week 132	20	65.5	13.39	43	52	65.5	76	92
	Week 144	10	65.3	16.35	48	53	59.0	80	92
	Week 156	5	58.0	11.98	44	51	55.0	66	74
	Post Disc + 12 Weeks (With Prog)	66	58.3	12.85	14	52	59.0	66	88
	Post Disc + 24 Weeks (With Prog)	11	60.3	13.50	33	51	59.0	73	80
	Post Disc + 36 Weeks (With Prog)	38	59.5	15.37	17	48	61.0	69	90
	Post Disc + 48 Weeks (With Prog)	6	54.2	14.32	30	46	57.5	64	70
	Post Disc + 60 Weeks (With Prog)	20	56.5	14.48	32	46	56.0	64	86
	Post Disc + 72 Weeks (With Prog)	2	79.5	16.26	68	68	79.5	91	91
	Post Disc + 84 Weeks (With Prog)	13	56.4	11.44	42	49	55.0	60	84
	Post Disc + 96 Weeks (With Prog)	2	88.0	1.41	87	87	88.0	89	89
	Post Disc + 108 Weeks (With Prog)	4	52.0	12.38	35	43	55.0	61	63
	Post Disc + 132 Weeks (With Prog)	1	71.0	NC	71	71	71.0	71	71
	Post Disc + 12 Weeks (No Prog)	5	56.0	11.14	39	51	61.0	62	67
	Post Disc + 24 Weeks (No Prog)	2	68.0	2.83	66	66	68.0	70	70
	Post Disc + 36 Weeks (No Prog)	3	51.3	22.74	26	26	58.0	70	70
Anastrozole 1 mg (N=232)	Post Disc + 48 Weeks (No Prog)	2	69.5	6.36	65	65	69.5	74	74
	Post Disc + 60 Weeks (No Prog)	1	74.0	NC	74	74	74.0	74	74
	Post Disc + 72 Weeks (No Prog)	1	67.0	NC	67	67	67.0	67	67
	Post Disc + 84 Weeks (No Prog)	1	66.0	NC	66	66	66.0	66	66

PAGE 4 OF 4

[a] Baseline is defined as the last evaluable assessment on or prior to the first randomised treatment dose.
This table summarises all trial outcome index (TOI) score assessments between randomisation and the data cut off for the final PFS analysis. The higher the score the better the HRQoL or symptoms.
Up to and including discontinuation, visits have been mapped based on the first dose of randomised treatment. Visits post-discontinuation have been mapped on the discontinuation date. If more than one value per patient within a time window then the closest will be summarised, or the earliest in the event of equidistant values from the planned study day.
TOI=sum of un-weighted prorated scores of PWB, FWB and BCS if all of them are not missing.
PWB=Physical well-being. FWB=Functional well-being. BCS=Breast cancer subscale.
Score ranges per scale: TOI (0-92), PWB (0-28), FWB (0-28), BCS (0-36).
SD=Standard deviation. NC=Not calculable due to insufficient data.
Visit labelling referring to progression relates to reported progression only, not calculated progression.

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A4. **Priority question** Table 20 CS p. 76 reports expected duration of response (EDoR) and expected duration of clinical benefit (EDoCB). Are these mean or median values? CS p. 58 states that EDoCB and EDoR were calculated using the method described by Ellis and colleagues (citing reference 6 in the reference list) but the ERG has not found the method described in this reference. Please supply the method for calculating EDoCB and EDoR. Please also provide mean values alongside the medians reported in this table.

Reference 6 was referred to in error. The correct reference is included in the reference pack to this response document(8). The Expected Duration of Response (EDoR) is the product of the proportion of patient responding to treatment and the mean DoR in responding patients. It provides an estimate based on all randomised patients, not just the subset of responding patients. The mean DoR and mean DoCB are presented in the tables below sourced from the CSR (7)

Table 22 Duration of response in patients with measurable disease at baseline (ITT analysis set)

Group	N	Response Rate (%)	Mean DoR[a]	SE Mean DoR[b]	EDoR[c]	Ratio of EDoR[d]	95% CI	2-sided p-value
Fulvestrant 500 mg	193	46.1	752.14	0.138	346.84	1.52	(1.23, 1.89)	0.0001
Anastrozole 1 mg	196	44.9	506.88	0.097	227.58			

Note: The analysis was performed using the method described by Ellis et al 2008.
[a] DoR = Duration of Response in responding patients (days) on the basis of a Weibull distribution.
[b] SE Mean DoR = Standard Error of Mean Duration of Response (days) on the basis of a Weibull distribution.
[c] EDoR = Expected Duration of Response (days).
[d] Ratios >1 favour fulvestrant.
DoR duration of response; EDoR expected duration of response; CI confidence interval; ITT intention to treat; SE standard error.
Data source: Table 11.2.1.16.3.

Table 24 Duration of clinical benefit in patients receiving clinical benefit (ITT analysis set)

Group	N	Clinical Benefit Rate (%)	Mean DoCB[a]	SE Mean DoCB[b]	EDoCB[c]	Ratio of EDoCB[d]	95% CI	2-sided p-value
Fulvestrant 500 mg	230	78.3	853.48	0.083	667.94	1.26	(1.13, 1.39)	<0.0001
Anastrozole 1 mg	232	74.1	717.64	0.068	532.04			

Note: The analysis was performed using the method described by Ellis et al 2008.
[a] DoCB = Duration of Clinical Benefit in responding patients (days) on the basis of a log-normal distribution.
[b] SE Mean DoCB = Standard Error of Mean Duration of Clinical Benefit (days) on the basis of a log-normal distribution.
[c] EDoCB = Expected Duration of Clinical Benefit (days).
[d] Ratios >1 favour fulvestrant.
CI confidence interval; ITT intention to treat.
Data source: Table 11.2.1.17.4.

A5. **Priority question** Table 25 CS p. 85. The ERG believes the sample size of PO25 trial is 907, not 916 as reported (and as also reported in Table 11). Please confirm if the ERG is correct. Asterisk indicates study reports subgroup data for the population of interest but n for the subgroup is not reported. Appendix B Table 124 gives 916

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with 599 sample size in brackets. Is the 599 the correct subgroup sample size (this would correspond to the ER and /or PgR positive subgroup n=294 +305 = 599)?

In PO25, 916 patients were randomly assigned to letrozole 2.5 mg (n=458) or tamoxifen 20 mg (n = 458); however nine patients were excluded due to a Good Clinical Practice (GCP) noncompliant site (n=4) or because they did not have actively progressive breast cancer at enrolment (n=5). Therefore, 907 patients were included in the ITT population (453 assigned to letrozole and 454 to tamoxifen).
Table 11 (p43), Table 25 (p85), and Table 124 (p249) should therefore report n=907 (instead of n=916) as the sample size for PO25.
In Table 124 (p249), n=599 is the correct sample size for hormone receptor-positive patients (294+305).

A6. **Priority question**. Table 25 CS p. 85. Which TTP data were extracted from the PO25 study? TTP is reported for the receptor status positive subgroup in Table 4 of the Mouridsen et al 2001 paper but there is no separate Kaplan–Meier plot for this subgroup. Page 90 of the CS states that reported Kaplan-Meier curves were digitised and an algorithm run to reconstruct patient-level data so was the curve used for this for the whole PO25 study population and not the subgroup of interest? Furthermore, there is no overall survival KM plot in the Mouridsen et al 2001 paper. Did overall survival data come from the KM plot presented as Figure 4 in Mouridsen et al 2003 (CS reference 76)?

For the NMA, TTP (from Figure 2 in Mouridsen 2001 (9)) and OS (from Figure 4 in Mouridsen 2003 (10)) data for the full study population of PO25 were used.
The relevant figures are presented in Figure 1 and Figure 2 here.

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Figure 1: Time to progression for letrozole and tamoxifen as reported in Mouridsen 2001 (9)

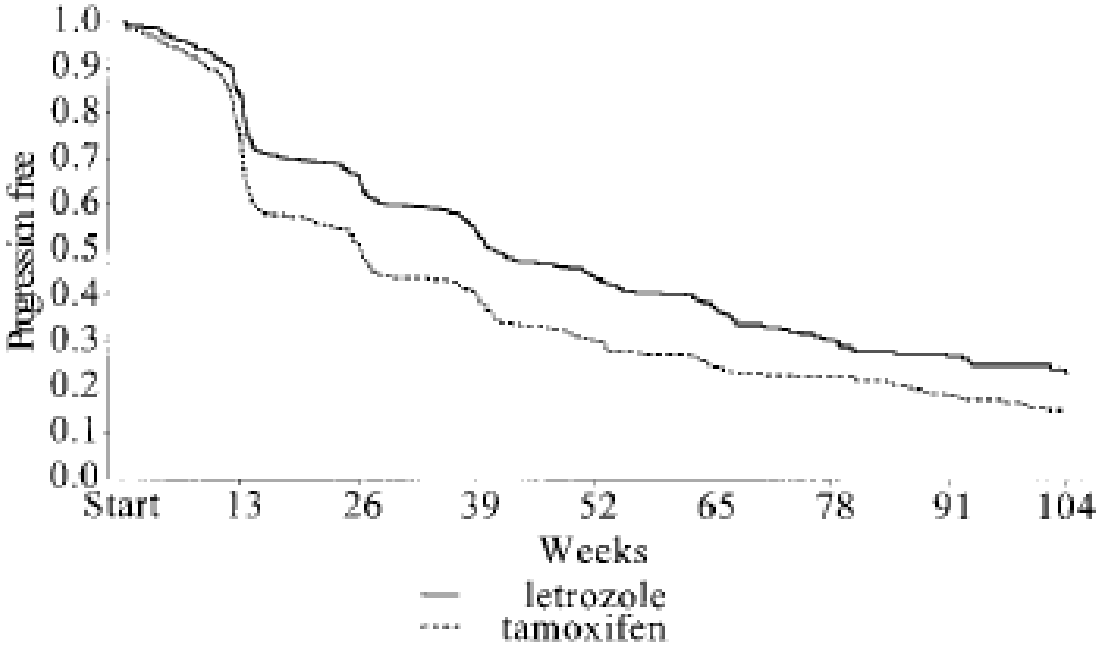

Fig 2. Time to progression: for letrozole (n = 453), the median TTP was 41 weeks (9.4 months); for tamoxifen (n = 454), median TTP was 26 weeks (6.0 months).

Figure 2: Overall survival for letrozole and tamoxifen as reported in Mouridsen 2003 (10)

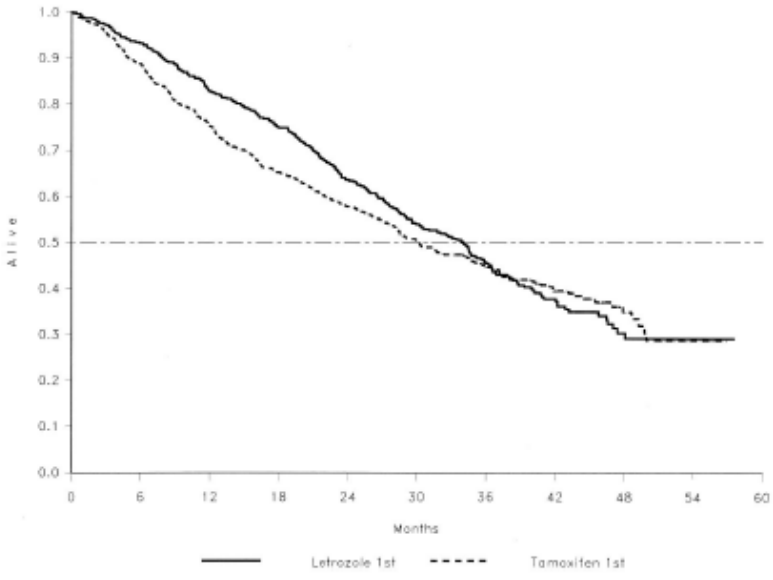

Fig 4. Overall survival (OS) at median follow-up of 32 months, by randomized treatment arm. Median OS was not significantly different (overall log-rank, $P = .53$). There was a significant difference in favor of the randomized letrozole arm between 6 and 20 months (Kolmogorov-Smirnov-type test, $P = .003$).

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A7. **Priority question** CS p.90 indicates that combined OS results were used from the North American and Target trials and cites reference 71 as the source of the combined data. However, reference 71 is the same as reference 10 which is the North American trial alone. Please supply the correct reference for the combined North American and Target trial data.

Reference 71 was referred to in error. The correct reference is included in the reference pack for this response document (Nabholtz 2003 (11)

A8. **Priority question**. CS p. 90 Section 4.10.1 Method of network meta-analysis states that "For those trials identified in the systematic literature review and where patient-level data was available (FIRST and NorthAmTarget) the inclusion and exclusion criteria from the FALCON trial was applied to each treatment arm in both trials to better match the FALCON trial population (12)." Were all of the inclusion and exclusion criteria from the FALCON Trial applied? If so, how were criteria that were not reported by all trials matched e.g. an exclusion criterion of the FALCON trial was human epidermal growth factor receptor over-expression or gene amplification but data on this was not reported by the North American or Target studies? What methodology was used for the matching process?

Criteria were applied so that data for ER/PR+ patients plus endocrine naive patients would be included and hence these patients were selected from FIRST and North American and Target. The North American and Target data does not include HER2 status so this is unknown for this trial. Page 39 states that if HER2 was unknown, a pragmatic decision was made to include HER2 in the analysis since testing for HER2 positivity was not routine practice before the mid-2000's.

A9. **Priority question** CS p. 90 section 4.10.1 please provide the numbers of participants whose data were retained after the matching process and a table summarizing the socio-demographic and clinical characteristics of the remaining participants from each trial after matching (i.e. the trial participants that contributed data to the NMA).

The numbers of study participants in the ITT cohorts for each study in the NMA, as well as the numbers retained after matching eligibility to the FALCON study are presented in Table 3.

Table 3: Patient numbers in studies included in NMA before and after matching to FALCON study

Study	Cohort	Fulvestrant	Anastrozole	Tamoxifen	Letrozole	TOTAL
FALCON	**ITT**	230	232	-	-	**462**
FIRST	**ITT**	102	103	-	-	**205**
	FALCON-like	73	80	-	-	**153**
	ITT	-	171	182	-	**353**

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North America	**FALCON-like**	-	119	134	-	**253**
Target	**ITT**	-	340	328	-	**668**
	FALCON-like	-	132	128	-	**260**
North America/ Target	**ITT**	-	511	510	-	**1021**
	FALCON-like	-	251	262	-	**513**
PO25	**ITT**	-	-	453	454	**907**
	FALCON-like	-	-	-	-	

The clinical characteristics of patients in each study, for both ITT and 'FALCON-matched' cohorts, are presented in Table 4, Table 5, Table 6, Table 7 and Table 8.

Table 4: Baseline characteristics of participants in the FALCON study (7)

	Fulvestrant ITT N=230	**Anastrozole ITT N=232**
Median age (years)	64	62
ER and/or PR +ve	**220 (96%) 10 patients unknown**	**225 (97%) 7 patients unknown**
Visceral disease	135 (59%)	119 (51%)
Bone only disease	24 (10%)	24 (10%)
Soft tissue only disease	8 (4%)	6 (3%)
No prior chemo	151 (66%)	151 (65%)
Prior chemo for ABC	36 (16%)	43 (19%)
Prior (neo) adjuvant chemo	43 (19%)	40 (17%)
Prior endocrine therapy	**2 (1%)**	**1 (0.4%)**
Measurable disease	193 (84%)	196 (84%)
Locally advanced	28 (12%)	32 (14%)

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Table 5: Baseline characteristics of participants in the FIRST study (ITT and matched to FALCON study)

	fulvestrant ITT N=102	anastrozole ITT N=103	fulvestrant endocrine naïve subgroup N=73	anastrozole endocrine naïve subgroup N=80
Median age (years)	66	68	67	69
ER and/or PR +ve	**102 (100%)**	**103 (100%)**	**73 (100%)**	**80 (100%)**
Visceral disease	48 (47%)	58 (56%)	33 (45%)	43 (54%)
Bone only disease	10 (10%)	8 (8%)	2 (3%)	2 (3%)
Soft tissue only disease	1 (1%)	0	0	0
No prior chemo	73 (72%)	78 (76%)	63 (86%)	68 (85%)
Prior chemo for ABC	0	0	0	0
Prior adjuvant chemo	29 (28%)	25 (24%)	10 (14%)	12 (15%)
Prior endocrine therapy*	**29 (28%)**	**23 (22%)**	**0**	**0**
Measurable disease	89 (87%)	93 (90%)	69 (95%)	78 (98%)
Locally advanced	19 (19%)	18 (18%)	19 (26%)	18 (23%)

* Adjuvant endocrine therapy for early disease

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Table 6:Baseline characteristics of participants in the pooled analysis of North America & Target studies (ITT and matched to FALCON study)

	anastrozole ITT N=511	Tamoxifen ITT N=510	anastrozole HR+ / endocrine naïve subgroup N=251	Tamoxifen HR+ / endocrine naïve subgroup N=262
Median age (years)	67	67	67	66
ER and/or PR +ve	**305 (60%)**	**306 (60%)**	**251 (100%)**	**262 (100%)**
Visceral disease	186 (36%)	211 (41%)	103 (41%)	132 (50%)
Bone only disease	101 (20%)	86 (17%)	53 (21%)	50 (19%)
Soft tissue only disease	142 (28%)	138 (27%)	53 (21%)	45 (17%)
No prior chemo	391 (77%)	385 (75%)	191 (76%)	198 (76%)
Prior chemo for ABC	0	0	0	0
Prior adjuvant chemo	120 (23%)	125 (25%)	60 (24%)	65 (25%)
Prior endocrine therapy	**78 (15%)**	**68 (13%)**	**0**	**0**
Measurable disease	418 (82%)	425 (83%)	195 (78%)	208 (79%)
Locally advanced	-	-	-	-

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Table 7: Baseline characteristics of participants in the North American study (ITT and matched to FALCON study)

	anastrozole ITT N=171	Tamoxifen ITT N=182	anastrozole HR+ / endocrine naïve subgroup N=119	Tamoxifen HR+ / endocrine naïve subgroup N=134
Median age (years)	68	67	67	67
ER and/or PR +ve	**151 (88%)**	**162 (89%)**	**119 (100%)**	**134 (100%)**
Visceral disease	83 (49%)	87 (48%)	59 (50%)	68 (51%)
Bone only disease	46 (27%)	42 (23%)	34 (29%)	33 (25%)
Soft tissue only disease	18 (11%)	32 (18%)	11 (9%)	19 (14%)
No prior chemo	124 (73%)	132 (73%)	88 (74%)	98 (73%)
Prior chemo for ABC	0	0	0	0
Prior adjuvant chemo	47 (27%)	50 (27%)	31 (26%)	36 (27%)
Prior endocrine therapy	**36 (21%)**	**33 (18%)**	**0**	**0**
Measurable disease	117 (68%)	139 (76%)	82 (69%)	101 (75%)
Locally advanced	-	-	-	-

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Table 8:Baseline characteristics of participants in the TARGET study (ITT and matched to FALCON study)

	anastrozole ITT N=340	Tamoxifen ITT N=328	anastrozole HR+ / endocrine naïve subgroup N=132	Tamoxifen HR+ / endocrine naïve subgroup N=128
Median age (years)	67	66	67	64
ER and/or PR +ve	**154 (45%)**	**144 (44%)**	**132 (100%)**	**128 (100%)**
Visceral disease	103 (30%)	124 (38%)	44 (33%)	64 (50%)
Bone only disease	55 (16%)	44 (13%)	19 (14%)	17 (13%)
Soft tissue only disease	128 (38%)	106 (32%)	42 (32%)	26 (20%)
No prior chemo	267 (79%)	253 (77%)	103 (78%)	100 (78%)
Prior chemo for ABC	0	0	0	0
Prior adjuvant chemo	73 (21%)	75 (23%)	29 (22%)	28 (22%)
Prior endocrine therapy	**42 (12%)**	**35 (11%)**	**0**	**0**
Measurable disease	301 (89%)	286 (87%)	113 (86%)	107 (84%)
Locally advanced	-	-	-	-

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For comparison, a similar table for PO25 (Table 9) is provided to demonstrate the differences in patient characteristics for that study compared to the ones contributing patient-level data to the network of evidence.

Table 9: Baseline characteristics of participants in the PO25 study

	Letrozole N=453	Tamoxifen N=454
Median age (years)	65	64
ER and/or PR +ve	294 (65%) 156 patients unknown	305 (67%) 149 patients unknown
Visceral disease	194 (43%)	208 (46%)
Bone only disease	69 (15%)	72 (16%)
Soft tissue only disease	113 (25%)	116 (25%)
No prior chemo	320 (71%)	301 (66%)
Prior chemo for ABC	40 (9%)	48 (11%)
Prior adjuvant chemo	93 (21%)	105 (23%)
Prior endocrine therapy*	84 (19%)	83 (18%)
Measurable disease	-	-
Locally advanced	145 (32%)	146 (32%)

* Labelled as prior AO

Table 10: Summary statistics of baseline characteristics for participants in studies contributing to NMA (regardless of treatment randomisation).

	FALCON (ITT)	FIRST	Target	North America	Target & N. America	PO25 (ITT)
	N=462	N=153	N=260	N=253	N=513	N=907
Age	-	-	-	-	-	-
ER+ and/or PR+	**96%**	**100%**	**100%**	**100%**	**100%**	**66%**
Visceral disease	55%	50%	42%	50%	46%	44%
Bone only	10%	3%	14%	26%	20%	16%
Soft tissue only	3%	0%	26%	12%	19%	25%
No prior chemo	65%	86%	78%	74%	76%	68%
Prior chemo for ABC	17%	0%	0%	0%	0%	10%
Prior chemo for (neo) adjuvant disease	18%	14%	22%	26%	24%	22%
Prior endocrine therapy	**<1%**	**0%**	**0%**	**0%**	**0%**	**18%**
Measurable disease	84%	96%	85%	72%	79%	-
Locally Advanced disease	13%	24%	-	-	-	32%

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A10. **Priority question** Please provide results for fixed effect and random effects pairwise comparisons of interventions in the NMA (i.e. fulvestrant vs anastrozole; anastrozole vs tamoxifen 20mg; letrozole vs tamoxifen; fulvestrant vs tamoxifen 20mg; fulvestrant vs letrozole).

The North America and Target trials were prospectively designed to allow for a combined analysis, and results from the combined analysis have been published. The pooled North American and Target dataset, after matching to the FALCON study using ER/PR+ and endocrine treatment-naïve criteria, was therefore used in the network meta-analyses of PFS and OS. The use of the combined dataset leaves only one link in the network (fulvestrant to anastrozole) that is comprised of two studies (FALCON and FIRST); please see the diagram below.

Given that there is only one link in the network with more than one study, FALCON and FIRST are the only two trials which warrant the use of random effects. A recent paper (13) outlines the problems inherent in the use of a random-effects model when only two studies are included in the meta-analysis. The paper concludes that:

> *"Bayesian random-effects meta-analyses with a reasonable prior yield interpretable results" (13).*

Given this finding, the follow-on question then becomes what constitutes a reasonable prior in this context? The paper suggests estimating the plausible amount of heterogeneity expected between trials. An attempt has been made to quantify the variability in the intervention effects being evaluated in FALCON and FIRST by using a model in which an interaction effect of study and treatment is included (only using FALCON and FIRST). The generalised gamma (base case distribution used to extrapolate PFS) model with interaction effect for study and treatment did not converge for PFS. The Weibull distribution (base case distribution used to extrapolate OS) model with interaction effect for study and treatment for OS did converge, but did not demonstrate a significant difference from the model without an interaction effect. It is believed that the choice of an informative prior is a difficult question to answer and conclude, as before, that the more robust approach would be to use fixed-effects meta-analysis

A further limiting factor in the use of a random-effects model when a limited amount of studies is used is that an assessment of goodness-of-fit cannot be undertaken (a standard error can be estimated based on two studies, but the uncertainty in the standard error cannot).

The results of a fixed effects pairwise comparison for all treatment comparisons are presented in Table 11 (for PFS using a generalised gamma model) and Table 12 (for OS using a Weibull model).

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Table 11: Posterior mean, standard error (SE) and 95% confidence interval of the relative effect of comparator compared to reference for all possible treatment comparisons for the pairwise meta-analyses of PFS with fixed effects generalised gamma model

Cmp	Ref	Scale	SE	L95%	U95%	Shape	SE	L95%	U95%
Fulvestrant	Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	Letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Cmp, comparator; L, lower; PFS, progression-free survival; R, reference; SE, standard error; U, upper.

Table 12: Posterior mean, standard error (SE) and 95% confidence interval of the relative effect of comparator compared to reference for all possible treatment comparisons for the pairwise meta-analyses of OS with fixed effects Weibull model

Cmp	Ref	Scale	SE	L95%	U95%	Shape	SE	L95%	U95%
Fulvestrant	Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	Letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Cmp, comparator; L, lower; OS, overall survival; R, reference; SE, standard error; U, upper.

A11. **Priority question** NMA results section 4.10.2. Please also provide results from a random effects NMA for the outcomes of PFS and OS. Please report the model fit statistics for both the fixed effect and random effects models so that these can be compared.

We refer the reader to the response provided in A10 for the request for the results of a random effects model.

A12. **Priority question** Please provide NMA and full cost-effectiveness results obtained using all study data from FIRST and NorthAmTarget, i.e. without undertaking the matching process. If the ITT populations are used is the assumption of proportional hazards for PFS and OS still violated?

This is considered out of scope for this appraisal as approximately a third of the patients in the resulting network (560/1688, assuming number for FALCON, FIRST and NorthAmTarget from Table 3) will not be covered by the expected marketing authorisation for fulvestrant.

A13. **Priority question** As noted in the CS (CS p. 96) study PO25 differs from the other studies included in the NMA in that individual patient data were not available so the data could not be matched to the FALCON trial, cross-overs between treatment arms took place and, as clarification question A6 indicates, it is not clear to the ERG whether data for TTP and OS came from the whole population or the hormone receptor positive subgroup (66%). Furthermore, as CS p97 indicates, the efficacy of

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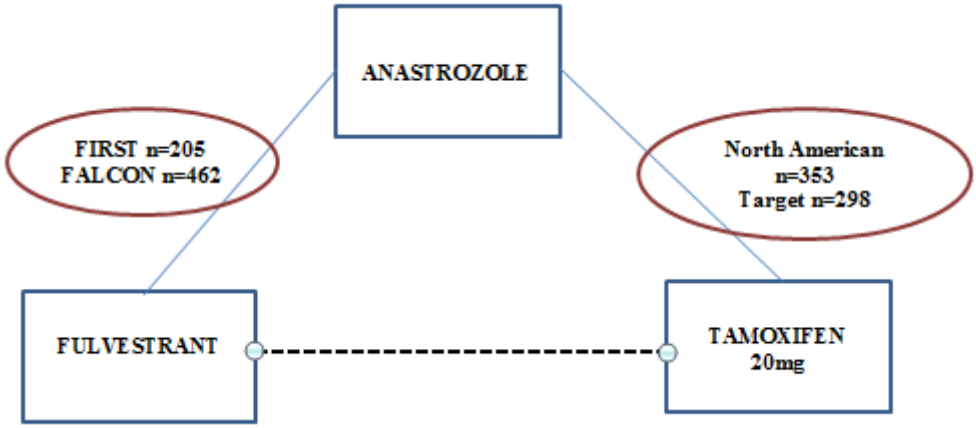
letrozole is widely accepted to be equivalent to that of anastrozole. Therefore please also provide NMA and full cost-effectiveness results (pairwise fixed and random effects as well as fixed and random effects NMA) from a network omitting the PO25 study as well as the Milla-Santos study i.e. for the network shown in the diagram below:



As previously explored, a random effects model was not considered feasible based on the nature of the available data; therefore, the following results are solely from the fixed effects pairwise meta-analyses/ NMA when the PO25 study, as well as the Milla-Santos study, is excluded. Please note that in this scenario the PFS and OS for letrozole are assumed to be equivalent to anastrozole.

Results of the pairwise fixed-effects meta-analyses when excluding the PO25 trial from the network of evidence for PFS and OS are presented below.

Table 13: Posterior mean, standard error (SE) and 95% confidence interval of the relative effect of comparator compared to reference for all possible treatment comparisons for the pairwise meta-analyses of PFS with fixed-effects generalised gamma model (excluding PO25)

Cmp	Ref	Scale	SE	L95%	U95%	Shape	SE	L95%	U95%
Fulvestrant	Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Cmp, comparator; L, lower; PFS, progression-free survival; R, reference; SE, standard error; U, upper.

Table 14: Posterior mean, standard error (SE) and 95% confidence interval of the relative effect of comparator compared to reference for all possible treatment comparisons for the pairwise meta-analyses of OS with fixed-effects Weibull model (excluding PO25)

Cmp	Ref	Scale	SE	L95%	U95%	Shape	SE	L95%	U95%
Fulvestrant	Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Cmp, comparator; L, lower; PFS, progression-free survival; R, reference; SE, standard error; U, upper.

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13.1 Fixed effects NMA for 'all shapes' model

a. Progression-free survival (PFS)

The results of fitting the standard parametric distributions to the NMA PFS dataset, excluding the PO25 trial from the network of evidence, are presented below. For contrast, the fitting statistics, mean and median survival estimates and results of the NMA with the PO25 study included in the network of evidence (which were included in the original submission) are also presented.

Table 15: AIC and BIC statistics for PFS based on fixed-effects NMA model (including PO25 - Table 31, p109 CS)

Distribution	AIC	AIC rank	BIC	BIC rank
Log-logistic	8624.747	1	8703.403	1
Generalised gamma	8627.055	2	8711.329	2
Lognormal	8636.065	3	8714.721	3
Weibull	8687.484	4	8766.140	4
Gompertz	8720.786	5	8799.441	5

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; NMA, network meta-analysis; PFS, progression-free survival.

Table 16: AIC and BIC statistics for PFS based on fixed-effects NMA model (excluding PO25)

Distribution	AIC	AIC rank	BIC	BIC rank
Generalised gamma	5546.512	1	5601.822	2
Lognormal	5549.671	2	5599.953	1
Log logistic	5555.259	3	5605.541	3
Weibull	5573.932	4	5624.214	4
Gompertz	5597.020	5	5647.302	5

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; NMA, network meta-analysis; PFS, progression-free survival.

The AIC and BIC statistics for PFS based on fixed-effects NMA model (excluding PO25, Table 16) concur with the original estimates (Table 15) with regards to the Weibull and Gompertz distributions: in both instances, the Weibull and Gompertz distributions are ranked 4th and 5th, respectively, in terms of relative fit to the observed data. The generalised gamma, the base case distribution for extrapolating PFS, is now ranked 1st and 2nd according to the AIC and BIC respectively, when the PO25 trial was removed. The generalised gamma was ranked 2nd both AIC and BIC when the PO25 trial was included. The log-logistic is now ranked 3rd best fit by both AIC and BIC in the absence of the PO25 trial, as opposed to the best fit with the inclusion of PO25. The lognormal distribution is now ranked 2nd best fit according to AIC and the best fit according to BIC in the absence of the PO25 trial. The lognormal was ranked 3rd best fit by both the AIC and BIC when the PO25 trial was included.

Table 17: Generalised gamma parameter estimates for PFS based on fixed-effects NMA (including PO25 trial- Table 33, page 112)

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Generalised gamma	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Common parameter	Estimate	L95%	U95%	-	-	-
Q	[redacted]	[redacted]	[redacted]	-	-	-

Abbreviations: L, lower; U, upper.

Table 18: Generalised gamma parameter estimates for PFS based on fixed-effects NMA (excluding PO25 trial)

Generalised gamma	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Common parameter	Estimate	L95%	U95%	-	-	-
Q	[redacted]	[redacted]	[redacted]	-	-	-

Abbreviations: L, lower; U, upper.

Table 19: Time in PFS (mean and median [months]), undiscounted; generalised gamma

Treatment	Results ***including*** PO25 trial (Table 78, p185. CS)		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	16.56	29.58	16.56	29.63
Anastrozole	11.96	19.56	11.96	19.58
Letrozole	14.72	22.16		
Tamoxifen	9.20	13.16	9.20	13.17

The removal of the PO25 trial appears to have a minimal impact upon both the estimated curve parameters for anastrozole, fulvestrant and tamoxifen (Table 17 and Table 18) and the mean and median survival estimates (Table 19). The letrozole estimates are now assumed to be equivalent to the anastrozole estimates.

b. Overall survival (OS)

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The results of fitting the standard parametric distributions to the NMA OS dataset excluding the PO25 trial from the network of evidence are presented below (Table 21 and Table 23). For contrast, the fitting statistics(Table 20), mean and median survival estimates and results of the NMA (Table 22) with the PO25 included in the network of evidence are also presented (Table 24).

Table 20: AIC and BIC statistics for OS based on fixed-effects NMA model (including PO25- Table 34, p114 CS))

Distribution	AIC	AIC rank	BIC	BIC rank
Weibull	10499.131	1	10577.848	1
Generalised gamma	10500.300	2	10584.640	2
Gompertz	10508.995	3	10587.713	3
Log-logistic	10513.882	4	10592.599	4
Lognormal	10552.618	5	10631.335	5

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; NMA, network meta-analysis; OS, overall survival.

Table 21: AIC and BIC statistics for OS based on fixed-effects NMA model (excluding PO25)

Distribution	AIC	AIC rank	BIC	BIC rank
Weibull	5242.794	1	5293.076	1
Generalised gamma	5244.528	2	5299.839	3
Gompertz	5246.951	3	5297.233	2
Log-logistic	5256.334	4	5306.616	4
Lognormal	5278.057	5	5328.339	5

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; NMA, network meta-analysis; OS, overall survival.

The AIC statistics for OS based on fixed-effects NMA model (excluding PO25) produces a ranking of distributions which matches the ranking of distributions when the PO25 trial was included in the network of evidence (Table 20 and Table 21). The BIC statistics produce a near identical ranking of distributions but, in the case where the PO25 trial is removed from the network, the generalised gamma and Gompertz distributions are ranked 3rd and 2nd best fit, respectively. In contrast, when the PO25 trial is included, the generalised gamma is ranked 2nd and the Gompertz 3rd.

Table 22: Weibull parameter estimates for OS based on fixed-effects NMA (including PO25 trial- Table 36, p117)

Weibull	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: L, lower; U, upper.

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Table 23: Weibull parameter estimates for OS based on fixed-effects NMA (excluding PO25 trial)

Weibull	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: L, lower; U, upper.

Table 24: Time in OS (mean and median [months]), undiscounted; Weibull

Treatment	Results ***including*** PO25 trial (Table 78, p185. CS)		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	47.84	60.08	47.84	60.09
Anastrozole	39.56	48.95		
Letrozole	38.64	43.42	39.56	48.95
Tamoxifen	36.80	45.05	36.80	45.05

The removal of the PO25 trial appears to have a minimal impact upon both the estimated curve parameters for anastrozole, fulvestrant and tamoxifen (Table 22 and Table 23) and the mean and median survival estimates (Table 24). The letrozole estimates are now assumed to be equivalent to the anastrozole estimates.

c. Cost-effectiveness

Incremental cost-effectiveness results using fixed-effects NMA for PFS and OS ('all shapes') in which the PO25 trial is removed from both networks are presented below.

Total costs, life years gained (LYG), QALYs and incremental cost per QALY that patients would experience whilst on either the intervention treatment (fulvestrant 500 mg), or the comparator treatments (anastrozole, letrozole and for those patients in which aromatase inhibitors are not tolerated or are contraindicated, tamoxifen), over the model time horizon (30 years, lifetime). The Weibull distribution from the fixed-effects NMA was used to extrapolate OS and the generalised gamma distribution estimated from the fixed-effects NMA was used to extrapolate PFS in the base case analysis.

The results of fulvestrant when compared against the AIs (anastrozole and letrozole) and the results of fulvestrant when compared against tamoxifen (in those patients in which AIs are not tolerated or are contraindicated) separately.

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Pair-wise comparisons of fulvestrant versus anastrozole, letrozole and tamoxifen from the deterministic analysis are presented below.

Table 25: Incremental cost-effectiveness analysis results from the original submission and when PO25 is excluded from the NMA.

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Fulvestrant vs. anastrozole							
Including PO25							
Anastrozole	£30,261	3.736	2.676	-	-	-	-
Fulvestrant	£49,165	4.475	3.229	£18,904	0.739	0.553	£34,179
Excluding PO25							
Anastrozole	£30,564	3.736	2.676	-	-	-	-
Fulvestrant	£49,435	4.475	3.230	£18,872	0.739	0.553	£34,105
Fulvestrant vs. letrozole							
Including PO25							
Letrozole	£25,928	3.399	2.455	-	-	-	-
Fulvestrant	£49,165	4.475	3.229	£23,237	1.076	0.774	£30,025
Excluding PO25							
Letrozole	£30,544	3.736	2.676	-	-	-	-
Fulvestrant	£49,435	4.475	3.230	£18,891	0.739	0.553	£34,145
Fulvestrant vs. tamoxifen							
Including PO25							
Tamoxifen	£31,941	3.479	2.469	-	-	-	-
Fulvestrant	£49,165	4.475	3.229	£17,223	0.996	0.760	£22,655
Excluding PO25							
Tamoxifen	£32,326	3.479	2.469	-	-	-	-
Fulvestrant	£49,435	4.475	3.230	£17,109	0.996	0.761	£22,496

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

An incremental analysis of fulvestrant versus the AIs is presented in Table 26 and Table 27.

Table 26: Incremental analysis (including PO25- Table 77, page 184)

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Letrozole	£25,928	3.399	2.455	-	-	-	-
Anastrozole	£30,261	3.736	2.676	£4,333	0.337	0.221	£19,621
Fulvestrant	£49,165	4.475	3.229	£18,904	0.739	0.553	£34,179

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

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[Please note that a transcription error was noticed in table 77, page 184 of the submission. The incremental costs, LYG and QALYs for fulvestrant versus anastrozole presented were for the fulvestrant versus letrozole comparison; the values have been amended in Table 26 above; the ICER is not affected].

Table 27: Incremental analysis (excluding PO25)

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Letrozole	£30,544	3.736	2.676	-	-	-	-
Anastrozole	£30,564	3.736	2.676	£20	0.000	-0.0001	Dominated
Fulvestrant	£49,435	4.475	3.230	£18,872	0.739	0.553	£34,145

The removal of the PO25 trial appears to have a minimal impact upon the deterministic ICERs for fulvestrant versus anastrozole (a difference of £74) and fulvestrant versus tamoxifen (a difference of £159). In assuming equivalent efficacy between AIs, the ICER for letrozole increases from £30,025 to £34,145; this estimate is very similar to the base case ICER for fulvestrant versus anastrozole, £34,179, when the PO25 is included in the network of evidence.

As opposed to the base case incremental analysis with the inclusion of the PO25 trial, anastrozole is now dominated by letrozole, and the relevant comparison then becomes fulvestrant versus letrozole; the ICER for this comparison is £34,145.

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A14. Were participants allowed to cross over between trial arms in either FIRST or FALCON?

Neither FIRST (14) nor FALCON (12) were designed to formally allow crossover between trial arms.

A15. CS p. 67 states that concordance rates between local investigator and blinded independent review were high and similar between the two treatment arms "(88.4% [84/95] in the fulvestrant arm compared to 86.3% [82/95] in the anastrozole arm)". What do the numerator and denominator (the 84/95 and the 82/95) in this text represent?

The numerators in this text represent those patients for whom the assessments of the central reviewer agreed with the local investigator (i.e. 84 = 63 + 21 and 82 = 59 + 23). The denominators represent all patient records provided to the central reviewer (95 and 95). All data for these outcomes are provided in Table 28

Table 28: Cross-tabulation of clinical benefit assessments by local and independent investigators in FIRST (Table 11.2.13.2, FIRST CSR (6))

D6995C00006

Table 11.2.13.2 Cross-tabulation of clinical benefit assessed by BioImaging and AstraZeneca by randomised treatment group
Population=Full Analysis Set[a]

	Number (%) patients					
	Fulvestrant 500 mg n=95			Anastrozole 1 mg n=95		
	AZ Clinical Benefit	AZ No Clinical Benefit	Total	AZ Clinical Benefit	AZ No Clinical Benefit	Total
Bioimaging Clinical Benefit	63 (66.3)	3 (3.2)	66 (69.5)	59 (62.1)	4 (4.2)	63 (66.3)
Bioimaging No Clinical Benefit	8 (8.4)	21 (22.1)	29 (30.5)	9 (9.5)	23 (24.2)	32 (33.7)
Total	71 (74.7)	24 (25.3)	95 (100.0)	68 (71.6)	27 (28.4)	95 (100.0)

[a]Number of patients for whom central reviewer radiologically determined disease at baseline

AZ Clinical Benefit means clinical benefit, as defined by the study protocol and SAP, determined from investigator data with RECIST algorithm applied to it

BI Clinical Benefit is determined from overall visit responses and BOR determined by BioImaging with are then checked against the clinical benefit criteria in the SAP

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A16. CS Table 18 p.67 presents data that the ERG assumes is numbers of patients with percentages in brackets, is this correct? Additionally, in this table the clinical benefit definition includes stable disease ≥24 weeks (i.e. stable disease greater than or equal to 24 weeks). The ERG therefore presumes that the patients included in the no clinical benefit group are those with stable disease of less than 24 weeks duration (<24 weeks) and not less than or equal to 24 weeks (≤ 24 weeks) as indicated in the table. Please would the company confirm whether our understanding is correct or not.

We can confirm that the table presents numbers of patients with percentages in brackets [i.e. n(%)] and that patients included in the no clinical benefit group are those with stable disease of less than 24 weeks duration (<24 weeks). We apologise for the confusion.

A17. CS Subgroup analysis for Falcon p.78. Please clarify which of the subgroup analyses were prespecified as there are differences between the subgroups reported in CS, those reported in the published paper, and those specified in the CSR.

According to the Clinical Study Protocol (Refs 68 and 97 in the original submission), analysis of subgroups as defined by 6 covariates were planned (if numbers permitted):

- ER +ve and PgR +ve at baseline (no/yes)
- Metastatic disease at baseline (no/yes)
- Used bisphosphonates as concomitant medication at baseline (no/yes)
- Measurable disease at baseline (no/yes)
- Prior chemotherapy for locally advanced or metastatic breast cancer (yes versus no)
- Geographic region (geographic split to be defined in the SAP)

The subgroup analyses were planned to be performed on the primary endpoint; PFS only, using the stratified log-rank test. However, a number of changes to these planned analyses were incorporated into the Statistical Analysis Plan, which was finalised before unblinding, the most pertinent of which are:

- Inclusion of prior oestrogen containing HRT (yes/no)
- inclusion of more geographic regions
- inclusion of visceral disease (yes/no)
- expanded the bisphosphonate use at baseline subgroup to include denosumab use
- inclusion of subgroup analysis for OS
- Analysis method for PFS by subgroup changed to an unstratified log-rank test

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These changes are reflected in the complete CSR (7), the publication by Robertson et al, 2016 (12) and the original submission.

A18. CS section 4.10.2 p.100 Network meta-analysis results. The text states that fulvestrant and tamoxifen demonstrated statistically significant differences in the scale parameter. Please indicate how statistical significance was determined (e.g. is this due to non-overlapping credible intervals of the two treatments?).

Statistical significance was determined by assessing whether the confidence intervals for each parameter crossed 0. If the confidence interval did not contain 0, then the estimate of the difference was determined to be statistically significant.

A19. CS section 4.10.2 p.101 Network meta-analysis results. Please confirm that the upper and lower 95% limits presented in Tables 29 and 30 represent the bounds of the credible interval.

The network meta-analysis was performed under a frequentist framework, thus the upper and lower 95% limits presented in Tables 29 and 30 represent the limits of the confidence interval, not the credible interval.

Section B: Clarification on cost-effectiveness data

B1. **Priority Question.** CS Section 5.5 Cost and healthcare resource use identification, measurement and valuation (p. 163). Please comment on whether health care resources were collected for the FALCON trial. Where data are available, provide a summary of resource use for patients in the progression-free and progressed health states.

We can confirm that health care resource use data were not collected for the FALCON trial.

B2. CS p. 148 states that adverse events experienced by more than 2% of patients were included, however it seems adverse events with less than 2% have also been included (Table 49 and company model). Please comment on the reason for this discrepancy.

In Table 49 (p149 of the original submission), two adverse events show an incidence less than 2%: AST and bilirubin increased. The incidence of AST increased for tamoxifen should read 4.8%, this is correct in the model. Bilirubin increased should have been excluded due to incidence rates below 2% for all comparators.

B3. CS Table 49 p. 149. The ERG has two queries about adverse events in this table. Firstly, the literature (Finn 2016) reports the frequency of dyspnoea as 1.4% but CS (Table 49) and the company model report 0.5% for letrozole, please explain this difference. Secondly please clarify for 'AST increased' why in the CS (Table 49) the frequency for Tamoxifen is 1.6% but in the model the frequency is 4.8%.

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The discrepancy in the frequency of dyspnoea used in the submission document and model, and that reported in the literature, is due to differences in the reported percentage of patients in which the adverse events (AEs) occurred. The frequency of dyspnoea reported in Table 49 and used in the economic modelling, 0.5%, was initially sourced from an internal AZ document, which reported the frequency of AEs occurring in ≥15% of patients in the placebo + letrozole arm of the PALOMA-2 trial. The publication (15), reports the frequency of AEs occurring in at least 10% of patients in the placebo + letrozole arm. The frequency of dyspnoea as reported in Finn 2016 (15), 1.4%, should have been used in the model and reported in Table 49.

The reported frequency of AST increased for tamoxifen in Paridaens 2008 (1) is 4.8%; therefore, the value presented in the CS (Table 49, p149) is a transcription error; the value used in the model is correct.

B4. In CS p152, the health utility search was restricted to new publications from October 2013, 'the date the last NICE Technology Appraisal search was conducted'. Please clarify which NICE submission this refers to and explain why more recent NICE Technology Appraisals have not been considered.

This refers to the submission for trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane (TA 371). The submission for pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer (TA 424) is more recent; however, it was not yet published at the time the utility review was conducted. The systematic review of utility values conducted for the pertuzumab submission did not identify any further studies. TA421 (everolimus with exemestane for treating advanced breast cancer after endocrine therapy) and TA423 (eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens) were also published in December 2016, and neither have identified any additional studies that report health state utility values. A search of health-related quality-of-life (HRQoL) studies in the current, at the time of writing, ongoing TA for palbociclib in combination with an aromatase inhibitor, did not identify any studies published after 2013.

B5. CS Table 57 p. 162. The disutility for dyspnoea is cited to be derived from Lloyd et al. However, this parameter does not appear to be reported in this publication. Please clarify where this parameter has been derived from. Similarly the disutility for pleural effusion is cited to be derived from Swinburn et al (CS Table 57). However this parameter does not appear to be reported in this publication. Please clarify where this parameter has been derived from.

The source of the disutility for dyspnoea should be Doyle et al. (2008)(16). Regarding pleural effusion, your observation is correct. We seem to have carried over a mistake in TA306 as a disutility value could not be identified from Swinburn et al (pleural effusion potentially confused with PPE, palmar-plantar erythrodysesthesia or hand-foot syndrome). To our knowledge an alternative value for pleural effusion is not available as no other recent TAs in advanced breast cancer have included it.

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B6. CS Table 72 p.179. Please provide the NHS reference costs codes that have been used to calculate 'Pain, other'

The following NHS reference cost codes were used to calculate 'Pain, other':

Code	Description
AB11Z	Cognitive Behavioural Therapy as part of a Pain Management Programme
AB12Z	Insertion of Neurostimulator for Pain Management
AB13Z	Insertion of Intrathecal Drug Delivery Device for Pain Management
AB14Z	Insertion of Neurostimulator Electrodes for Pain Management
AB15Z	Radiofrequency Ablation or Cryoablation, for Pain Management
AB16Z	Denervation or Injection Around Spinal Facet, for Pain Management
AB17Z	Nerve Block or Destruction of Nerve, for Pain Management
AB18Z	Continuous Infusion of Therapeutic Substance for Pain Management
AB19Z	Injection of Therapeutic Substance into Joint for Pain Management
AB20Z	Epidural Under Image Control for Pain Management
AB21Z	Epidural or Therapeutic Spinal Puncture, for Pain Management
AB22Z	Trigger Point Injection for Pain Management
AB23Z	Acupuncture for Pain Management
EB12A	Unspecified Chest Pain with CC Score 11+
EB12B	Unspecified Chest Pain with CC Score 5-10
EB12C	Unspecified Chest Pain with CC Score 0-4
FZ90A	Abdominal Pain with Interventions
FZ90B	Abdominal Pain without Interventions
HC32G	Low Back Pain with Interventions
HC32H	Low Back Pain without Interventions, with CC Score 6+
HC32J	Low Back Pain without Interventions, with CC Score 3-5
HC32K	Low Back Pain without Interventions, with CC Score 0-2
WH08A	Unspecified Pain with CC Score 1+
WH08B	Unspecified Pain with CC Score 0

B7. CS Table 73 p. 180. The Shape and Scale parameter values for PFS reported in Table 73 of the CS do not seem to have been used within the model. The ERG notes that PFS parameters reported in "Surv_calcs" Sheet are derivable from CS Table 47. Please confirm that these values in Table 73 are not used in the model.

The Shape and Scale values for PFS reported in Table 73 are the result of a transcript error; the values shown represent the generalised gamma values for OS. The Generalised gamma values for PFS are presented in Table 29:

Table 29: Parameter values for the Generalised gamma function for PFS

Variable	Shape	Scale	Q
fulvestrant	[redacted]	[redacted]	[redacted]
anastrozole	[redacted]	[redacted]	
letrozole	[redacted]	[redacted]	

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tamoxifen	[redacted]	[redacted]	

The Shape and Scale values for PFS and OS for anastrozole reported in Table 73 (correct values presented in Table 29) are direct inputs in the model; these values are also reported in CS Table 47 and Table 48. The Shape and Scale values for PFS and OS for the other treatments considered in the analysis are derivable from CS Table 29 and Table 30, but are not direct inputs into the model.

B8. CS Table 79 and Table 80 p. 186. Please provide the references of the studies obtained from the systematic literature review which provide the data reported in column 3 of Table 79 and Table 80.

The references of the studies obtained from the systematic literature review which provide the data reported in column 3 of Table 79 and Table 80 are provided below. Please note that the estimates provided in the column 3 of Table 79 and 80 are based on calculated median values based on either patient-level data (PLD), as in the case of the FALCON, FIRST, North American and Target trials, or digitised Kaplan-Meier (KM) plots, as in the case of the PO25 trial.

Progression-free survival

Trial	Trial arm	Median (months) calculated using PLD or digitised KM plots	Median (months) reported in reference (ITT)	Reference
FALCON	Anastrozole	13.8	13.8	Robertson et al 2016 (12)
	Fulvestrant	16.6	16.6	
FIRST	Anastrozole	12.9	13.1	Robertson et al 2012(17)
	Fulvestrant	25.9	23.4	
PO25	Letrozole	9.6	9.4	Mouridsen et al 2001 (9)
	Tamoxifen	5.9	6.0	
NorthAmTarget	Anastrozole	14.8	8.5	Naboltz et al 2003 (11)
	Tamoxifen	10.4	7.0	

Overall survival

Trial	Trial arm	Median (months) calculated using PLD or	Median (months) reported in reference (ITT)	Reference

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		digitised KM plots		
FIRST	Anastrozole	46.5	48.4	Ellis et al 2015 (18)
	Fulvestrant	62.5	54.1	
PO25	Letrozole	34.0	34.0	Mouridsen et al 2003 (10)
	Tamoxifen	30.3	30.0	
NorthAmTarget	Anastrozole	44.9	39.0	Naboltz et al 2003 (11)
	Tamoxifen	43.6	40.0	

B9. CS Table 100 p.205. The base case results (ICERs) obtained from using the "All shapes model" and "No shape model" are the same in Table 100 whereas in the economic model, the results obtained are different. Please clarify the difference in the results reported in the CS and the model.

On page 96 of the CS, it is reported that due to the complexity in the interpretation of setting two of the three-parameter generalised gamma model equal, the generalised gamma distribution was not included in the 'no shape arm' models. In the base case analysis (using 'all shape' models), the generalised gamma distribution was used to model PFS; however, as this was not included in the 'no shape arm' models, the base case ICERs from the 'all shapes' models were presented. In hindsight, a note to this effect should have been included as a footnote, or "N/A" presented instead of results.

Please disregard any results when the 'no shape arm' models are used and generalised gamma distribution chosen for PFS. The results under this scenario are nonsensical, as 100% of patients start the model in the progressed disease health state.

Section C: Textual clarifications and additional points

C1. Please supply an abbreviations list for the CS.

ABC	Advanced Breast Cancer
AEs	Adverse Events
AIC	Akaike's Information Criterion
AI	Aromatase Inhibitor
ALT	Alanine aminotransferase
ANA	Anastrozole
AO	Anti-Oestrogen
ASCO	American Society of Clinical Oncology
AST	Aspartate Transaminase
BEV	Bevacizumab
BIC	Bayesian Information Criterion
BNF	British National Formulary

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BOR	Best Objective Response
CAP	Capecitabine
CB	Clinical Benefit
CBR	Clinical Benefit Rate
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMF	Cyclophosphamide, Methotrexate, 5-Fluoro-uracil
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
(E)DoCB	(Expected) Duration of Clinical Benefit
(E)DoR	(Expected) Duration of Response
EMA	European Medicines Agency
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D(-3L)	EuroQOL-5 Dimensions(-3 Level)
ER	Oestrogen receptor
ER+	Oestrogen receptor positive
ERG	Evidence Review Group
ESMO	European Society of Medical Oncology
EU	European Union
EVE	Everolimus
EXE	Exemestane
FACT-B	Functional Assessment of ChemoTherapy - Breast
FDA	Federal Drug Administration
FE	Fixed Effects
FSH	Follicle Stimulating Hormone
FUL	Fulvestrant
HER2	Human Epidermal growth factor Receptor 2
HER2+	Human Epidermal growth factor Receptor 2 positive
HR	Hazard ratio
HR+ve	Hormone Receptor positive
HRQL	Health-related quality of life
HRQoL	Health-related quality of life
HRT	Hormone Replacement Therapy

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ICER	Incremental cost-effectiveness ratio
IM	Intra-Muscular
ITT	Intention-To-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KOL	Key Opinion Leader
KM	Kaplan-Meier
LAP	Lapatinib
LET	Letrozole
LHRH	Luteinising Hormone
LYG	Life Year Gained
mBC/MBC	metastatic Breast Cancer
mg	milligrams
mITT	modified ITT
ml	Mililitres
MMRM	Mixed Models with Repeated Measurements
N/A	Not Applicable
NC	Not Calculable
NCCN	National Comprehensive Cancer Network
NE	Not Evaluable
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
ONS	Office of National Statistics
OR	Objective Response
OR	Odds Ratio
ORR	Objective Response Rate
OS	Overall survival
PCL	Placebo
pCODR	pan-Canadian Oncology Drug Review
PD	Progressive Disease
PFS	Progression-Free Survival
PgR	Progesterone receptor
PgR+	Progesterone receptor positive
PgR-	Progesterone receptor negative
PO	orally

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PP	Per Protocol
PR	Partial Response
PRO	Patient Reported Outcome
PS	Performance Status/Score
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of Life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SERD	Selective Oestrogen Receptor Degrader
SG	Standard Gamble
SLR	Systematic Litereature Review
SMC	Scottish Medicines Consortium
SoC	Standard of Care
TA	Technology Appraisal
TAM	Tamoxifen
TNBC	Triple Negative Breast Cancer
TOI	Trial Outcome Index
TRA	Trastuzumab emtansine
TTF	Time to Treatment Failure
TTP	Time To Progression
UK	United Kingdom
VAS	Visual Analogue Scale
WHO	World Health Organisation

C2. CS p. 33 - Please confirm whether or not the experts on the panel are associated with Astra Zeneca, and whether or not they worked on Fulvestrant clinical trials?

We can confirm that the experts (n=6) on the panel have attended advisory board meetings and worked for AstraZeneca in an advisory capacity only. None have been employed directly by AstraZeneca.

According to data on an independent database of clinical trials (Trial Trove available at https://pharmaintelligence.informa.com/products-and-services/data-and-analysis/trialtrove) of

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the six experts on the panel, 2 have been investigators on a clinical trial involving fulvestrant; SOFEA (19).

C3. CS p. 78 Section 4.8.2 states “As discussed previously in XXX, “please would the company confirm the section/page being cross referenced here.

The sections (and pages) referred to in this passage are: Section 4.3.2 (page 53) and Table 14: Study design of the FALCON and FIRST trials, in Section 4.3.3 (page 56).

C4. References 68 and 97 seem to be duplicates of the same Clinical Study Protocol (FALCON CSR). Figure 15 and Table 49 cite reference 68 and 97, respectively, but the corresponding references do not contain these results. Please confirm this discrepancy and provide the correct reference source.

This is correct. The Clinical Study Protocol was included in the reference pack in error for the Clinical Study Results. The correct document is provided here in the reference pack for this response document.

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Appendix

Please find below (Table 30) a summary of the base case results included in the submission and the results from the corrected model.

Table 30: Summary of results from corrected economic model.

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Fulvestrant vs. anastrozole							
Original results							
Anastrozole	£30,261	3.736	2.676	-	-	-	-
Fulvestrant	£49,165	4.475	3.229	£18,904	0.739	0.553	£34,179
Results using corrected model							
Anastrozole	£30,572	3.736	2.676	-	-	-	-
Fulvestrant	£49,431	4.475	3.229	£18,859	0.739	0.553	£34,099
Fulvestrant vs. letrozole							
Original results							
Letrozole	£25,928	3.399	2.455	-	-	-	-
Fulvestrant	£49,165	4.475	3.229	£23,237	1.076	0.774	£30,025
Results using corrected model							
Letrozole	£26,221	3.399	2.455	-	-	-	-
Fulvestrant	£49,431	4.475	3.229	£23,210	1.076	0.774	£29,991
Fulvestrant vs. tamoxifen							
Original results							
Tamoxifen	£31,941	3.479	2.469	-	-	-	-
Fulvestrant	£49,165	4.475	3.229	£17,223	0.996	0.760	£22,655
Results using corrected model							
Tamoxifen	£32,328	3.479	2.469	-	-	-	-
Fulvestrant	£49,431	4.475	3.229	£17,103	0.996	0.760	£22,498

Details of the cells affected and associated calculation amendments are presented in Table 31 below. Please note that only those cells highlighted in **bold** have an effect on the results.

Table 31: Cells affected by the errors identified in the model and the changes to calculations required

Worksheet	Cells affected	Amendment
Duration of subsequent treatments		
Country_Data	**H282**	=9.16*((365.25/7)/12)
Country_Data	**H283**	=6.1*((365.25/7)/12)
Country_Data	**H284**	=9.16*((365.25/7)/12)
Country_Data	**H285**	=6.17*((365.25/7)/12)

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Worksheet	Cells affected	Amendment
Country_Data	**H286**	=6.1*((365.25/7)/12)
Standard errors for subsequent treatment durations		
Country_Data	**I282**	=(6.2*((365.25/7)/12))/SQRT(113)
Country_Data	**I283**	=(7.5*((365.25/7)/12))/SQRT(68)
Country_Data	**I284**	=(6.2*((365.25/7)/12))/SQRT(113)
Country_Data	**I285**	=(7.9*((365.25/7)/12))/SQRT(49)
Country_Data	**I286**	=(4.4*((365.25/7)/12))/SQRT(62)
Country_Data	**H156**	0.05
Terminal care costs		
Cost_calcs	**H210:H537**	Drag down formula in H209
Cost_calcs	K210:K537	Drag down formula in K209
Cost_calcs	**S210:S537**	Drag down formula in S209
Cost_calcs	V210:V537	Drag down formula in V209
Cost_calcs	AG210:AG537	Drag down formula in AG209
Cost_calcs	AO210:AO537	Drag down formula in AO209
Cost_calcs	AR210:AR537	Drag down formula in AR209
Cost_calcs	**AZ210:AZ537**	Drag down formula in AZ209
Cost_calcs	BC210:BC537	Drag down formula in BC209
Cost_calcs	BK210:BK537	Drag down formula in BK209
Cost_calcs	BN210:BN537	Drag down formula in BN209
Cost_calcs	BV210:BV537	Drag down formula in BV209
Cost_calcs	BY210:BY537	Drag down formula in BY209
Cost_calcs	CG210:CG537	Drag down formula in CG209
Cost_calcs	CJ210:CJ537	Drag down formula in CJ209
Cost_calcs	CR210:CR537	Drag down formula in CR209
Cost_calcs	CU210:CU537	Drag down formula in CU209
Cost_calcs	DC210:DC537	Drag down formula in DC209
Cost_calcs	DF210:DF537	Drag down formula in DF209
Cost_calcs	DN210:DN537	Drag down formula in DN209
Cost_calcs	DQ210:DQ537	Drag down formula in DQ209

The following sections present more technically detailed tables of data from the updated analysis of the evidence network when the PO25 study is excluded. Complete analysis of the all shapes model is presented first, followed by the no shapes scenario.

Fixed effects NMA 'all shapes' model for PFS

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Table 32: Fixed-effects NMA for PFS ('all shapes')

PFS	NMA results ***including*** PO25 study						NMA results ***excluding*** PO25 study					
Wei	Scale			Shape			Scale			Shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ana	[redacted]											
	Difference in log scale			Difference in log shape			Difference in log scale			Difference in log shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ful	[redacted]											
Let	[redacted]						-	-	-	-	-	-
Tam	[redacted]											
Gom	Scale			Shape			Scale			Shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ana	[redacted]											
	Difference in log scale			Difference in log shape			Difference in log scale			Difference in log shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ful	[redacted]											
Let	[redacted]						-	-	-	-	-	-
Tam	[redacted]											
Log-L	Scale			Shape			Scale			Shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ana	[redacted]											
	Difference in log scale			Difference in log shape			Difference in log scale			Difference in log shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ful	[redacted]											
Let	[redacted]						-	-	-	-	-	-

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Tam	[redacted]											
LogN	Scale			Shape			Scale			Shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ana	[redacted]											
	Difference in log scale			Difference in log shape			Difference in log scale			Difference in log shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ful	[redacted]											
Let	[redacted]						-	-	-	-	-	-
Tam	[redacted]											
Gen-g	Scale			Shape			Scale			Shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ana	[redacted]											
	Difference in log scale			Difference in log shape			Difference in log scale			Difference in log shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ful	[redacted]											
Let	[redacted]						-	-	-	-	-	-
Tam	[redacted]											
	Est.	L95%	U95%	-	-	-	Est.	L95%	U95%	-	-	-
Q	[redacted]			-	-	-				-	-	-

Abbreviations: Ana, anastrozole; Est, estimate; Ful, fulvestrant; Gen-g, generalised gamma; Gom; Gompertz; L, lower; Let, letrozole; Log-L, loglogistic; LogN, lognormal; NMA, network meta-analysis; Tam, tamoxifen.

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Table 33: Time in PFS (mean and median [months]), undiscounted; Weibull

Treatment	Results ***including*** PO25 trial		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	17.48	24.09	17.48	24.09
Anastrozole	12.88	17.69	12.88	17.69
Letrozole	15.64	19.57	12.88	17.69
Tamoxifen	10.12	13.16	10.12	13.16

Table 34: Time in PFS (mean and median [months]), undiscounted; Gompertz

Treatment	Results ***including*** PO25 trial		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	17.48	21.93	17.48	21.93
Anastrozole	12.88	17.50	12.88	17.51
Letrozole	16.56	20.88	12.88	17.51
Tamoxifen	10.12	13.98	10.12	13.98

Table 35: Time in PFS (mean and median [months]), undiscounted; log-logistic

Treatment	Results ***including*** PO25 trial		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	16.56	35.73	16.56	35.74
Anastrozole	11.96	23.58	11.96	23.58
Letrozole	13.80	25.45	11.96	23.58
Tamoxifen	8.28	14.95	8.28	14.95

Table 36: Time in PFS (mean and median [months]), undiscounted; lognormal

Treatment	Results ***including*** PO25 trial		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	16.56	33.82	16.56	33.82
Anastrozole	11.96	21.11	11.96	21.11
Letrozole	14.72	25.21	11.96	21.11
Tamoxifen	8.28	13.57	8.28	13.57

Table 37: Time in PFS (mean and median [months]), undiscounted; generalised gamma

Treatment	Results ***including*** PO25 trial		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	16.56	29.58	16.56	29.63
Anastrozole	11.96	19.56	11.96	19.58
Letrozole	14.72	22.16	11.96	19.58
Tamoxifen	9.20	13.16	9.20	13.17

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Fixed effects NMA 'all shapes' model for OS

Table 38: Fixed-effects NMA for OS ('all shapes')

OS	NMA results ***including*** PO25 study						NMA results ***excluding*** PO25 study					
Wei	Scale			Shape			Scale			Shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ana	[redacted]											
	Difference in log scale			Difference in log shape			Difference in log scale			Difference in log shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ful	[redacted]											
Let	[redacted]						-	-	-	-	-	-
Tam	[redacted]											
Gom	Scale			Shape			Scale			Shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ana	[redacted]											
	Difference in log scale			Difference in log shape			Difference in log scale			Difference in log shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ful	[redacted]											
Let	[redacted]						-	-	-	-	-	-
Tam	[redacted]											
Log-L	Scale			Shape			Scale			Shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ana	[redacted]											
	Difference in log scale			Difference in log shape			Difference in log scale			Difference in log shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%

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Ful	[redacted]						[redacted]					
Let	[redacted]						-	-	-	-	-	-
Tam	[redacted]						[redacted]					
LogN	Scale			Shape			Scale			Shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ana	[redacted]						[redacted]					
	Difference in log scale			Difference in log shape			Difference in log scale			Difference in log shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ful	[redacted]						[redacted]					
Let	[redacted]						-	-	-	-	-	-
Tam	[redacted]						[redacted]					
Gen-g	Scale			Shape			Scale			Shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ana	[redacted]						[redacted]					
	Difference in log scale			Difference in log shape			Difference in log scale			Difference in log shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ful	[redacted]						[redacted]					
Let	[redacted]						-	-	-	-	-	-
Tam	[redacted]						[redacted]					
	Est.	L95%	U95%	-	-	-	Est.	L95%	U95%	-	-	-
Q	[redacted]			-	-	-	[redacted]			-	-	-

Abbreviations: Ana, anastrozole; Est, estimate; Ful, fulvestrant; Gen-g, generalised gamma; Gom; Gompertz; L, lower; Let, letrozole; Log-L, loglogistic; LogN, lognormal; NMA, network meta-analysis; Tam, tamoxifen.

[Please note that a transcription error was noticed in table 30, page 105 of the submission. The Q parameter estimate and the lower and upper confidence interval were a copy of the fulvestrant difference in log scale results; the values have been amended in the table above; the values used in the model are correct].

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Table 39: Time in OS (mean and median [months]), undiscounted; Weibull

Treatment	Results ***including*** PO25 trial		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	47.84	60.08	47.84	60.09
Anastrozole	39.56	48.95	39.56	48.95
Letrozole	38.64	43.42	39.56	48.95
Tamoxifen	36.80	45.05	36.80	45.05

Table 40: Time in OS (mean and median [months]), undiscounted; Gompertz

Treatment	Results ***including*** PO25 trial		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	40.48	46.05	40.48	46.09
Anastrozole	38.64	41.47	38.64	41.47
Letrozole	57.03	58.26	38.64	41.47
Tamoxifen	42.32	44.64	42.32	44.63

Table 41: Time in OS (mean and median [months]), undiscounted; log-logistic

Treatment	Results ***including*** PO25 trial		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	50.60	87.82	50.60	87.81
Anastrozole	41.40	76.13	41.40	76.11
Letrozole	44.16	66.93	41.40	76.11
Tamoxifen	39.56	71.14	39.56	71.11

Table 42: Time in OS (mean and median [months]), undiscounted; lognormal

Treatment	Results ***including*** PO25 trial		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	56.11	100.42	56.11	100.42
Anastrozole	46.00	88.46	46.00	88.46
Letrozole	47.84	83.93	46.00	88.46
Tamoxifen	43.24	84.03	43.24	84.03

Table 43: Time in OS (mean and median [months]), undiscounted; generalised gamma

Treatment	Results ***including*** PO25 trial		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	48.76	63.65	46.92	57.42
Anastrozole	39.56	51.83	38.64	46.70
Letrozole	40.48	45.05	38.64	46.70
Tamoxifen	37.72	47.44	36.80	42.96

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Fixed effects NMA 'no shapes' model for PFS

Please note that Table 127 (CS page 258) and Table 128 (CS page 261) have estimates included of difference in log shape for the comparator treatments. This is incorrect as the model holds the shape parameter constant. The estimates of difference in log scale in the CS are correct. The NMA results including PO25 study below are a replication of the results presented in the CS, and represent how the table should have looked in the CS.

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Table 44: Fixed-effects NMA ('no shape arm') models for progression-free survival

PFS	NMA results ***including*** PO25 study						NMA results ***excluding*** PO25 study					
Wei	Scale			Shape			Scale			Shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ana	[redacted]											
	Difference in log scale			Difference in log shape			Difference in log scale			Difference in log shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ful	[redacted]			-	-	-	[redacted]			-	-	-
Let	[redacted]			-	-	-	-	-	-	-	-	-
Tam	[redacted]			-	-	-	[redacted]			-	-	-
Gom	Scale			Shape			Scale			Shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ana	[redacted]											
	Difference in log scale			Difference in log shape			Difference in log scale			Difference in log shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ful	[redacted]			-	-	-	[redacted]			-	-	-
Let	[redacted]			-	-	-	-	-	-	-	-	-
Tam	[redacted]			-	-	-	[redacted]			-	-	-
Log-L	Scale			Shape			Scale			Shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ana	[redacted]											
	Difference in log scale			Difference in log shape			Difference in log scale			Difference in log shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%

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Ful	[redacted]			-	-	-	[redacted]			-	-	-
Let	[redacted]			-	-	-	-	-	-	-	-	-
Tam	[redacted]			-	-	-	[redacted]			-	-	-
LogN	Scale			Shape			Scale			Shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ana	[redacted]			[redacted]			[redacted]			[redacted]		
	Difference in log scale			Difference in log shape			Difference in log scale			Difference in log shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ful	[redacted]			-	-	-	[redacted]			-	-	-
Let	[redacted]			-	-	-	-	-	-	-	-	-
Tam	[redacted]			-	-	-	[redacted]			-	-	-

Abbreviations: Ana, anastrozole; Est, estimate; Ful, fulvestrant; Gom; Gompertz; L, lower; Let, letrozole; Log-L, loglogistic; LogN, lognormal; NMA, network meta-analysis; Tam, tamoxifen.

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Table 45: Time in PFS (mean and median [months]), undiscounted; Weibull

Treatment	Results ***including*** PO25 trial		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	17.48	23.66	17.48	23.66
Anastrozole	12.88	17.77	12.88	17.77
Letrozole	14.72	20.29	12.88	17.77
Tamoxifen	10.12	13.68	10.12	13.68

Table 46: Time in PFS (mean and median [months]), undiscounted; Gompertz

Treatment	Results ***including*** PO25 trial		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	17.48	23.05	17.48	23.05
Anastrozole	12.88	17.60	12.88	17.60
Letrozole	14.72	19.40	12.88	17.60
Tamoxifen	9.20	13.69	9.20	13.69

Table 47:Time in PFS (mean and median [months]), undiscounted; log-logistic

Treatment	Results ***including*** PO25 trial		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	16.56	32.75	16.56	32.76
Anastrozole	11.96	25.16	11.96	25.16
Letrozole	14.72	29.18	11.96	25.16
Tamoxifen	9.20	19.93	9.20	19.93

Table 48:Time in PFS (mean and median [months]), undiscounted; lognormal

Treatment	Results ***including*** PO25 trial		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	15.64	29.75	15.64	29.75
Anastrozole	11.96	23.22	11.96	23.22
Letrozole	14.72	27.60	11.96	23.22
Tamoxifen	9.20	18.95	9.20	18.95

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Table 49: Fixed effects NMA 'no shapes' model for OS for a network including or excluding PO25

OS	NMA results ***including*** PO25 study						NMA results ***excluding*** PO25 study					
Wei	Scale			Shape			Scale			Shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ana	[redacted]											
	Difference in log scale			Difference in log shape			Difference in log scale			Difference in log shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ful	[redacted]			-	-	-	[redacted]			-	-	-
Let	[redacted]			-	-	-	-	-	-	-	-	-
Tam	[redacted]			-	-	-	[redacted]			-	-	-
Gom	Scale			Shape			Scale			Shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ana	[redacted]											
	Difference in log scale			Difference in log shape			Difference in log scale			Difference in log shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ful	[redacted]			-	-	-	[redacted]			-	-	-
Let	[redacted]			-	-	-	-	-	-	-	-	-
Tam	[redacted]			-	-	-	[redacted]			-	-	-
Log-L	Scale			Shape			Scale			Shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ana	[redacted]											
	Difference in log scale			Difference in log shape			Difference in log scale			Difference in log shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%

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Ful	[redacted]	[redacted]	[redacted]	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-
Let	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-	-	-	-
Tam	[redacted]	[redacted]	[redacted]	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-
LogN	Scale			Shape			Scale			Shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ana	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in log scale			Difference in log shape			Difference in log scale			Difference in log shape		
	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%	Est.	L95%	U95%
Ful	[redacted]	[redacted]	[redacted]	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-
Let	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-	-	-	-
Tam	[redacted]	[redacted]	[redacted]	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-

Abbreviations: Ana, anastrozole; Est, estimate; Ful, fulvestrant; Gom; Gompertz; L, lower; Let, letrozole; Log-L, loglogistic; LogN, lognormal; NMA, network meta-analysis; Tam, tamoxifen.

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Table 50: Time in OS (mean and median [months]), undiscounted; Weibull

Treatment	Results ***including*** PO25 trial		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	47.84	59.80	47.84	59.80
Anastrozole	39.56	49.01	39.56	49.01
Letrozole	38.64	48.97	39.56	49.01
Tamoxifen	36.80	46.61	36.80	46.61

Table 51: Time in OS (mean and median [months]), undiscounted; Gompertz

Treatment	Results ***including*** PO25 trial		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	46.00	48.20	46.00	48.21
Anastrozole	38.64	41.52	38.64	41.53
Letrozole	37.72	41.31	38.64	41.53
Tamoxifen	36.80	40.00	36.80	40.00

Table 52: Time in OS (mean and median [months]), undiscounted; log-logistic

Treatment	Results ***including*** PO25 trial		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	50.60	88.14	50.60	88.15
Anastrozole	41.40	75.93	41.40	75.94
Letrozole	46.92	83.22	41.40	75.94
Tamoxifen	40.48	74.17	40.48	74.18

Table 53: Time in OS (mean and median [months]), undiscounted; lognormal

Treatment	Results ***including*** PO25 trial		Results ***excluding*** PO25 trial	
	Median	Mean	Median	Mean
Fulvestrant	57.95	103.23	57.95	103.23
Anastrozole	45.08	86.55	45.08	86.55
Letrozole	50.60	94.52	45.08	86.55
Tamoxifen	43.24	83.62	43.24	83.62

Incremental cost-effectiveness results using fixed-effects NMA for PFS and OS ('no shape arm') in which the PO25 trial is removed from both networks are presented below.

Total costs, life years gained (LYG), QALYs and incremental cost per QALY that patients would experience whilst on either the intervention treatment (fulvestrant 500 mg), or the comparator treatments (anastrozole, letrozole and for those patients in which aromatase inhibitors are not tolerated or are contraindicated, tamoxifen), over the model time horizon

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(30 years, lifetime). The Weibull distribution from the fixed-effects NMA was used to extrapolate OS and PFS in the base case analysis.

The results of fulvestrant when compared against the AIs (anastrozole and letrozole) and the results of fulvestrant when compared against tamoxifen (in those patients in which AIs are not tolerated or are contraindicated) separately.

Pair-wise comparisons of fulvestrant versus anastrozole, letrozole and tamoxifen from the deterministic analysis are presented below.

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Fulvestrant vs. anastrozole							
Anastrozole	£31,344	3.739	2.671	-	-	-	-
Fulvestrant	£49,081	4.461	3.198	£17,737	0.722	0.526	£33,710
Fulvestrant vs. letrozole							
Letrozole	£31,323	3.739	2.672	-	-	-	-
Fulvestrant	£49,081	4.461	3.198	£17,758	0.722	0.526	£33,756
Fulvestrant vs. tamoxifen							
Tamoxifen	£32,558	3.574	2.538	-	-	-	-
Fulvestrant	£49,081	4.461	3.198	£16,522	0.887	0.660	£25,036

An incremental analysis of fulvestrant versus the AIs is presented below.

Incremental analysis

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Letrozole	£31,323	3.739	2.672	-	-	-	-
Anastrozole	£31,344	3.739	2.671	£21	0.000	-0.0001	Dominated
Fulvestrant	£49,081	4.461	3.198	£17,737	0.722	0.526	£33,756

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

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Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Procedure note and summary page for the technology appraisal of fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer [ID951]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation:
Are you (tick all that apply):ASSOCIATION OF BREAST SURGERY

- a specialist in the treatment of people with the condition for which NICE is considering this technology? X
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Procedure note and summary page for the technology appraisal of fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer [ID951]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Currently post-menopausal patients with either locally advanced breast cancer or metastatic breast cancer are treated with an aromatase inhibitor (AI's). Randomised trials have shown that AI's are more effective than Tamoxifen in this situation.

There is a problem with compliance in patients taking oral medication, we know that in the adjuvant setting up to 25% of patients prescribed oral endocrine therapy do not take it. An IM injection may well be more acceptable to many patients.

There are also patients who are unable to tolerate oral medication in tablet form and again an IM preparation will ensure that the drug can be administered.

This drug would be prescribed and the disease monitored in the secondary care setting however the IM injection could be administered in the primary care setting by a district nurse or at the GP surgery.

Comprehensive Cancer Network. NCCN Clinical Practice

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Procedure note and summary page for the technology appraisal of fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer [ID951]

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The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of

life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

As this drug is not yet licensed for LABC or metastatic breast cancer it is not frequently used at present. When it has been used for patients who cannot tolerate oral medication there have not been any adverse events which have not come to light in clinical trials.

There are newer endocrine drugs the cyclin-dependent 4 and 6 which are being trialed in this situation but they appear to be associated with adverse effects which lead to a permanent discontinuation of the treatment. These newer are drugs are also significantly more expensive.

In the FALCON study discontinuation was the same in both arms of the trial and the toxicity profile was similar in both groups. There is no increased or added toxicity with fulvestrant compared to Anastrozole,

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Procedure note and summary page for the technology appraisal of fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer [ID951]

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

No extra resource would be needed. The IM injection could be administered in either primary or secondary care.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

This medication as it is IM as opposed to oral may be easier for people protected by equality legislation to take.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Procedure note and summary page for the technology appraisal of fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer [ID951]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer [ID951]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. *About you and your organisation*

Your name:

Name of your organisation: Breast Cancer Care

Your position in the organisation: Policy Manager

Brief description of the organisation:

Breast Cancer Care is the only specialist UK-wide charity providing support for women, men, families and friends affected by breast cancer.

Our free services include support over the phone with a nurse or someone who's been there, our welcoming online forums, reliable information and local group support.

Every day, our care, support and information help thousands of people to find a way to live with, through and beyond breast cancer.

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None to declare

2. *Living with the condition*

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Breast Cancer Care offers supports people living with or affected by metastatic breast cancer. We hear from many people about their experiences of living with the condition, as well as their hopes for new treatments.

Uncertainty is a key element of living with metastatic breast cancer. On average, people live with the disease for two to three years after diagnosis. However, this can vary considerably from person to person, with some only living for months after their diagnosis, while others live for many years longer. As a result, many people tell us that they live from "scan to scan", and feel unable to plan their lives in any long-term way. Many are keen to reach a

personal milestone, such as seeing their child go to secondary school, or attending a family wedding.

The physical impact of metastatic breast cancer differs greatly, depending on where a person's breast cancer has spread (for example, the lungs or brain), the extent of this progression, and treatment received. Broadly, physical effects include: pain, fatigue, nausea, poor appetite, and sleep difficulties.

However, if these symptoms and side effects can be managed successfully, metastatic breast cancer can become more like a chronic condition, with people experiencing a good quality of life for some time.

One person living with metastatic (also known as secondary) breast cancer told us:

"My diagnosis of secondary breast cancer has changed my life in so many ways. I live in pain despite being on morphine constantly. I live with the fear of my death. I live knowing that I will not be able to see my son grow to adulthood. I live knowing he will have no parent to help him in his life. I live knowing that my life is a series of treatments, scans, appointments.

"I know that in the near future my career will be taken from me as the pain and treatments, fatigue and side effects take a grip. Cancer frightens other people: they don't know what to say; they don't know how they can help. My friends disappeared. My family also disappeared. I have had to keep my fears to myself: how can I tell anyone the truth and reality of living with incurable breast cancer? I have gone from being the person that was there to help other people, to being an ill, disabled person; a condition, a diagnosis."

3. *Current practice in treating the condition*

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Treatment outcomes and expectations will vary for each individual according to their own personal circumstances, goals and priorities.

However, in general, we know what people living with metastatic breast cancer place a high value on treatments which provide them with valuable additional months or years. One person living with metastatic breast cancer told us that they value:

"... maximum life expectancy and time with loved ones. Some people I know have young children, and are desperate to extend their time, even if it only gives 6 months extra."

We also know from speaking with people living with the disease that living well is often preferable to treatments which are effective but have significant side effects that impact on everyday quality of life. A good quality of life is important. Treatments which have few or manageable side effects allow

people to continue with their day-to-day activities as much as possible, be that going to work, parenting and social responsibilities and activities.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

People with hormone receptor positive metastatic breast cancer face limited treatment options. Current treatment options for this patient group include hormone treatments including aromatase inhibitors, and chemotherapy.

Aromatase inhibitors provide an alternative or additional option to chemotherapy. Where applicable, it may be preferable for many people, helping to defer the use of chemotherapy and its side effects which often impact heavily on quality of life.

Chemotherapy may be used in cases where the use of hormone therapy is clinically unsuitable, or when it has become ineffective. However, chemotherapy has increased side effects and requires frequent trips to hospital to receive treatment.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Fulvestrant offers people with a diagnosis of metastatic breast cancer a valuable additional first-line treatment option.

The FALCON phase III trial showed a median progression-free survival (PFS) of 16.6 months for fulvestrant, compared with 13.8 months for the comparator anastrozole.

This extension in PFS means that other treatments such as chemotherapy, which have greater side effects, can be delayed for longer.

Fulvestrant can allow people to live with a good quality of life for longer, meaning that they may be able to continue with their day-to-day activities as much as possible, such as going to work or caring for their family.

For people living with metastatic breast cancer, this additional time is unquestionably invaluable.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

As mentioned above, the potential for an extended period of PFS with a good quality of life means that fulvestrant could be an additional first-line option, in addition to aromatase inhibitors such as anastrozole. Postponing or avoiding the need for chemotherapy is also a significant benefit.

In terms of administration method, fulvestrant is given via intramuscular injections. For some patients, this may be preferable to other treatments which are administered orally. This may be the case for people who struggle to remember to take a tablet at regular intervals, or prefer the convenience and routine of attending treatment at hospital or in a primary care setting.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

None that we are aware of

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)

- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

People living with metastatic breast cancer have limited treatment options, and have concerns about the future availability of new treatments on the NHS.

The current uncertainty around the future availability of CDF funded drugs, plus planned changes to the system in England (such as the proposed £20 million Budget Impact Test), add to the feeling of uncertainty felt by people living with metastatic breast cancer.

Please list any concerns patients or carers have about the treatment being appraised.

Many people treated with fulvestrant experience only mild side effects, which are tolerable. These include nausea and hot flushes.

Some people may find the method of administration problematic, preferring the tablet form of aromatase inhibitors such as anastrozole. Additionally, fulvestrant would require more frequent trips to hospital or primary care for the injections, which may be a disadvantage of the treatment for some people.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None that we are aware of

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Not that we are aware of

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Not that we are aware of

7. *Research evidence on patient or carer views of the treatment*

Is your organisation familiar with the published research literature for the treatment?

X Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Breast Cancer Care speaks with many women who are on/have received fulvestrant who tolerate it well.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

FALCON captured outcomes for progression-free survival, which is highly valued by people with a diagnosis of metastatic breast cancer.

The secondary endpoints included overall survival and health-related quality of life, which are also important to patients.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not that we are aware of

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes X No

If yes, please provide references to the relevant studies.

8. *Equality*

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership;

being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Not that we are aware

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Not that we are aware

9. *Other issues*

Do you consider the treatment to be innovative?

☐ Yes X No

If yes, please explain what makes it significantly different from other treatments for the condition.

Are there any other issues that you would like the Appraisal Committee to consider?

10. *Key messages*

In no more than 5 bullet points, please summarise the key messages of your submission.

- Fulvestrant provides a valuable additional treatment option for people with metastatic breast cancer

- The FALCON phase III trial showed a median progression-free survival (PFS) of 16.6 months for fulvestrant, compared with 13.8 months for the comparator anastrozole.

- Fulvestrant is well tolerated by patients, with many reporting few if any side effects

- Some people may prefer the convenience of having an injection of fulvestrant over taking tablets.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Fulvestrant for untreated hormone-receptor positive metastatic breast cancer [ID951]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Breast Cancer Now

Your position in the organisation: [redacted]

Brief description of the organisation: Breast Cancer Now is the UK's largest breast cancer charity, dedicated to funding ground-breaking research into the disease. Our ambition is that by 2050, everyone who develops breast cancer will live. We're bringing together all those affected by the disease to improve the way we prevent, detect, treat and stop breast cancer. And we're committed to working with the NHS and governments across the UK to ensure that breast cancer services are as good as they can be, and that breast cancer patients benefit from advances in research as quickly as possible.

This submission reflects the views of Breast Cancer Now, based on our experience of working with people who are affected by breast cancer. We know that access to effective drugs is hugely important to our supporters and that quality of life is valued just as much as length of life.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Metastatic breast cancer is when cancer originating in the breast has spread to other parts of the body; most commonly the lungs, brain, bones and liver. There is no cure for metastatic breast cancer, so most medicines aim to extend the length of life and to improve quality of life for patients. A patient can be diagnosed with metastatic (stage 4) cancer initially, or they can develop the condition years after treatment for their primary breast cancer has ended.

Living with metastatic breast cancer is difficult to come to terms with for both patients and family. Patients' time is limited and the treatments usually have some side effects. Patients' tell us that quality of life is just as important

to take into account as length of life, as this means that they would be able to spend quality time with their loved ones.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

A recent diagnosis of metastatic breast cancer will come as a shock to most patients and their families, as it is a terminal condition with a short life expectancy. Patients are keen to find treatments that will halt progression and extend life for as long as possible. The vast majority of recently-diagnosed patients would feel it is important to start treatment quickly to get their disease under control. The type and severity of side effects experienced is also important for patients as these could impact negatively on their quality of life. Quality time with their loved ones will be a key objective in their treatment.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Patients whose cancer is hormone receptor positive are usually offered aromatase inhibitors to control a new diagnosis of advanced disease. Aromatase inhibitors are generally tolerated well by patients, but some patients will experience strong menopausal side effects, such as night sweats. Patients will continue on aromatase inhibitors until their disease progresses, indicating that their cancer has become resistant to the treatment. There are three aromatase inhibitors currently offered to this group of patients in England – anastrozole, letrozole and exemestane. Whether patients will be able to move from one aromatase inhibitor to another, once they progress, will depend on their particular cancer and also on how well they tolerate the side effects of a particular drug. Once patients progress on an aromatase inhibitor, the next step after progression would be systemic (non-targeted) chemotherapies, which are associated with serious side effects.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

The 2017 Cochrane Review of fulvestrant for hormone sensitive metastatic breast cancer used a pooled analysis of nine clinical trials of fulvestrant from before July 2015. This included four in a first-line setting and five in a second-line setting. However, there was no difference in results between the different settings. The study shows that fulvestrant is at least as effective and safe as three other standard endocrine therapies used in the treatment of advanced hormone-sensitive breast cancer. It also concluded that at a higher dose of 500mg, which was used in only one of the nine trials, fulvestrant may be more effective than other therapies.

More recent evidence also suggests that fulvestrant is more effective than anastrazole at the new standard fulvestrant dose of 500mg. The phase III trial FALCON is a progression of the phase II FIRST trial, which was one of the nine trials analysed in the Cochrane study, using the higher dose of 500mg. This trial shows the PFS was significantly longer for patients in the fulvestrant group by 2.8 months than patients in the anastrozole group. Delaying progression of the disease is important for patients as it provides quality time to spend with friends and family. Overall survival data has not yet been reported from FALCON.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

As this treatment has been proved at least as effective and safe as other treatments for this type of metastatic breast cancer, it adds to the options available for patients. Use of fulvestrant could delay the need to start on systemic (non-targeted) chemotherapies, which are traditionally associated with more severe side effects and a poorer quality of life for patients.

The more recent evidence from the FALCON III trial showing that fulvestrant is more effective than anastrazole at the 500mg dose at delaying disease progression is also an advantage over other NHS treatments. Delaying progression means more quality time with family and loved ones. Delay can also have benefits for the mental health of patients, as lack of progression indicates that the medicine is working. A longer time to progression may mean that the patient is able to lead a more or less normal daily life throughout this time. Lack of progression of a metastatic cancer is also likely to bring some comfort to relatives and friends of the patient, as this is the best possible outcome for a terminal illness.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

Not that we are aware of.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)

- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

The current treatments available on the NHS are aromatase inhibitors. These are quite effective in controlling advanced hormone positive breast cancer. However, all patients will eventually progress on this treatment, after which point patients will only have the option of taking traditional chemotherapies to control their disease. Since traditional chemotherapies are generally associated with severe side effects and usually have a negative impact on quality of life for patients, patients generally prefer to delay this stage of treatment for as long as possible.

Please list any concerns patients or carers have about the treatment being appraised.

Similar side effects exist for fulvestrant and aromatase inhibitors. Each patient's situation will be different and this will impact on their willingness and ability to take fulvestrant. However, as long as all the side effects are clearly discussed with the patient, they will be able to make their own choice as to the level of risk they will be willing to take on.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

We are not aware of any particular differences of opinion between patients or carers for this treatment but we do know that patients will have different approaches and attitudes to the levels of risk they are happy to undertake. It is therefore important that the side effects of this drug are clearly discussed with the patient so that they can make an informed decision about whether this treatment is suitable for them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

This treatment has been tested in post-menopausal people with locally advanced or metastatic hormone receptor-positive breast cancer. This

treatment could benefit a significant proportion of the metastatic breast cancer population. Hormone positive breast cancer is the most common type of breast cancer making up around 80% of all breast cancer patients.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Not that we are aware of.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☒ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Yes, as far as we are aware.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Yes, to the best of our knowledge.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not to the best of our knowledge.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☒ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Not that we are aware of.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Not that we are aware of.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Are there any other issues that you would like the Appraisal Committee to consider?

Not that we are aware of.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of

your submission.

- Fulvestrant could benefit a large proportion of the advanced breast cancer population. Hormone positive breast cancer is the most common type of breast cancer making up around 80% of all breast cancer patients.
- Evidence shows that fulvestrant is at least as effective and safe as other endocrine therapies used in the treatment of advanced hormone positive breast cancer on the NHS.
- This treatment adds to the drug options available for patients with this type of metastatic breast cancer. Use of fulvestrant could delay the need to start on systemic (non-targeted) chemotherapies, which are traditionally associated with more severe side effects and a poorer quality of life for patients
- More recent evidence shows that fulvestrant is more effective than anastrazole at a new standard dose of 500mg at delaying disease progression. PFS was 2.8 months longer than anastrazole. Delaying progression means more quality time with family and loved ones.

NHS England submission into the NICE appraisal of fulvestrant in hormone-naïve advanced/metastatic breast cancer August 2017

1. Fulvestrant is given as two deep intramuscular injections (one in each buttock) once every month after the first month of treatment (this first month has an extra loading dose of drug). Its current use is mainly as a 3rd/4th line of hormone treatment in the palliation of advanced breast cancer. Such use is variable across England: despite the negative NICE recommendation in this setting, it has been used historically in some areas. Most patients cope with the two painful injections, one reason for this being that currently fulvestrant is often viewed as a potential way of delaying chemotherapy with its associated side-effects.
2. The fulvestrant vs anastrazole double blind study in endocrine-naïve hormone-receptor positive patients with advanced breast cancer demonstrates a modest increase in progression free survival. This comes at the expense of some increase in side-effects and a significant increase in discomfort (the injections) and inconvenience (monthly visits).
3. Patients value greater efficacy in the palliation of their breast cancer but they also take note of alternative treatment options and the consequences of all the treatment options in terms of the impact of such treatments on their lives.
4. Fulvestrant is a hormone medication for the treatment of breast cancer and is not considered to meet the definition of a supportive drug or an intrinsic part of a chemotherapy regimen. It is thus not commissioned by Specialised Commissioning in NHS England (unlike all cytotoxic chemotherapy, -inibs and –mabs used in the systemic therapy of cancer).
5. Fulvestrant (like anastrazole, letrozole, exemestane and tamoxifen) is commissioned by CCGs. Nearly all of these oral hormone agents are prescribed by GPs. The first month of treatment after diagnosis may be started by the hospital but GPs continue further prescriptions.
6. As these drugs are not excluded from national tariff (as chemotherapy is), any hormonal breast cancer treatment prescribed and delivered by a hospital Trust is paid for with a single tariff payment which covers the cost of any hormonal treatment of breast cancer. CCGs pay for this tariff, the size of the payment attached to the national tariff being a balance of the cost and dispensing of all the hormone drugs in that tariff based on reference costs: from inexpensive generic drugs (eg tamoxifen, anastrazole) to much more costly ones (eg fulvestrant).
7. The tariff payment is much less than the list price of the two injections of fulvestrant. Hospitals thus gain financially from the use of the tariff when a cheap oral generic is used (but GPs then take on the responsibility for such prescriptions) but lose financially when they supply fulvestrant.
8. As a consequence of the tariff mechanism and payment, hospitals do not wish to prescribe fulvestrant as they have to fund the difference between the cost of the drug to them and the tariff payment.
9. The tariff system can adapt to incorporate price changes over time but does this over 2-3 year periods in order to be sure of more permanent changes to clinical practice but also to see the stability of the relevant pricings of the constituent drugs. The tariff system is wary too of introducing perverse incentives for hospitals and thus is cautious in terms of change.

10. For any confidential pricing arrangement which deviates from the list price for a drug prescribed by GPs, the drug has to be traded at list price and a rebate back to the CCG applied via a confidential arrangement with the CCG. Astra Zeneca would have to make such confidential agreements with all CCGs in England.
11. The Cancer Drugs Fund only admits cancer drugs excluded from tariff and funded by Specialised Commissioning and so there can be no consideration of fulvestrant for the CDF.
12. In summary, fulvestrant as 1st line hormonal treatment for women with hormone-receptor positive and hormone-naïve advanced breast cancer offers a modestly greater efficacy at the expense of more side-effects, inconvenience and discomfort. It is funded by CCGs. When used in hospital, the tariff structure within which fulvestrant sits does not recompense the Trust for the full cost of the drug and thus, without a significant price discount, any NICE recommendation for the use of fulvestrant will have to be translated into prescription and administration in the GP practice. If a confidential pricing reduction is necessary for such a NICE recommendation, the arrangements for pursuing this will have to be at an individual CCG level unless Regional Medicines Optimisation Committees have the remit to agree this on a regional basis

[redacted]

August 2017

NICE National Institute for Health and Care Excellence

Clinical expert statement

Procedure note and summary page for the technology appraisal of Fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer [ID951]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Daniel Rea**

2. Name of organisation	**University of Birmingham**
3. Job title or position	**Professor of Medical Oncology**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐ yes

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of treatment is to induce tumour regression and or delay the onset of disease progression. This is intended to reduce symptoms from the disease, pro-long survival and improve quality of life. Presentation with locally advanced or metastatic disease is much less common that presentation with early disease probably accounting for around 5 % of new breast cancer diagnosis. Sometimes the primary cancer is not obvious or can be completely occult even after comprehensive breast imaging but this group will also include patients where a primary cancer has been neglected for a variety of social psychological or physical reasons. Patients presenting with de novo advanced disease are more likely to be vulnerable patients. They tend to be older with more comorbidity than patients with early disease. The presentation is different and they are likely to present to a variety of clinical services.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Disease control is the key metric for determination of efficacy. We use conventional RECIST criteria in trials and also determine clinical benefit response which includes patient where either a response or prolonged disease stabilisation has been achieved. For an individual patient, clinically significant response means a response that results in alleviation of symptoms or that the onset of new symptoms has been delayed or where survival has been prolonged.

x cm, or a reduction in disease activity by a certain amount.)	
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	YES: Current treatment in this condition is only able to provide a temporary improvement or delay in disease progression, there is always a need for more effective treatment in this situation.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Primarily with an aromatase inhibitor (the control l arm of the FALCON Study on which this extended indication is based)
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidance is used but often with expanded details written within local treatment guidelines is used. NCCN guidelines are also useful and often a combination of both of the above are used as a basis to local guidelines.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Some clinical variation will exist in the decision to use primary chemotherapy or primary hormone therapy for individual patients. The majority of patients with ER positive HER-2 negative patients without visceral crisis or high volume visceral disease will be treated with an aromatase inhibitor with the addition of Denosumab for patients with bone metastasis in accordance with NICE guidance. Most clinicians will use either letrozole or anastazole these two agents are almost indistinguishable in terms of efficacy or toxicity

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	This will provide a more effective treatment with low toxicity and may delay the need for palliative chemotherapy with the attendant toxicity and cost.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Fulvestrant is not commonly used as first line therapy. Its current role is as second or third line hormone therapy but access depends on local commissioning arrangements. These are variable and there remains inconsistent access to fulvestrant thus use of this agent is variable
• How does healthcare resource use differ between the technology and current care?	Currently patients are placed on oral therapy. The technology will require administration by 4-weekly intramuscular injection.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This treatment should in most instances be initiated in secondary care under the supervision of an oncologist, experienced in the management of advanced breast cancer. Transfer to administration of the drug in a community setting is desirable but ongoing specialist supervision is required to monitor response and determine the ned for a change in therapy.
• What investment is needed to introduce the technology? (For	Most breast units are familiar with the technology but may need more capacity to meet the requirements but this is not a major issue as the number of patients presenting will be small .

example, for facilities, equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, undoubtedly.
• Do you expect the technology to increase length of life more than current care?	This is not possible to state with certainty. I would anticipate based on cross-trial comparisons, that a survival benefit will be seen. The survival benefits from the "CONFIRM" Study of 250 vs 500mg Fulvestrant in the 'second line' setting alongside the "equivalent efficacy " ot Fulvestrant 250mg vs Anastrazole in the same setting.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes but the trial data is somewhat disappointing in this regard.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The subgroup analysis of visceral vs non visceral disease is fairly convincing but I would caution against a very tight distinction here. I would favour an approach where the dominant site of disease is considered rather than an absolute exclusion of patient with any visceral organ involvement. Thus a patient with extensive locally advanced breast cancer with a few asymptomatic lung metastasis is likely to derive the benefit seen in the non visceral group in contrast to say a patient with extensive liver replacement.

The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	There has been some reluctance to deliver this drug outside specialist care as non-specialists are unfamiliar with the drug. The formulation is such that 500 mg must be given as two separate 250mg Im injections. The volume of each injection is 5 ml which is at the upper limit for an IM depot injection. Hence the need for two separate injections one in either gluteal muscle This technology is however very well tolerated. Facilities for administration of a slow IM injection into both gluteals is required alongside an education programme to ensure this is not a barrier to administration in outpatient areas or in the community. It is important that delivery of this technology is not confined to highly specialised cancer services thus inappropriately consuming resources (manpower and facilities) designed for complex anticancer treatments such as cytotoxic chemotherapy. The treatment is safe with few complications and has high patient acceptability.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No, there is no need for any additional monitoring or testing over and above the monitoring needed for current standard treatment with the exeption of simple checking of coagulation status (INR) and adequate platelet count

16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I have concerns that the QOL instruments in use in clinical trials are not picking up benefits that intuitively must be present as a result of improved progression free survival. As survival analysis is immature any survival benefit may not be captured unless correctly modelled against the PFS advantage. This is a challenging area to model accurately.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, this technology has a clear PFS advantage over standard treatment which will be beneficial to patients.
• Is the technology a 'step-change' in the management of the condition?	Yes, I think so – perhaps at this stage a small step but an important one for this group of patients.

• Does the use of the technology address any particular unmet need of the patient population?	Yes, the population includes some vulnerable patients who may find compliance with daily medicine difficult so supervised monthly IM treatment will aid compliance.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	By and large the toxicity of this treatment is similar to current standard treatment. A few patients will find IM treatment uncomfortable/painful but this is offset by the increased efficacy and minor difference in other side effects.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. The control arm is the main standard of care in the UK. Currently Fulvestrant as the first line of therapy is very limited. It is used where tablets can not be taken or oral endocrine therapy is not tolerated.
• If not, how could the results be extrapolated to the UK setting?	Trial results are applicable to the UK
• What, in your view, are the most important outcomes, and were they measured in the trials?	PFS, OS, clinical benefits, QOL, Toxicity – yes all XXX but survival is immature.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The relationship between PFS and OS is a complex issue and interpretation difficult particularly where multiple lines of post progression treatment impact on survival.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	There is an abundance of low quality data of Fulvestrant as second or third line therapy. Very little on first line treatment at the dose used in the FALCON Study.
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s)	

and renumber subsequent sections]	
22. How do data on real-world experience compare with the trial data?	The limited experience of Fulvestrant 500mg as first line therapy is generally supportive of the FALCON trial experience.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Many patients presenting with untreated locally advanced or metastatic breast cancer are atypical compared to the early disease patient, older, more frail, more co-morbidities, socially, economically deprived or psychologically compromised hence presenting late.
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24.	

Key messages
25. In up to 5 bullet points, please summarise the key messages of your statement. • The technology is more effective than standard care, is well tolerated and easily adopted. • The patient group is more vulnerable than average with a variety of medical and psychosocial reasons for delayed presentation. • The trial data is immature with respect to survival analysis. • Cross-trial comparisons indicate a reasonable possibility that a survival gain can be expected. •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

[Insert appraisal title here]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: CATHERINE PRIESTLEY

Name of your nominating organisation: BREAST CANCER CARE

Do you know if your nominating organisation has submitted a statement?

☑ Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

☑ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes ☑ No

- a carer of a patient with the condition?

☐ Yes ☑ No

- a patient organisation employee or volunteer?
-

☑ Yes ☐ No

Do you have experience of the treatment being appraised?

☑ Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☑ (If you tick this box, the rest of this form will be deleted after submission.)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer [ID951]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Gwyn Fraser
Name of your nominating organisation: Breast Cancer Now
Do you know if your nominating organisation has submitted a statement?

☒ Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

☒ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☒ Yes ☐ No

- a carer of a patient with the condition?

☐ Yes ☒ No

- a patient organisation employee or volunteer?
-

☐ Yes ☒ No

Do you have experience of the treatment being appraised?

☒ Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I was diagnosed with metastatic breast cancer over 5 years ago. During the past 5 years I have received various treatments including anastrazole, exemestane and evoralimus, paclitaxel and fulvestrant. I am currently receiving Herceptin and vinorelbine. These treatments have had varying effects on my wellness and quality of life, with anastrazole and fulvestrant being the best for these. I do not generally suffer a great deal of pain, although I have other symptoms such as fatigue and ascites which impact on what I can do. It is sometimes difficult to say which symptoms are caused by the cancer and which by treatments.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

I would like to live as long as possible. Quality of life is obviously important but having time to spend with my family and friends and to get various things tied up is most important to me.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

I have had reasonably good NHS care with some exceptions. So far there has always been another treatment available when one has stopped working. I have tolerated all treatments reasonably well, though chemotherapy is much harder to cope with and has a much greater effect on quality of life than other treatments.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain

- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

I was on fulvestrant for 14 months altogether (from March 2016 to April 2017) so it gave me that amount of time before I had to go onto another chemotherapy. My quality of life and well-being was very good while I was on the fulvestrant and it was working – I was able to dance, play table tennis, cycle, swim and lead a psychology group for the U3A, all of which I am too tired to do at present.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

For me it has advantages over chemotherapy in that it allowed me to lead a relatively normal life.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

I am not aware of any.

5. What do you consider to be the disadvantages of the treatment being appraised?

The fact that it is an injection may be considered a disadvantage. Sometimes this was painful while being administered or afterwards, but this depended on the skill of the nurse giving the injection and usually it was fine. It also means a monthly trip to hospital for some people but I was able to have mine at my GP's surgery. I am aware that other patients have had side effects, particularly tiredness and menopausal symptoms but feel that in many cases

people would be prepared to tolerate these if the medication was extending their life.

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

My major concern is the relative lack of research being carried out into causes and treatments of metastatic breast cancer.

Please list any concerns you have about the treatment being appraised.

I cannot think of any.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

I am not aware of any.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Not sure.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

I am aware of some people for whom fulvestrant has had little benefit. I believe that this depends on the patient and their particular cancer.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes ☒ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

Not that I am aware of.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Is there anything else that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- It is good to have as many treatments available as possible as benefits of each treatment will vary from one patient to another.
- More research is needed to provide more treatments and eventually a cure for metastatic breast cancer.
- For some people (myself included) fulvestrant can have positive effects on wellness and quality of life.
- Chemotherapy is much harder to cope with than many other treatments.
- Many people are prepared to put up with some side-effects as long as the treatment will extend their lives.

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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer

Produced by Southampton Health Technology Assessments Centre

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Dr. Keith Cooper, critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Ms. Neelam Kalita, critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Ms. Petra Harris, critically appraised the clinical effectiveness systematic review and drafted the report; Mr. Olu Onyimadu, critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Dr. Wendy Gaisford, critically appraised the clinical effectiveness systematic review and drafted the report; Dr. Joanna Picot, critically appraised the clinical effectiveness systematic review, drafted the report, project managed the review and is the project guarantor.

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Commercial in confidence (CIC) information in blue
Academic in confidence (AIC) information in yellow.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABC	Advanced breast cancer
AE	Adverse event
AI	Aromatase inhibitor
AIC	Akaike information criteria
BIC	Bayesian information criteria
CBR	Clinical Benefit Rate
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
CS	Company submission
CSR	Clinical study report
DoCB	Duration of clinical benefit
DoR	Duration of response
EDoCB	Expected duration of clinical benefit
EMA	European Medicines Agency
EQ-5D	EuroQoL5 Dimensions questionnaire
ER	Oestrogen receptor
ERG	Evidence review group
FACT-B	Functional Assessment of Cancer Therapy – Breast questionnaire
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HR+	Hormone receptor-positive
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IM	Intramuscular
IPD	Individual patient data
ITT	Intention-to-treat
KM	Kaplan-Meier
MMRM	Repeated measures mixed effects regression models
NHS	National Health Service

NICE	National Institute of Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressed disease
PFS	Progression-free survival
PgR	Progesterone Receptor
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal Social Services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluations Criteria in Solid Tumours
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product characteristics
TOI	Trial Outcome Index
TTP	Time to treatment progression

SUMMARY

Scope of the company submission

The company's submission (CS) reflects the scope of the appraisal issued by the National Institute for Health and Care Excellence (NICE). The submission assesses the clinical effectiveness and cost effectiveness of fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer in comparison to aromatase inhibitors (AIs) (anastrozole and letrozole) or, when these are not tolerated or are contraindicated, tamoxifen.

Summary of submitted clinical effectiveness evidence

The company's systematic review of clinical effectiveness identified two relevant randomised controlled trials (RCTs) of fulvestrant:

- The FIRST trial (phase II, open label, non-inferiority trial) compared fulvestrant (500 mg) versus anastrozole (1 mg) in postmenopausal women with hormone-receptor positive (HR+) advanced breast cancer (ABC) who had either never received endocrine therapy for advanced disease or who had received previous adjuvant endocrine therapy for ABC completed at least 12 months prior to randomisation into the study.
- The FALCON trial (phase III, double blind, superiority trial) compared fulvestrant 500 mg versus anastrozole 1 mg in postmenopausal women with oestrogen receptor positive (ER+) and/or progesterone receptor positive (PgR+) ABC who had not previously been treated with any endocrine therapy.

In these trials anastrozole is considered the standard of care.

There are some differences between the trials:

- in terms of patient inclusion criteria, the chief differences were the requirement in FALCON for all participants to be endocrine therapy naive and also human epidermal growth factor (HER2) negative. In FALCON patients were allowed to have received one line of prior chemotherapy for ABC whereas prior chemotherapy for ABC was not permitted in the FIRST trial.
- in terms of design, the chief differences were that FALCON was a double blind phase III trial, whereas FIRST was open-label phase II trial and the trials had different primary outcomes [clinical benefit rate (CBR) in FIRST and progression-free survival (PFS) in FALCON]

Both trials were judged by the Evidence Review Group (ERG) to be of good methodological quality. The ERG believes that the company has identified all the relevant RCTs of fulvestrant.

There are no head-to-head RCTs of fulvestrant versus tamoxifen or letrozole so the company conducted a Bayesian fixed-effect network meta-analysis (NMA) to perform an indirect treatment comparison. The company's systematic review identified a further four RCTs for inclusion in the NMA initially, of which three compared anastrozole versus tamoxifen (the North American trial; the TARGET trial and a trial by Milla-Santos et al.) and one compared letrozole versus tamoxifen (the PO25 trial). The North American and TARGET studies were prospectively designed to allow for combined data analysis and the combined data are described as NorthAmTarget in the CS. The Milla-Santos trial was subsequently excluded from the NMA as its inclusion led to heterogeneity, used a dose of tamoxifen not recommended by the European Medicines Agency (EMA) and reported the outcomes of interest only for a subset of participants.

The CS summarises the methodological and patient characteristics for all six trials (two for fulvestrant, four for other comparators) that were identified for inclusion in the NMA. Individual patient data (IPD) were available for the two fulvestrant trials and also the combined NorthAmTARGET data set. This enabled the company to select patient data from the FIRST and NorthAmTARGET trials that matched the criteria of the FALCON trial in respect of ER+/PgR+ status and endocrine treatment naive status. Only aggregate data were available for the PO25 study which therefore could not be matched to FALCON. The possible advantages and disadvantages of this matching process were not discussed in the CS. The ERG understands that by matching to FALCON it was possible to exclude participants [redacted] (except for study PO25). Although the ERG has concerns about whether there may be unknown potential disadvantages to this matching approach, the ERG has concluded that these would likely be outweighed by the benefits of reduced heterogeneity in the NMA. The company used appropriate methods to investigate whether there was a constant relative treatment effect over time. The company concluded that methods for NMA that rely on the assumption of proportional hazards were inappropriate and therefore used an alternative method (Ouwens et al.). Fixed-effect NMA results are presented for the outcomes of PFS and overall survival (OS) and these inform the economic model. The company provided reasons for the use of a fixed-effect model and why it was not possible to run the NMA using a random-

effects model. The ERG accepts that with few trials in the network and the features of the modelling methodology the company have used, a random-effects NMA has not been possible but this does leave a concern that uncertainty in the NMA outcomes may be under-represented.

The CS reports the effects of fulvestrant treatment across a range of outcomes relevant to the NICE scope and company decision problem which are summarised below.

PFS (FALCON trial primary outcome) and time to progression (TTP, FIRST secondary outcome) both favoured fulvestrant and in both cases the difference in medians (fulvestrant versus anastrozole) was statistically significant. However, the median PFS in the FALCON trial was only 2.8 months longer in the fulvestrant arm than the anastrozole arm [hazard ratio (HR) = 0.80, 95% confidence interval (CI) 0.64 to 1.0, p = 0.049] which the two clinical experts the ERG consulted did not believe was a clinically significant difference. Median TTP in the FIRST trial was 10.3 months longer in the fulvestrant arm than the anastrozole arm (HR 0.66, 95% CI 0.47 to 0.92, p = 0.01).

Results from the PFS fixed-effect NMA indicated that fulvestrant is statistically significantly better than anastrozole and tamoxifen is statistically significantly worse than anastrozole.

OS is a secondary outcome for the FALCON trial and OS data are immature. A median OS could not be calculated at the time of PFS analysis. There was a slightly lower proportion of deaths in the fulvestrant arm than the anastrozole arm (29% vs 32% respectively) but the difference is not statistically significant. The CS states OS will be re-assessed after a longer follow-up period. In the FIRST trial, OS was added as a secondary outcome after TTP data were analysed. Results of the OS analysis (undertaken after approximately 65% of deaths had occurred) demonstrated a lower proportion of deaths in the fulvestrant arm (61.8% versus 71.8% in the anastrozole arm). The difference in median survival times, 54.1 months with fulvestrant in comparison to 48.4 months with anastrozole, is statistically significant (HR 0.70, 95% CI 0.50 to 0.98, p=0.04) but as the analysis was not originally specified confirmation of the results from the ongoing FALCON trial is needed.

The only statistically significant differences observed in the OS fixed-effect NMA related to the letrozole versus anastrozole comparisons, but the direction of the differences is not consistent.

Subgroup analyses conducted for PFS and OS indicated that across the subgroups tested, the results were consistent with those of the whole study populations of FIRST and FALCON. Consideration of subgroups of people with visceral disease and those with non-visceral disease (if evidence allows) was included in the company's decision problem and the largest numerical difference in the reported hazard ratios for PFS of subgroups was observed for the visceral disease versus no visceral disease at baseline but the company do not discuss this subgroup result in the CS.

CBR was the primary outcome for the FIRST trial and a secondary outcome of the FALCON Trial. CBR was defined in both trials as the proportion of all randomly assigned patients with a best overall response of either complete response (CR), partial response (PR) or stable disease (≥24 weeks). In both trials the CBR numerically favoured fulvestrant, but the difference between fulvestrant and anastrozole was not statistically significant (as the FIRST trial was designed as a non-inferiority trial it was not powered to detect a statistically significant difference in CBR).

Among the other secondary outcomes the results were either similar between treatment arms or favoured the fulvestrant arm but with no statistically significant differences between fulvestrant and anastrozole.

Included among the other secondary outcomes was health-related quality of life (HRQoL) which was only assessed in the FALCON trial, using both the EuroQoL5 Dimensions-3L (EQ-5D-3L) and Functional Assessment of Cancer Therapy – Breast (FACT-B) questionnaires. Data from the EQ-5D-3L was used to inform the economic model. Results from both questionnaires indicated that HRQoL was similar between treatment arms and maintained in both arms during treatment.

Adverse events (AEs) were reported from both the fulvestrant trials. The proportions of AEs and serious adverse events were similar between treatment arms of both trials. The proportion of patients discontinuing study treatment due to an AE was also similar in the fulvestrant and anastrozole treatment groups. Deaths considered to be related to AEs were reported (3% in each arm of the FALCON trial, 3% in the fulvestrant arm and 4.9% in the anastrozole arm of the FIRST trial) but none of these were reported as being causally related to study treatment.

Summary of submitted cost effectiveness evidence

The CS includes:

- A review of submissions made to national reimbursement agencies and technology assessment organisations of treatments for locally advanced or metastatic breast cancer
- An economic evaluation undertaken for the NICE STA process to assess fulvestrant for post-menopausal women with locally advanced or metastatic hormone receptor-positive (HR+) breast cancer who have not received endocrine therapy.

A review was conducted by the company to identify submissions, of locally advanced or metastatic breast cancer, to national reimbursement agencies and technology assessment organisations, including the Canadian Agency for Drugs and Technologies in Health (CADTH), the pan-Canadian Oncology Drug Review, NICE, Pharmaceutical Benefits Advisory Committee (PBAC) and Scottish Medicines Consortium. However, the company only selected submissions published by NICE for review. The company identified 10 technology appraisals relating to advanced or metastatic breast cancer.

Five of these 10 submissions relate to first-line therapy but none relate to the same population as in the current submission. As the company did not search for published cost-effectiveness literature, the ERG completed a search of published cost-effectiveness studies. We identified two studies that compared fulvestrant in patients previously treated with an AI or anti-oestrogen therapy.

The company constructed a cohort partitioned survival model in Microsoft Excel. The model compared first-line treatment with fulvestrant compared to anastrozole, letrozole and tamoxifen for post-menopausal women with HR+ locally advanced or metastatic breast cancer. The model had a lifetime horizon of 30 years, with discounting at 3.5% per annum for costs and benefits, a four-week cycle length and a half-cycle correction. The perspective of the analysis is the National Health Service and Personal Social Services. The model has three health states: PFS, 'progressed disease' (PD) and 'death'.

The model uses clinical effectiveness data from head-to-head trials comparing fulvestrant and anastrozole (FIRST and FALCON). Fulvestrant is compared to letrozole and tamoxifen via an indirect treatment comparison. The model uses parametric survival modelling to fit survival curves using results from the company's NMA. The company considered that the most

appropriate method for extrapolating best fit to the observed data for PFS was to use a generalised gamma distribution. The Weibull distribution was chosen as the most appropriate method of extrapolating OS. The model derives the proportion of patients in the PD health state as the difference between the PFS and OS curves. Treatment duration was assumed to be until objective disease progression.

Utility estimates were taken from the company's FALCON trial, in which quality of life values from the EQ-5D 3L questionnaire were collected. Fulvestrant is administered intramuscularly into the buttocks in the first month and then monthly thereafter. The recommended dose is two injections (one in each buttock) of 250 mg at a list price of £522.41 for both injections. Comparator treatments consisted of oral treatments taken daily with a cost of between £0.75 and £1.62 per month. The cost of comparator treatments are taken from the pharmaceutical electronic market information tool (eMit) and their doses are as recommended by their Summary of Product Characteristics. Health state costs are based upon those recommended in the NICE Clinical Guidance on ABC. Subsequent therapies were included for second- and third-line treatment.

The results of the economic model are presented as incremental cost effectiveness ratios (ICERs), measured as the incremental cost per quality-adjusted life-year (QALY). For the base case the incremental cost per QALY gained is £34,099 for fulvestrant compared to anastrozole.

Table 1 Base case cost effectiveness results

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
Letrozole	£26,221	2.46	--	--	--
Anastrozole	£30,572	2.68	£4,351	0.22	£19,702
Tamoxifen	£32,328	2.47	£1,756	-0.21	Dominated
Fulvestrant	£49,431	3.23	£18,859	0.55	£34,099

This table draws on information presented in Table 30 within the appendix to the company's written response to the clarification questions.

In probabilistic sensitivity analyses, the probability of first-line fulvestrant being cost-effective compared to anastrozole, letrozole and tamoxifen is 1.1% and 26.5% at willingness to pay

thresholds of £20,000 and £30,000 per QALY respectively. At both these willingness to pay thresholds, both letrozole and anastrozole were more cost-effective than fulvestrant.

The company conducted sensitivity analyses and scenario analyses and concluded that the key drivers to the cost-effectiveness results were the OS extrapolation parameters, PFS, utility values and fulvestrant treatment acquisition costs.

Commentary on the robustness of submitted evidence

Strengths

The company's systematic review of clinical effectiveness was of good methodological quality. The ERG does not believe that any key studies of fulvestrant or of potential comparators are missing. Two RCTs provide evidence for the effectiveness of fulvestrant versus anastrozole for people with untreated hormone-receptor positive locally advanced or metastatic breast cancer. Three additional RCTs provide evidence, which is used in an NMA for the outcomes of PFS and OS, for the other comparators of interest, letrozole and tamoxifen.

The model structure is representative of the clinical pathway for patients with advanced or metastatic breast cancer. The company used methods for the economic evaluation that are consistent with NICE methodological guidelines. The company's clinical trial collected EQ-5d 3L HRQoL data.

Weaknesses and Areas of uncertainty

The initial phase II study FIRST demonstrated a clinically significant and statistically significant improvement with fulvestrant in TTP in comparison to anastrozole. The pivotal phase III trial FALCON demonstrated a statistically significant improvement in PFS but the magnitude of the improvement was not as great as that observed in the FIRST study (median TTP 10.3 months longer with fulvestrant versus median PFS 2.8 months longer). Furthermore, clinical advice to the ERG was that a median PFS of 2.8 months longer with fulvestrant would not be considered clinically significant. The median OS in FIRST was almost 6 months longer with fulvestrant versus anastrozole but median OS in the FALCON study has not yet been reached. The ERG is concerned that the OS benefit in FALCON may mirror that of PFS and not be as great as observed in the FIRST study. This has an impact on the cost-effectiveness modelling.

There is no direct evidence comparing fulvestrant to either letrozole or tamoxifen so the company conducted an NMA. For all comparisons in the NMA except fulvestrant versus anastrozole there was only one data set (although in one case this single data set was obtained from two replicate trials). The company were unable to conduct a random-effects meta-analysis so it is possible that uncertainty in the outcomes of the NMA is not adequately represented.

The model results are sensitive to changes in the estimation of overall survival. The OS data from the FALCON trial are immature. There is some uncertainty in what the cost-effectiveness estimates would be if complete FALCON OS were available. The ICERs are likely to be higher when the full results of the FALCON become available.

Summary of additional work undertaken by the ERG

We conducted a number of scenario analyses to examine the robustness of the company's base case economic analyses. These are:

- Scenario 1: Varying the parametric survival distribution for overall survival
- Scenario 2: Varying the treatment effectiveness of fulvestrant by changing the scale parameter of the OS
- Scenario 3: Varying units of resource use and costs associated with progression-free and PD health states
- Scenario 4: Varying the proportion of patients receiving endocrine therapy, chemotherapy and targeted therapy as second-line treatment
- Scenario 5: Exclusion of PO25 trial and Milla-Santos study from the network-meta analysis used to obtain PFS and OS curves, and assuming that anastrozole and letrozole have similar clinical efficacy
- Scenario 6: Change of administration cost for fulvestrant, assuming that all patients receive treatment in an outpatient setting

The ICERs were mostly not particularly sensitive to the selection of the parametric distribution for extrapolating OS curve, with the exception of the Gompertz distribution which produced an ICER of £59,953 per QALY for fulvestrant vs anastrozole. The ERG considered that the Gompertz distribution had a poor fit to the observed data. Changing the treatment effectiveness of fulvestrant by varying the OS scale parameter increased the ICERs of fulvestrant vs comparators considerably. Decreasing the value of incremental scale parameter of the OS curve increased the ICERs. For instance, an incremental scale parameter of [redacted] (near the

upper range of the confidence interval) increased the ICER of fulvestrant vs anastrozole to £208,231 (an increase of £174,132 per QALY from the base case ICER) whereas the ICER increased to £40,761 per QALY (an increase of £6,662 from the base case ICER) when the incremental scale parameter was set at [redacted]. The incremental results obtained from scenario 3 to 6 were comparable to the company's base case results, with ICERs ranging between £32,084 and £35,496 per QALY for fulvestrant vs anastrozole.

For the ERG base case, we combined scenarios 3, 4, 5 and 6. The incremental results obtained are presented in Table 2. The ERG base case ICER for fulvestrant vs anastrozole is £33,455 per QALY which is slightly less than the company's base case ICER of £34,099 per QALY.

Table 2 ERG base case results

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
Letrozole	£11,336	2.68	--	--	--
Anastrozole	£11,356	2.68	--	--	--
Tamoxifen	£11,852	2.47	£496	-0.21	Dominated
Fulvestrant	£29,866	3.23	£18,510	0.54	£33,455

1 Introduction to ERG Report

This report is a critique of the company's submission (CS) to the National Institute of Health and Care Excellence (NICE) from AstraZeneca on the clinical effectiveness and cost effectiveness of fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer. It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the Evidence Review Group (ERG) and to help inform this review.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on 01 June 2017. A response from the company via NICE was received by the ERG on 16 June 2017 and this can be seen in the NICE committee papers for this appraisal.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The ERG considers that the CS provides a clear and fairly accurate overview of the prevalence, cause and prognosis of breast cancer (CS pp. 26-27), including the impact of the disease on patients, carers and society (CS pp. 31-34). The CS details the different subcategories of breast cancer based on the expression of hormone receptors (which may also be termed endocrine receptors) for oestrogen and progesterone, and the human epidermal growth factor 2 receptor (HER2) (CS p27). A detailed explanation of the role of endocrine receptors is provided, including the receptor for the subgroup of interest [oestrogen receptor positive (ER+)]. The CS highlights that approximately 6% of women at initial presentation have advanced breast cancer (ABC). However, the NICE final scope[1] suggests that around 13% of women with invasive breast cancer have locally advanced or metastatic disease when diagnosed (of which around 5% have Stage IV ABC according to expert opinion). The CS states that of these patients, a panel of UK breast cancer oncologists estimated that 40% have visceral disease and our clinical experts concur with this estimate (the NICE final scope suggests this figure to be around 35%). The CS acknowledges that ER+ HER2 negative ABC is largely incurable; 44% of women die within five years of diagnosis, rising to over 70% in patients with Stage IV disease.

The subgroups of ABC of interest in the NICE final scope[1] are people with visceral and non-visceral disease. The CS acknowledges that visceral metastatic breast cancer (defined as metastasis to internal organs of the body, including liver, lungs or brain) confers a worse

prognosis than bone metastasis alone, which is not normally immediately life-threatening. Around 15% to 30% of women with ABC go on to develop brain metastases, with a median survival time of three to six months from development (CS p. 27).

2.2 Critique of company's overview of current service provision

The CS provides a clear and accurate overview of how ER+ breast cancer is currently managed in patients with ABC. An illustration of the NICE treatment pathway for ABC[2] is provided (CS p. 31) which was designed and adapted to illustrate the suggested positioning of fulvestrant in the pathway. Figure 1 shows this pathway omitting fulvestrant.

The target population of the submission are post-menopausal women with ER+ ABC, without life threatening disease, who receive endocrine therapy [with the aromatase inhibitor (AI) anastrozole or letrozole] in the first instance, or tamoxifen if AI's are not tolerated or are contraindicated under current guidance.[2] The CS states (CS p. 31) that NICE have recently recommended that women suffering recurrence or progression after a first line of AI therapy may be switched to a second line AI such as exemestane (potentially in combination with everolimus).[3] However, this population group are outside of the NICE scope[1] for this submission. For those with life-threatening disease or requiring early symptom relief, NICE Clinical Guideline CG81[2] recommends chemotherapy. The CS states that there is an absence of detailed data on how many lines of different endocrine therapies are typically administered in the UK, which a panel of UK Breast Cancer Oncologists estimates to be around 2.5 lines and our clinical experts concur with this estimate (CS p. 32).

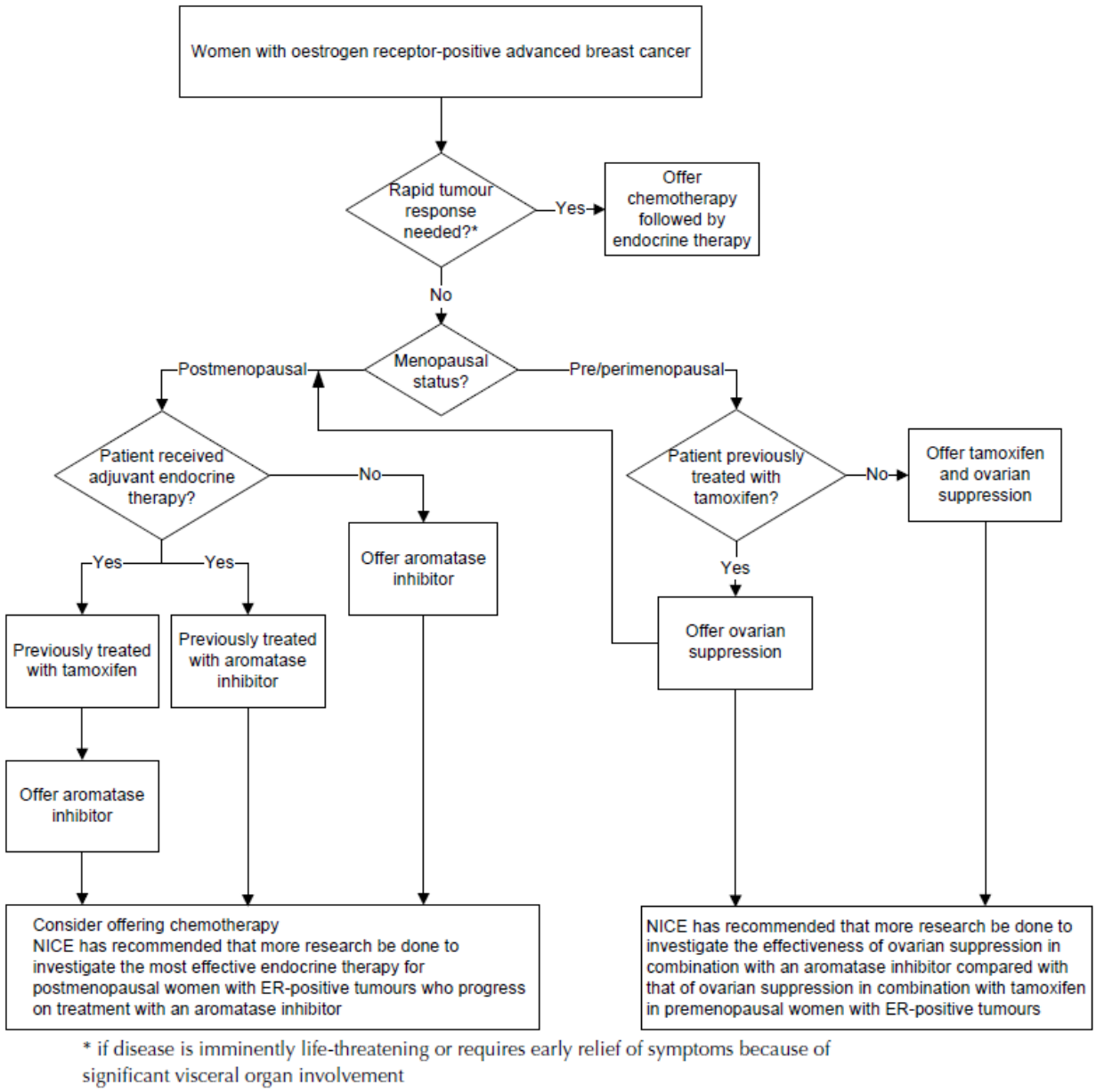


Figure 1 Treatment pathway for women with oestrogen receptor-positive ABC (from NICE CG81)

2.3 Critique of company's definition of decision problem

Population

The population specified in the company's decision problem is post-menopausal people with locally advanced or metastatic hormone receptor-positive (HR+) breast cancer, who have not received endocrine therapy. The patient population matches that specified in the final scope issued by NICE.[1]

Intervention

In accordance with the final scope,[1] the intervention described in the company's decision problem is fulvestrant (brand name: Faslodex®). Fulvestrant is a selective oestrogen receptor degrader and works by binding to endocrine receptors and downregulating oestrogen receptor (ER) protein expression in human breast cancer cells.

The Summary of Product Characteristics (SmPC) (2009),[4] indicates that fulvestrant (500 mg) is administered by two pre-filled syringes each containing 250 mg fulvestrant in 5ml solution. It is administered by slow intramuscular (IM) injection (1-2 minutes/injection), one in each buttock (gluteal area). The recommended dose is 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose. It is currently indicated for the treatment of postmenopausal women with ER+, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-oestrogen therapy, or disease progression on therapy with an anti-oestrogen.

The current marketing authorisation for the 500 mg dose was received from the European Medicines Agency (EMA) on 16th March 2010 and was launched in the UK on 3rd June 2010. Fulvestrant is currently being considered for a change in the marketing authorisation to enable its use for the treatment of ER+, locally advanced or metastatic breast cancer in postmenopausal women;

[redacted]

- *with disease relapse on or after adjuvant anti-oestrogen therapy, or disease progression on anti-oestrogen therapy*

Committee for Medicinal Products for Human Use (CHMP) opinion is expected in [redacted]

[redacted] with full marketing authorisation anticipated in [redacted]

The recommended dose regimen for the proposed new indication is: 500 mg to be slowly delivered IM as two 5 ml injections, one in each buttock, on days 1, 15, 29 and once monthly thereafter. The intervention described in the decision problem is appropriate for the National Health Service (NHS) and reflects its draft licence indication.

Comparators

The comparators described in the company's decision problem are AIs (such as anastrozole and letrozole) and tamoxifen (if AIs are not tolerated or are contraindicated). The comparators match those in the NICE scope[1] and are appropriate for the NHS.

Outcomes

The company has listed all the outcomes specified in the final scope in their decision problem.

- overall survival (OS)
- progression-free survival (PFS)
- response rate
- adverse effects of treatment
- health-related quality of life (HRQoL).

Clinical expert opinion agreed that outcomes are appropriate and clinically meaningful.

Economic analysis

The CS states that the economic analysis specified in the decision problem is the same as the final scope issued by NICE[1] (CS p. 11 Table 1) and the ERG agrees. The company have conducted a cost-utility analysis with a time horizon of 30 years (CS p. 142). Given the starting age of the modelled cohort is 63.5 years, this time horizon is appropriate for considering differences in costs and outcomes between treatments for patients with untreated hormone-receptor positive locally advanced or metastatic breast cancer. Costs are considered from the NHS and Personal Social Services (PSS) perspective.

No Patient Access Scheme (PAS) discount has been proposed and none of the comparators are subject to a PAS.

Other relevant factors

The NICE scope[1] states that, if the evidence allows, subgroups of people with visceral disease and people with non-visceral disease should be considered. The CS presents subgroup analyses for the visceral disease and non-visceral disease subgroups in section 4.8 (CS p. 77) alongside other subgroup analyses. In the FIRST trial post-hoc subgroup analyses were

conducted for time to progression (TTP) and OS, whereas in the FALCON trial subgroup analyses were prespecified and are presented for PFS and OS.

No equity or equality issues were specified in the final scope[1] or identified by the company. The ERG is not aware of any issues related to equity or equality in the use of fulvestrant in patients with untreated hormone-receptor positive locally advanced or metastatic breast cancer.

3 CLINICAL EFFECTIVENESS

3.1 Critique of company's approach to systematic review

3.1.1 Description of company's search strategy

The company's submission (CS) reports the following 3 literature searches:

- Clinical effectiveness: CS Appendix A (database inception - January 2017)
- Cost effectiveness: CS Section 5.1 (May 2016)
- HRQoL: CS Section 5.4.3 (October 2013 to June 2016)

The clinical effectiveness searches represent a one-step approach designed to identify trials relating to fulvestrant and comparator drugs, negating the need for additional indirect comparison searches. Simultaneous searches of Embase and Medline were undertaken on the host Embase.com. Separate searches were conducted in The Cochrane Library and on Pubmed to identify in-process records. The list of drug terms in the search strategy is comprehensive, using a mix of free text and descriptor terms, including an appropriate clinical trials filter. However there is an error in the Embase.com tabulation, where sets are incorrectly linked (line 37: where sets 1 and 10 and 36 should have been combined rather than 1 and 10 and 37), and also in the Cochrane search (line 37: where lines 4 and 37 should have been combined rather than lines 7 and 36), although these could be typographical errors in the CS. The Pubmed search is linked correctly. The ERG ran a search for fulvestrant trials from database inception on Embase and Medline and found no additional relevant trials. Pertinent conference proceedings were searched by the company which the ERG deemed sufficient. It is stated in section 4.14 that there are no other ongoing studies to provide further relevant evidence due to be completed within the next year. The ERG concurs, after conducting an ongoing trials search on the UK Clinical Trial Gateway (UKCTG), clinicaltrials.gov, the World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP), Prospero and Astra Zeneca's website.

The cost effectiveness searches took an unusual approach as the company elected to search only for health technology assessments (HTA) of therapies for locally advanced or metastatic breast cancer. The review included a search of national reimbursement and technology assessment organisations [Canadian Agency for Drugs and Technologies in Health (CADTH, Canada); the Canadian Oncology Drug Review; National Institute for Health and Clinical Excellence (NICE, England and Wales); Pharmaceutical Benefits Advisory Committee (PBAC,

Australia); Scottish Medicine Consortium (SMC, Scotland)]. The websites were searched in May 2016 for any HTA in breast cancer and those related to advanced or metastatic breast cancer were included. The company did not include any additional inclusion or exclusion criteria. The ERG undertook checks on the CEA Registry and also on HTA and NHS Economic Evaluation Database (NHSEED) within the Cochrane Library. Medline and Embase were additionally searched over the last 10 years applying a standard cost filter to fulvestrant and to three chosen key comparator drugs: anastrozole, letrozole and tamoxifen. Two extra records were identified from the search results by a senior health economist and checked by a second health economist (see section 4.2).

The HRQoL searches were run to identify studies published between October 2013 and June 2016 on Embase. The ERG ran update searches (2016-2017) on Medline and Embase. ScHARR's Health utility Database (ScHARRHUD) was also searched and four additional records were identified from search results by a senior health economist (further detail is provided in Section 4.3.6.)

In summary the searches are of a reasonable quality, transparent and the CS contains Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow charts of results. Despite documentation errors within the search strategies, further searching by the ERG did not produce additional relevant clinical effectiveness evidence. Although the ERG identified additional cost and quality of life studies these were either not relevant or not suitable for use in the appraisal.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection.

The company provides an overview of the inclusion/exclusion criteria for the systematic literature review (SLR), evaluating the clinical effectiveness of fulvestrant (CS Table 8, p. 36). The criteria were designed to capture not only studies of fulvestrant, but also any studies that might be pertinent to the wider evidence network and relevant if an NMA had to be undertaken. The company's inclusion/exclusion criteria limited study design to randomised controlled trials (RCTs) (irrespective of blinding status) and only English language publications were eligible.

Population

The population of the SLR was restricted to female, post-menopausal patients (≥18 years of age) with HR+, HER2 negative, locally advanced or metastatic breast cancer. The CS states

that HER2 receptor testing was not usually carried out in regular clinical practice until the mid-2000s and so therefore eligibility was not restricted to a HER2 negative population in order not to exclude some important comparators (CS p. 38). Additional inclusion/exclusion criteria were applied to full-text copies of studies, to exclude pre-menopausal females (studies including both pre- and post-menopausal females could be included if sub-group data for the post-menopausal population was reported, CS p. 38). This ensured that the included population was in line with that stated in the final NICE scope.[1] The final inclusion criteria for treatment were aligned with the FALCON trial, including patients with either:

- locally advanced disease not amenable to surgery or radiotherapy of curative intent (patients may have had one line of cytotoxic chemotherapy, following which they must remain unsuitable for therapy of curative intent)

or

- metastatic disease (patients may have had one line of cytotoxic chemotherapy as previous treatment of breast cancer but must show progressive disease prior to enrolment.

Although the NICE scope[1] focuses on an endocrine treatment-naive population, the criteria of SLR allowed for the inclusion of studies in which >70% of patients met that criterion (CS p. 39).

Intervention

The inclusion criteria listed hormonal and chemo- or biologic therapies, including fulvestrant. The CS SLR therefore includes a wider variety of interventions than indicated in the NICE scope.[1] The CS states that both licensed and investigational pharmacological treatments for HR+ [expressing the ER and/or the progesterone receptor (PgR)] locally advanced or metastatic breast cancer were included in the SLR (based on recommendations of clinical guidelines, searching of clinicaltrials.gov and by expert input). As the inclusion criteria of the SLR were designed to also identify studies for the NMA, this may explain the variety of drugs included in the criteria.

Comparators

The inclusion criteria for the comparators in the submission were:

- any included intervention
- any other pharmacological intervention and
- placebo/best supportive care.

This is much broader than the criteria specified by the NICE final scope[1] for comparators, which is limited to AIs (such as anastrozole and letrozole) and tamoxifen (if AIs are not tolerated or are contraindicated). Again the broad scope was designed to also identify studies for the NMA.

Outcomes

The company has listed all the outcomes specified in the final scope in their decision problem. These outcomes are appropriate and clinically meaningful to patients, and the ERG considers that the company has included all important outcomes in the decision problem.

The CS provides a PRISMA diagram illustrating the number of records identified and included/excluded records at each stage of the SLR screening processes (CS Fig. 5, p. 42). Out of 12,498 records found by database searching, a final number of 44 studies (based on 91 publications) were data extracted. However, a further 38 studies were excluded from the wider evidence network (exclusion reasons were documented for most of these studies in CS Appendix B, missing exclusion reasons were supplied in the company's response to clarification question A1). This left six studies that were included in the main evidence review. Two of these studies provided heat to head comparisons between fulvestrant and anastrozole (Section 3.1.3). The other four studies included the other comparator drugs (letrozole and tamoxifen) and these contributed data for the NMA (Section 3.1.7).

The company did not specify treatment setting as an inclusion criterion nor place any limits on inclusion relating to the quality of the RCTs, which is appropriate. Overall, the ERG considers the inclusion criteria reasonable.

The CS does not highlight any potential bias in their selection of studies. Overall, the ERG considers that the eligibility criteria used in the SLR review were appropriate and matched the decision problem (notwithstanding the need for additional criteria to conduct an NMA).

3.1.3 Identified studies

The company's SLR included two RCTs, FIRST[5-7] and FALCON,[8] comparing fulvestrant and the AI anastrazole for the treatment of ABC. For the NMA a further four RCTs were identified, of which three compared anastrazole versus tamoxifen; the North American trial;[9] the TARGET trial[10] and a trial by Milla-Santos et al.[11] The fourth study was the PO25 trial[12,13] which

compared letrozole versus tamoxifen. RCT reports were provided electronically on 19th May as part of the submission reference pack.

Summary details of the two fulvestrant RCTs, FIRST[5-7] and FALCON[8] are presented in the CS (Sections 4.3 to 4.5, pp. 48-66). These studies were sponsored by the company.

- The differences between the two RCTs in terms of trial designs,-population, eligibility criteria, setting, intervention, outcomes and pre-planned subgroups are summarised in the CS (Table 14, p. 55).
- A diagram covering trial design, intervention description and initial patient numbers was provided for both the FIRST (CS Figure 7, p. 49) and the FALCON study (CS Figure 8, p. 51).
- QUORUM flow diagrams describing numbers randomised and drop out data are provided (FIRST RCT, CS Figure 9, p. 61, FALCON RCT, CS Figure 10, p. 64).
- For both studies, power/sample size calculations were provided (CS pp. 57-58).
- Analysis sets for the FIRST RCT are described on CS pp. 62-63 and summarised in CS Table 16, p63. For the FALCON trial they are described on CS pp. 65-66 and summarised in CS Figure 11, p66. There was an intention-to-treat (ITT) analysis for key outcomes in both trials.

The ERG has summarised some of the key trial characteristics in Table 3 and key patient characteristics in Table 4.

The fulvestrant trials were both multi-centre RCTs that were conducted across a variety of countries (Table 3). The FIRST trial was a phase II open-label non-inferiority trial with CBR as the primary outcome whereas FALCON was a phase III double-blind superiority trial with PFS as the primary outcome. The United Kingdom (UK) is listed one of the countries from which patients were recruited for the FIRST trial and the ERG believes that patients were also recruited from the UK for the FALCON trial because, although this is not explicitly stated, two of the listed study investigators who participated in the study have a UK location. The number of patients who were included from the UK in each trial is not stated.

Table 3 Summary of key design characteristics of the fulvestrant trials

Trial	FIRST[5-7]	FALCON[8]
Trial design	PHASE II open-label multicentre RCT.	PHASE III double blind multicentre RCT
Enrolled population	Postmenopausal women with ER + &/or PgR+ ABC who had either, never received endocrine therapy for advanced disease or had received previous endocrine therapy for early disease completed ≥12 months prior to randomisation.	Postmenopausal women presenting with ER +ve &/or PgR+, HER2-ve ABC who had never received endocrine therapy for breast cancer.
Number of centres (location)	62 (Brazil, Bulgaria, Czech Republic, France, Italy, Poland, Spain, United Kingdom, & United States).	113 (20 countries in Asia, Europe, North America, South America & South Africa).
Intervention (n in arm)	Fulvestrant (n=102)	Fulvestrant (n=230)
Comparator (n in arm)	Anastrazole (n=103)	Anastrazole (n=232)
Data analysis points	Primary analysis of CBR: 6 months after last patient randomly assigned[6] Data cut-off 10th January 2008	Primary analysis of PFS: planned for when 306 progression events had occurred (68% of planned sample size)[8] Data cut off 11th April 2016
	Follow-up analysis for TTP: planned for when 75% of patients had discontinued treatment.[5] Data cut-off 26th March 2010	Interim OS analysis: conducted at the same time as PFS analysis above[8]
	OS analysis: Protocol amendment to assess OS after approximately 65% of patients had died.[7] Data cut-off 15th July 2014	OS analysis: planned for when approximately 50% of patients have died (not yet reported). [redacted]
Primary outcome	CBR (non-inferiority)	PFS (superiority)

ABC, advanced breast cancer; CBR, clinical benefit rate; ER+, oestrogen receptor positive; HER2-ve, human epidermal growth factor 2 receptor negative; PFS, progression-free survival; PgR+, progesterone receptor positive; RCT, randomised controlled trial.

The CS states that baseline characteristics of enrolled patients were well balanced between treatment groups (CS Table 12, p. 44). Whilst this generally appears to be the case for FALCON (CS Table 17, p. 65), in FIRST (CS Table 15, p. 62), the fulvestrant treatment arm includes a

higher percentage of women with prior endocrine therapy completed >12 months prior to randomisation than the comparator arm (28% vs 22% anastrozole). The ERG believes difference is unlikely to have caused an imbalance in outcomes between the trial arms.

The CS contains a summary of the baseline characteristics of participants with fuller information reported in the published papers for the two trials. The ERG added some information from these publications to the table of baseline characteristics that are relevant to the assessment [e.g. receptor status (including HER2 status) and numbers of participants with visceral disease] (Table 4). In the FIRST trial a greater proportion of participants in the anastrozole group had any visceral disease (56% vs 47% in the fulvestrant group) and a greater proportion had lung metastases (41% vs 29% in the fulvestrant group). In the FALCON trial a smaller proportion of women in the anastrozole arm were aged 65 years or more (39% vs 47% in the fulvestrant group) and a greater proportion had 'Other non-visceral' as a disease site (35% vs 26% in the fulvestrant arm).

There were some differences between these two trials in baseline characteristics (see Table 4) The mean age of participants in the FALCON trial was slightly lower (63 years vs 67.1 years FIRST) and FALCON included more women categorised as 'Asian' or 'Black or Other' (24% vs 3% FIRST) than the FIRST trial. A slightly lower percentage of women in the FALCON trial had locally advanced disease (13% vs 18% FIRST), and therefore correspondingly slightly more had metastatic disease compared to women in the FIRST trial (87% vs 82% FIRST). The majority of women in both trials had ER+, PgR+ breast cancer (FIRST 76% vs Falcon 77%), and about 19% of women in the FIRST trial had a positive HER2 status (HER2 positive breast cancer patients were excluded from the FALCON trial). Nearly 10% more participants in FIRST trial received adjuvant chemotherapy compared to FALCON (26% vs 13.5% FALCON) and 23% of the FALCON population received radiotherapy (a characteristic not reported by FIRST). Clinical advice to the ERG indicated that in UK practice it would be unusual to give chemotherapy before endocrine treatment.

In summary, there are two important differences between the FIRST and FALCON trial populations, which are both a consequence of their different inclusion and exclusion criteria. As noted previously, a quarter of all participants in the FIRST trial (n=52) had received prior endocrine therapy (in all but one case this occurred >12 months prior to randomisation). In FALCON, previous hormonal treatment was an exclusion criterion so 99.4% of the population

were endocrine therapy naïve (protocol errors meant that three women who had previously received endocrine therapy were included). As noted in the published paper for the FALCON study,[8] the aim of limiting the included population to women who were prior endocrine therapy naive was to avoid reducing the efficacy of anastrozole in the control group through exposure to prior adjuvant endocrine therapy. The second important difference, also noted above, is that approximately 19% of women in the FIRST trial had a positive HER2 status whereas these patients were excluded from the FALCON trial. HER2 positive breast cancers are typically more aggressive and spread more quickly than HER2 negative breast cancers. The HER2 positive breast cancer patients in FIRST might have been expected to have less favourable outcomes than the HER2 negative patients but this is not commented on in the CS or the FIRST trial publications.[5-7] The other differences between the trials in patient baseline characteristics and treatment experience appear to be minor.

Table 4 Baseline characteristics of patients in the included fulvestrant RCTs

	FIRST		**FALCON**	
Patient demographic and disease characteristics	**Fulvestrant 500 mg (n=102)**	**Anastrozole 1 mg (n=103)**	**Fulvestrant 500 mg (n=230)**	**Anastrozole 1 mg (n=232)**
Gender, % Female	100	100	100	100
Age (years), Mean (SD)	67 (9)	68 (9)	63.8 (9.86)	63.3 (10.38)
Median	66	68	64.0	62.0
Range	40–89	48–87	38-87	36-90
Race, n (%)	**Caucasian**		**White**	
	97 (95.1)	102 (99)	175[a] (76)	174[a] (75)
	Black		**Black or other**	
	3 (2.9)	0	19[a] (8)	24[a] (10)
	Other		**Asian**	
	2 (2.0)	1 (1)	36[a] (16)	34[a] (15)

Patient demographic and disease characteristics	FIRST		FALCON	
	Fulvestrant 500 mg (n=102)	**Anastrozole 1 mg (n=103)**	**Fulvestrant 500 mg (n=230)**	**Anastrozole 1 mg (n=232)**
Receptor status,[b] n (%)				
HR+	102 (100.0)	103 (100.0)	230 (100.0)	232 (100.0)
ER+, PgR+	78 (76.5)	78 (75.7)	175 (76%)	179 (77%)
ER+, PgR–	19 (18.6)	19 (18.4)	44 (19%)	43 (19%)
ER+, PgR unknown	1 (1.0)	3 (2.9)	10 (4%)	7 (3%)
ER–, PgR+	3 (2.9)	3 (2.9)	1 (<1%)	3 (1%)
ER unknown, PgR+	1 (1.0)	0	0	0
HER2 status[b] n (%)	**2+/3+**		**Positive**	
	19 (18.6)	19 (18.4)	0	1 (<1%)
Negative	48 (47.1)	49 (47.6)	230 (100%)	231 (100%)
Unknown	35 (34.3)	35 (34.0)	0	0
Disease stage, n (%)				
Locally advanced only	19 (18.6)	18 (17.5)	28[a] (12)	32[a] (14)
Metastatic	83 (81.4)	85 (82.5)	202[a] (88)	200[a] (86)
Measurable disease	89 (87.3)[b]	93 (90.3)[b]	193[a] (84)	196[a] (84)
Site of disease[b] n (%)				
Any visceral disease	48 (47.1)	58 (56.3)	135 (59%)[c]	119 (51%)[c]
Previous treatment modalities[d,e]				
Prior endocrine therapy n (%)				
None	73 (71.6)	80 (77.7)	228 (99.1)[f]	231 (99.6)[f]
Completed ≤12 months prior to randomisation	1 (1.0)	0	2[a] (1)	1[a] (<1)
Completed >12 months prior to randomisation	28 (27.5)	23 (22.3)		

Patient demographic and disease characteristics	FIRST		FALCON	
	Fulvestrant 500 mg (n=102)	**Anastrozole 1 mg (n=103)**	**Fulvestrant 500 mg (n=230)**	**Anastrozole 1 mg (n=232)**
Prior chemotherapy, n (%)				
None	73 (71.6)	78 (75.7)	152 (66)[f]	151 (65)[f]
Any chemotherapy	NR	NR	78[f] (34)	81[f] (35)
Advanced disease[g]	NR	NR	36[a] (16)	43[a] (19)
Adjuvant chemotherapy	29 (28.4)	25 (24.3)	35[a] (15)	27[a] (12)
Neo-adjuvant	NR	NR	11[a] (5)	16[a] (7)
Any radiotherapy, n (%)	NR	NR	53[a] (23)	50[a] (22)

Table based on CS Table 15 (p. 62) and Table 17 (p. 65).

ER, Oestrogen receptor; HER2, Human epidermal growth factor 2; HR+, Hormone receptor postive; NR, Not reported; PgR, Progesterone; SD, Standard deviation.

[a] number of participants obtained from trial publication[8].

[b] obtained from trial publications (FIRST,[6] FALCON[8]).

[c] Includes patients with site of baseline disease as any of the following: adrenal, bladder, CNS, oesophagus, liver, lung, peritoneum, pleura, renal, small bowel, stomach, pancreas, thyroid, colon, rectal, ovary, biliary tract, ascites, pericardial effusion, spleen, or pleural effusion.

[d] Previous study treatment, as deemed by the sponsor to be relevant to the interpretation of the results.

[e] Therapies prior to enrolment.

[f] Calculated by ERG.

[g] Includes 1L, 2L, 3L, metastatic and palliative chemotherapies.

Both FALCON and FIRST met the inclusion criteria of the submission and all relevant RCTs appear to have been identified in the CS.

The CS did not list any additional ongoing trials which included fulvestrant as a treatment that was not used in combination with another drug and this appears to be correct.

Information is given on the additional four RCTs in the NMA, though in less detail than the two fulvestrant RCTs.

- A summary of methodological characteristics is provided in CS Table 25 (p. 85)
- A summary of outcomes reported by the studies is provided in CS Table 23 (p. 83) and the definitions of PFS and TTP are compared in CS Table 24 (p. 84).

- Clinical characteristics of the participants in the trials are summarised in CS Tables 26 to 28 (pp. 87-89).

The CS did not include any non-randomised or non-controlled studies relevant to the decision problem.

3.1.4 Description and critique of the approach to validity assessment

The CS provided a quality assessment of all the included RCTs (CS Table 12, p. 44 to 45). While an assessment was provided (described as the NICE critical appraisal checklist), the table includes a Jadad score (known to be 1 to 5) and an Allocation Concealment Grade (presumed to be either A or B) for the RCTs. The use of quality assessment scores is discouraged by The Cochrane Collaboration.[14] The CS does not provide any information about the grading scales employed for the Allocation Concealment Grade or indeed interpretation of the final grading score supplied for each of the RCTs (FIRST: 2B and FALCON: 5A).

The ERG has used the NICE criteria for assessing the risk of bias in RCTs based on criteria from the Centre for Reviews and Dissemination for systematic reviews,[15] hence omitting the Jadad score and Allocation Concealment Grade.

The ERG's quality assessment mostly agrees with that of the company (see Table 5). However, contrary to the company, the ERG thinks that it is unclear if there was any bias in relation to allocation concealment in the FIRST trial, mainly due to insufficient details being reported in the CS and the publications. The trial used randomisation cards, but it is unclear if these were in sealed opaque envelopes. The use of unsealed cards or insufficiently opaque envelopes could leave the trial at a potential high risk of bias due to inadequate allocation concealment. The ERG also differs to the company in the assessment of baseline differences for the FIRST and FALCON trials. In both trials there were some differences in the treatment groups at the outset of the trials (as detailed in Table 5). The ERG sought the opinion of the clinical experts for their view on whether these differences could have had an impact on the reported outcomes. Their view was that in the FIRST trial the higher proportion of those with 'any visceral disease' in the anastrozole arm would be associated with worse prognosis. In the FALCON trial the difference in age was unlikely to have an impact and the anastrozole arm might have had a slightly better prognosis as a greater proportion had 'other non-visceral' disease this arm. The ERG agrees with the company's assessment of there being a potential high risk of bias in the FIRST trial in

relation to blinding, especially with regard to outcome assessors, as this was an open label trial. While a blinded independent review was carried out for the primary endpoint, it is unclear if this was applied to other endpoints. Both studies used an ITT analysis and although neither reported how missing data was dealt with in the analyses, missing data appeared to be balanced between trial arms. Overall, both studies appear to have been well conducted.

Table 5 Company and ERG assessment of trial quality

NICE Quality Assurance Criteria for RCT[15]	**Judgements* FIRST**		**Judgements* FALCON**	
1. Was the method used to generate random allocations adequate?	CS:	Low risk	CS:	Low risk
	ERG:	Yes, low risk	ERG:	Yes, low risk
ERG comment: FIRST – CS states central randomisation (CS p. 44) but this information is not present in any of the published papers. [redacted] [16] FALCON - computer generated randomisation scheme.[8]				
2. Was the allocation adequately concealed?	CS:	Low risk	CS:	Low risk
	ERG:	Unclear, uncertain risk	ERG:	Yes, low risk
ERG comment: FIRST - One of the publications states that patients were randomised sequentially using randomisation cards, with the clinical study team unaware of the randomisation scheme.[5] It is unclear if the cards were sealed in opaque envelopes, as unsealed randomisation cards or insufficiently opaque envelopes would leave the study at a potentially high risk of allocation bias. FALCON – integrated voice or web response system.[8]				
3. Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	CS:	Low risk	CS:	Low risk
	ERG:	Unclear, uncertain risk	ERG:	Unclear, uncertain risk
ERG comment: FIRST – around 6% more women in the fulvestrant arm had previous endocrine therapy for early disease compared to the comparator arm (28% vs 22% anastrozole), but fewer had any visceral disease (47% vs 56% anastrozole) and lung metastases (29% vs 41% anastrozole). FALCON - a smaller proportion in the anastrozole				

NICE Quality Assurance Criteria for RCT[15]	Judgements* FIRST		Judgements* FALCON	
arm were aged 65 years or more (39% vs 47% fulvestrant) and a greater proportion had 'Other non-visceral' as a disease site (35% vs 26% fulvestrant).				
4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	CS:	High risk	CS:	Low risk
	ERG:	No, high risk	ERG:	Yes, low risk
ERG comment: FIRST - was an open label study, although a blinded independent review was carried out by a radiologist at BioImaging Technologies to provide assurances that the open-label design did not bias the results of the tumour assessments in this study. The independent reviewers' evaluation was used to corroborate the local investigator read analysis of the primary endpoint (CBR) and concordance was high, but it is unclear if this applied to other outcomes. FALCON – was a double-blind, double-dummy trial and publication states that blinding included those assessing outcomes.[8]				
5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	CS:	Low risk	CS:	Low risk
	ERG:	No, low risk	ERG:	No, low risk
ERG comment: Both trials had higher discontinuation in the comparator arm largely due to disease progression/worsening condition. Participant numbers and reasons for discontinuations were detailed in both studies.				
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	CS:	Low risk	CS:	Low risk
	ERG:	No, low risk	ERG:	No, low risk
ERG comment: Outcomes listed in the methods sections of the published papers match those presented in the results. The ERG did not check trial protocols.				
7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	CS:	Low risk	CS:	Low risk
	ERG:	Yes & Unclear (low risk)	ERG:	Yes & Unclear (low risk)
ERG comment: Although there were insufficient details of how missing data was dealt with for both trials, missing data appears balanced between groups in each trial hence risk of bias is likely to be low.				

CS judgements taken from CS Table 12, p. 44.

3.1.5 Description and critique of company's outcome selection

As stated earlier the outcomes in the CS match those listed in the NICE scope[1] (CS p. 11), those being OS, PFS, objective response rate (ORR), AEs of treatment and HRQoL. For the FALCON study, data are reported from one analysis conducted following the 11th April 2016 data cut off (the point of PFS analysis). For the FIRST trial, data are available from three time points:

- the first data cut-off (10th January 2008)[6]
- the first follow-up (26th March 2010)[5]
- the final assessment of OS (15th July 2014)[7]

The ERG found that it was not always clear in the CS which of these three different points for FIRST was being used for reporting different outcomes.

The primary outcome in the FALCON trial was PFS, defined as time from randomisation until objective disease progression as defined by RECIST 1.1 (Response Evaluation Criteria in Solid Tumours), surgery or radiotherapy to manage worsening of disease or death by any cause (in the absence of progression) (CS Table 24 p. 84).[8]). PFS was not reported by the FIRST trial, instead the trial reported TTP (a secondary outcome), defined as time from randomisation to the time of the earliest evidence of objective disease progression or death from any cause prior to documented progression (CS Table 24 p. 84).

The primary outcome in the FIRST trial was clinical benefit rate (CBR), a secondary outcome in the FALCON trial. This was defined in both RCTs as the proportion of all randomly assigned patients who had best overall response of complete response (CR), partial response (PR) or stable disease (≥24 weeks), CS, p. 50.[6,8]

OS was defined as time from randomisation until death by any cause in both trials.[7,8] However, this was not a planned outcome in the original protocol of the FIRST trial, but added as an addendum after TTP results were analysed following ongoing monitoring and at which time approximately 65% of deaths had occurred (CS p 69).[7]

Key secondary outcomes were CR, PR, safety, HRQoL (FALCON only), ORR and duration of response (DoR; defined as time from response through to progression in FIRST and expected

DoR (EDoR) for the FALCON study) (CS p. 48 and 50). ORR was defined as the proportion of patients with a best overall response of CR or PR assessed only in patients with measurable disease at baseline in both trials.[6,8]

Other outcomes presented in the CS (not contained in the NICE final scope[1]) reported by both trials were median duration of clinical benefit (DoCB) and progressive disease. In addition, the CS presented outcomes such as expected duration of clinical benefit (EDoCB) and median time to onset of response for the FALCON trial.

Ten pre-specified adverse events (AEs) are presented for the FIRST trial, while AEs for FALCON were graded according to Common Terminology Criteria for Adverse Events [CTCAE], version 4·0 (no reference provided in either the CS or the published paper[8], but these are published by the U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute[17]). Incidence of serious adverse events (SAEs) and deaths are presented for FIRST at final data cut-off (65% OS), and for FALCON limited to frequency of ≥5% in any treatment group. Discontinuations due to AEs are presentenced in the CS by organ class for both trials.

For the NMA, outcomes were limited to PFS and OS.

All outcomes covered in the trials were reported in the CS.

Only the FALCON trial measured HRQoL, using the EuroQoL5 Dimensions Questionnaire-3L (EQ-5D-3L, visual analogue scale and health index score) (CS, p 72) reported at baseline (week 0) and the end of the trial (week 156). The ERG notes that the EQ-5D is a validated, generic measure of HRQoL and is NICE's favoured HRQoL measure.[18] The index was calculated using the utility value set for the UK (CS p. 148). Utilities for both time spent in PFS and progressed disease (PD) health states were calculated from the EQ-5D and used in the cost-effectiveness analysis (see Section 4.3.6 for more information). HRQoL was also assessed by the Functional Assessment of Cancer Therapy – Breast (FACT-B) questionnaire which is a self-reported questionnaire, comprising four general FACT-B subscales (physical well-being, functional well-being, social well-being and emotional well-being) along with the Breast Cancer-Specific subscale that assesses symptoms/concerns of particular relevance to breast cancer such as body image, arm swelling and tenderness,[19] assessed on a 5-point Likert scale (0 = Not at all to

4 = Very much). The main outcome measure from the FACT-B questionnaire was the trial outcome index (TOI), summarising the physical well-being, functional well-being and breast cancer subscales (CS p 72). The FACT-B is also a validated measure of HRQoL.

Overall, we consider that the CS appropriately addresses the outcomes listed in the NICE scope.[1]

3.1.6 Description and critique of the company's approach to trial statistics

The CS reports the results for all the relevant primary and secondary outcomes listed in CS Table 14 (CS p. 55) for the FIRST and FALCON trials. An interim analysis of OS is presented for the FALCON trial which was done at the time of the analysis of the primary outcome, PFS (CS p. 58).

The CS reports the statistical methods used to analyse data and details about power calculations (CS section 4.4 p. 57 to 60). Both trials were adequately powered.

Efficacy results are presented in the CS in terms of percentages, odds ratios or hazard ratios (HRs) with 95% confidence interval (CIs) and p-values. The number of participants included in the analyses is clearly identified and where only a percentage value is reported, the number of participants with an event can usually be calculated. HRQoL data are presented in CS Figure 16 and CS Figure 17 (CS p. 73 to 74), however these data are not presented in tabular form (values need to be read from the figures). The company confirmed in response to the ERG and NICE clarification question A14, that neither the FIRST nor the FALCON trial were designed to formally allow cross-over (treatment switch) between trial arms.

Analysis sets

The CS describes four different analysis sets for the FIRST trial which are summarised in CS Table 16 (CS p. 63), and three analysis sets for the FALCON trial which are summarised in CS Figure 11 (CS p. 66). The ITT analysis set (described as the full analysis set for the FIRST trial) includes all randomised patients analysed in the group to which they were assigned, regardless of actual treatment received.

In most cases the number of participants contributing data to the analyses matches one of the analysis sets described. The two exceptions are in CS Table 19 (CS p. 70, 'Summary of

additional secondary outcomes in FIRST') where the number of patients for the FALCON trial was given in error (confirmed by the company in response to the ERG and NICE clarification question A2) and in the reporting of FALCON HRQoL data, where number of patients at baseline for mean TOI does not match any of the FALCON analysis sets (CS Figure 16, p. 73) and numbers of patients for the EQ-5D-3L analysis are not provided (CS Figure 17, p. 74). In response to the ERG and NICE clarification question A3, the company indicated that although analyses of the TOI were performed on the ITT analysis set, however only [redacted] participants provided evaluable forms at baseline. The company also supplied a reference (which had been omitted in error from the original reference pack) that provided details of the number of patients contributing data to the EQ-5D-3L analysis.

Safety outcomes were analysed using the safety analysis set in both trials. This was defined as all randomised participants who received at least one dose of the trial drug (including placebo fulvestrant or placebo anastrozole). The proportion of participants excluded from the safety outcomes analyses was very low [FIRST trial 1/205 (0.49%); FALCON trial 2/462 (0.43%)].

Subgroups

The CS includes results from subgroup analyses. For the FALCON study analysis of subgroups was performed as defined by covariates and the same approach appears to have been taken in the FIRST study. For the FIRST trial, these were not pre-planned and not part of the initial analysis as published in 2009 by Robertson et al.,[6] however five covariates were pre-defined for the next analysis of TPP published in 2012[5] [age, receptor status, visceral involvement, prior chemotherapy, and measurable disease (CS p. 77)]. In addition six patient exploratory subgroups were prespecified for the post-hoc OS analyses[7] [age, receptor status, visceral involvement, prior chemotherapy, measurable disease, prior endocrine therapy (CS p. 78)].

For the FALCON trial, PFS analyses were pre-specified for six subgroups in the study protocol (if numbers permitted) (ER+ and PgR+ at baseline, metastatic disease at baseline, use of bisphosphonates, measurable disease, prior chemotherapy for locally advanced or metastatic breast cancer, geographic region). Some amendments were then made to the planned analyses before unblinding, which included adding two further subgroups [prior oestrogen containing hormone replacement therapy (HRT) and visceral disease]. The amendments at this stage also included adding subgroup analysis for OS.

The clinical experts the ERG consulted thought the choice of subgroups was on the whole appropriate. One clinical expert thought that the use of bisphosphonates and measurable disease were unlikely to be important prognostic factors whereas other important prognostic factors such as performance status, lactate dehydrogenase (LDH) and number of sites of disease had not been considered.

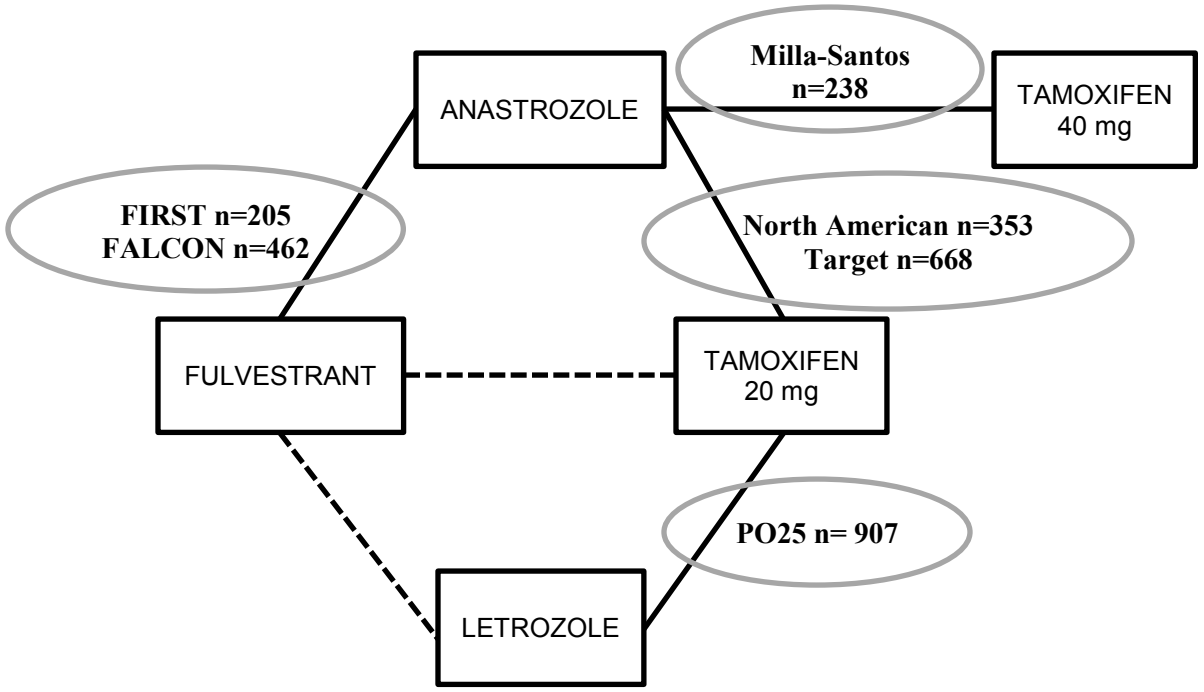
3.1.7 Description and critique of the company's approach to the evidence synthesis

A narrative review of the evidence from the key fulvestrant studies FIRST[5-7] and FALCON[8] is presented in the CS Section 4 (pp. 36 to 81 and 119 to 123). Where possible the ERG has checked key data presented in the CS against those in the publications and identified a few minor discrepancies, most of which appear to be typographical errors.

No pair-wise meta-analyses for the outcomes of interest are presented in the CS for FIRST and FALCON, only network meta-analysis (NMA) was conducted. The ERG and NICE asked the company to provide results for pairwise comparisons of interventions in the NMA (clarification question A10) and these were provided.

Although there were two RCTs that compared fulvestrant with anastrozole, there were no RCTs that compared fulvestrant with the other possible comparators, letrozole and tamoxifen. The company therefore conducted an NMA incorporating trials of anastrozole versus tamoxifen and one trial of letrozole versus tamoxifen to enable an indirect comparison of fulvestrant with letrozole and tamoxifen.

A diagram showing the core network of relevant evidence is presented in the CS (Figure 22, p. 82) however this does not show the indirect comparisons being made. The direct comparisons, evidence for these, and the indirect comparisons being made are shown in Figure 2.



Interventions are shown in rectangular boxes, available trial evidence is shown in oval shapes. Solid lines indicate direct comparisons, dashed lines indicate indirect comparisons.

Figure 2 Network of studies included in the NMA

Of the six trials contributing data to the network, patient level data were available for the two trials conducted by the company (FIRST and FALCON) and also for a combined data set for the two trials that compared anastrozole and tamoxifen 20 mg, TARGET and North American (which were both supported by grants from AstraZeneca and were prospectively designed to allow for combined data analysis). The combined data set is referred to as NorthAmTarget in the CS. For the single trials available for the anastrozole versus tamoxifen 40 mg comparison (Milla-Santos et al.[11]) and the letrozole versus tamoxifen comparison (PO25 trial[12]) the original patient level data were not available.

3.1.7.1 Outcome measures used in the NMA

The outcome measures reported by the six trials contributing to the network of evidence are summarised in a CS table which has been reproduced below (Table 6). All six trials report PFS (or TTP), and five trials report OS (the FALCON trial is not shown as reporting OS, presumably because those data are not yet mature), ORR, CBR, OS rate, and PFS rate. DoR and TTF were reported by two trials and safety outcomes by four trials.

Table 6 Outcomes reported across the studies to be included in the NMA (CS Table 23, p. 83)

Study Name	PFS	OS	ORR	CBR	OS rate	PFS rate	DoR	TTF	Safety
FALCON trial[8]	✓	-	✓	✓	✓	✓	✓	-	✓
FIRST study[6]	✓	✓	✓	✓	✓	✓	-	✓	✓
Milla-Santos 2003[11]	✓	✓	✓	✓	✓#	✓#	-	-	✓
North American trial[9]	✓	✓**	✓	✓	✓**#	✓#	✓	✓	✓
TARGET trial*[10]	✓	✓**	-	-	✓**#	✓	-	-	-
PO25 trial*[12]	✓	✓	✓	✓	-	-	-	-	-

OS: Overall survival; PFS: Progression-free survival; ORR: Overall response rate; CBR: Clinical benefit rate; DoR: Duration of response; TTF: Time to treatment failure
*Studies reporting subgroup data of interest
**OS data reported from combined analysis of North American trial and TARGET trial and not for individual studies
#Data reported graphically and were captured using Engauge software

Only PFS and OS were selected for the NMA. The CS does not provide a rationale for selecting just these two outcomes, but the ERG presumes this was because only these outcomes contribute to the economic model inputs. This is therefore considered reasonable.

The CS states that the heterogeneity of the six studies forming the evidence network was assessed for the PFS and OS outcomes and a discussion of the results for heterogeneity assessment for each comparison per outcome is provided (CS p. 83).

For the NMA of PFS, only one of the six studies (FALCON) actually reported PFS, the remainder reported TTP. The definitions of PFS and TTP are presented in a table (CS Table 24 p. 84). Theoretically TTP differs from PFS in that it should be defined as the time from randomisation until objective tumour progression i.e. it does not include deaths. However, in practice, death (either from breast cancer or from any cause) is often also counted as an event.[20] All the definitions of TTP for the five trials reporting this outcome are provided in the CS and include deaths. Death was specified as being due to any cause in the FALCON, FIRST and PO25 trials, but the types of death contributing to TTP in the Milla-Santos, North American and TARGET trials were not described. The Milla-Santos trial did not provide the starting point for the assessment of TTP, whereas in the other five trials the interval was calculated from the time of randomisation. The ERG agrees that the definitions of PFS and TTP for the six studies

are similar, but notes that Milla-Santos only calculated TTP for patients with a clinical benefit (CR or PR or stable disease ≥ 24 weeks).

The CS does not report the definitions for OS from the six studies. The ERG has checked these and for five of the studies these are the same (from random assignment to death from any cause) whereas the Milla-Santos trial measured OS from the beginning of treatment. The time difference between randomisation and the beginning of treatment in the Milla-Santos trial is not known, so there is the potential for OS to differ slightly from the other studies for this reason.

3.1.7.2 Methodological quality of NMA trials

The CS summarises the methodological and clinical characteristics of the participants in the six studies available for inclusion in the NMA in CS Table 25 and Tables 26 to 28 respectively (p. 85 and pp. 87 to 89).

In addition to the methodological summary presented in CS Table 25 (p. 85) a critical appraisal of the trials is presented in a table earlier in the CS (CS Table 12, p. 44-45). The ERG have done its own critical appraisal of the trials, based on NICE criteria, and this is presented alongside that of the company in Table 7. No judgements of a high risk of bias were made however for many items the judgement was 'unclear' because the details necessary to determine the risk of bias were not reported in the published papers.

Table 7 Quality assessment of the included NMA studies

(see section 3.1.4 Table 5 for the QA of the FIRST and FALCON trials)

QA Criteria for RCT	Milla-Santos[11]		North American[9]		TARGET[10]		PO25 trial[12]	
1. Was the method used to generate random allocations adequate?	CS:	Not clear	CS:	Adequate[a], low risk of bias	CS:	Adequate[a], low risk of bias	CS:	Adequate[b], low risk of bias
	ERG:	Unclear	ERG:	Unclear	ERG:	Unclear	ERG:	Yes, low risk of bias
ERG comments: The North American and TARGET papers[9,10] do not state the method used to generate random allocations. [a] Central randomisation; [b] Computer generated randomisation								
2. Was the allocation adequately concealed?	CS:	Grade B	CS:	Grade A	CS:	Grade A	CS:	Grade A
	ERG:	Unclear	ERG:	Unclear	ERG:	Unclear	ERG:	Unclear
ERG comments: None of the studies provide the information needed to determine whether allocation was adequately concealed.								
3. Were the groups similar at the outset of the trial in terms of prognostic factors, e.g. severity of disease?	CS:	Low risk	CS:	Low risk	CS:	Low risk	CS:	Low risk
	ERG:	Yes, low bias risk	ERG:	Unclear	ERG:	Unclear	ERG:	Yes, low risk of bias
ERG comments: The North American trial and Target trial publications state~~s~~ that the groups were well balanced however some differences are apparent in baseline characteristics, but these are not discussed in the papers (e.g. in both trials differences in proportions with metastatic disease at different sites such as the liver, and in the North American trial an approximate 9% difference in the proportion with measurable disease).								
4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	CS:	Not clear	CS:	Double blind, low risk	CS:	Double blind, low risk	CS:	Double blind, low risk
	ERG:	Unclear	ERG:	Yes, low risk of bias.	ERG:	Yes, low risk of bias.	ERG:	Yes, low risk of bias.

ERG comments: The North American, TARGET and PO25 studies had appropriate placebo tablets in each arm (i.e. intervention A + placebo B; placebo A + intervention B). In these three trials it was unclear if outcome assessors were blinded. PO25 trial – states that internal Novartis data evaluation committee reviewed in a blinded fashion all tumour assessment and overall response data.								
5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	CS:	Low risk	CS:	Not clear	CS:	Not clear	CS:	Not clear
	ERG:	No, low bias risk	ERG:	Unclear	ERG:	Unclear	ERG:	No, low risk of bias
ERG comments: Milla-Santos flow diagram indicates all patients completed the trial. North American & Target trials list the reasons why participants might be withdrawn but it is unclear if all withdrawals are described in the papers and there are no flow diagrams. PO25 does not present a flow diagram, however all participants appear to be accounted for with those excluded from the ITT analysis appearing balanced between groups.								
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	CS:	Not clear	CS:	Not clear	CS:	Not clear	CS:	Not clear
	ERG:	Unclear	ERG:	Unclear	ERG:	Unclear	ERG:	Unclear
ERG comments: The protocols for these studies were not referenced and so it has not been possible to ascertain whether there were any measured outcomes that were not reported in the published papers or indeed more outcomes than stated in the protocol.								
7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	CS:	Low risk	CS:	Low risk	CS:	Low risk	CS:	Low risk
	ERG:	Unclear; Unclear	ERG:	Yes, low risk of bias; Unclear	ERG:	Yes, low risk of bias; Unclear	ERG:	Yes, low risk of bias; Not applicable
ERG comments: Milla-Santos - CS states that the safety and efficacy analysis was done using ITT population, but this is not reported in the publication. In Trial PO25 all participants appear to be accounted for i.e. no missing data.								

CS judgements taken from CS Table 12, p. 44 and Table 25, p. 85

3.1.7.3 Assessment of NMA heterogeneity

The ERG has summarised key trial characteristics in Table 8.

Table 8 Summary characteristics of trials included in the NMA

Trial	FIRST[5-7]	FALCON[8]	Milla-Santos[11]	North American[9]	TARGET[10]	PO25[12,13]
Trial design	PHASE II open-label multicentre RCT	PHASE III double blind multicentre RCT	Phase III single centre RCT (blinding unclear)	PHASE III double blind multicentre RCT	PHASE II double blind multicentre RCT	PHASE III double blind multicentre RCT
Enrolled population	Postmenopausal women with ER+ &/or PgR+ ABC[a]	Postmenopausal women with ER+ &/or PgR+, HER-ve ABC[b]	Postmenopausal women with ER+ ABC[c]	Postmenopausal women with ER+ &/or PgR+ or of unknown receptor status ABC[d]	Postmenopausal women with ER+ &/or PgR+ or of unknown receptor status ABC[d]	Postmenopausal women with ER+ &/or PgR+ or of unknown receptor status ABC[e]
Number of centres (location)	62 (Brazil, Bulgaria, Czech Republic, France, Italy, Poland, Spain, United Kingdom, & United States).	113 (20 countries in Asia, Europe, North America, South America & South Africa).	1 (NR, but presumed to be Spain)	97 (USA & Canada)	83 (Europe, Australia, New Zealand, South America, & South Africa)	201 (29 countries. Countries NR)

Trial	**FIRST**[5-7]	**FALCON**[8]	**Milla-Santos**[11]	**North American**[9]	**TARGET**[10]	**PO25**[12,13]
Intervention (n in arm)	Fulvestrant (n=102)	Fulvestrant (n=230)	Anastrazole (n=121)	Anastrazole (n=171)	Anastrazole (n=340)	Letrazole (n=453)
Comparator (n in arm)	Anastrazole (n=103)	Anastrazole (n=232)	Tamoxifen, 40 mg (n=117)	Tamoxifen, 20 mg (n=182)	Tamoxifen, 20 mg (n=328)	Tamoxifen, 20 mg (n=454)
Primary outcome	CBR	PFS	NR[f]	TTP & ORR	TTP & ORR	TTP

ABC, advanced breast cancer; CBR, clinical benefit rate; ER+, oestrogen receptor positive; n, number; NR, not reported; ORR, objective response rate; PFS, progression-free survival; PgR+, progesterone receptor postive; RCT, Randomised controlled trial; TTP, time to progression.

[a] who had either, never received endocrine therapy for advanced disease or had received previous endocrine therapy for early disease completed ≥12 months prior to randomisation.

[b] who had never received endocrine therapy for breast cancer.

[c] who had not had previous therapy for advanced disease and no previous hormonal adjuvant therapy.

[d] Prior adjuvant chemotherapy or hormonal therapy for early BC was permitted, provided tamoxifen had not been received within 12 months prior to randomisation.

[e] No prior endocrine therapy for advanced breast cancer was permitted. Patients with disease relapse or recurrence during adjuvant anti-oestrogen therapy or who were within 12 months of completing such therapy were excluded.

[f] Not reported but main endpoints stated as overall response and clinical benefit.

The clinical characteristics summarised in CS tables 26 to 28 highlight some differences between the trial populations which are summarised in the CS on p. 86. The ERG presents selected characteristics in Table 9 and the ERG's view is summarised below:

- Measurable disease at baseline - in the North American trial the proportion of participants with measurable disease at baseline was lower than in most other studies (less than 80% in both arms), whereas it was approximately 85% or above in four of the other studies (CS Table 26 states not reported for PO25, but the ERG believes it can be deduced from details provided in the paper[12] that approximately 85% or more had measurable disease).
- Metastatic disease at baseline - a lower proportion of participants had metastatic disease at baseline in the FIRST and FALCON trials than in the other studies.
- Metastatic sites - participants in the FALCON and FIRST trials were less likely to have bone metastases than participants in the other trials, whereas those in the TARGET trial were less likely to have visceral metastases than the other trials.
- Endocrine therapy naïve - just fewer than 75% of the FIRST trial participants were endocrine therapy naïve. In the other studies 80% or more of the participants were endocrine therapy naïve and in two, FALCON and Milla-Santos, 99% or more were endocrine therapy naïve.
- Receptor status - the proportion of participants with breast cancer known to be HR+ where reported was lower in the North American, PO25 and TARGET trials than in the FALCON, FIRST and Milla-Santos trials where 100% of participants were known to have HR+ breast cancer.

Whilst some of the characteristics (e.g. being endocrine naive, lacking visceral metastases, absence of metastatic disease) are associated with better outcomes in individual patients, it is difficult to make cross-trial comparisons.

Table 9 Selected characteristics of patients included in the NMA trials

Trial	**FIRST[5-7]**	**FALCON[8]**	**Milla-Santos[11]**	**North American[9]**	**TARGET[10]**	**PO25[12,13]**
Age, years (median unless stated otherwise)	Ful = 66	Ful = 64	Ana = 60.2 Mean	Ana = 68	Ana = 67 Mean	Let = 65
	Ana = 68	Ana = 62	Tam = 60.6 Mean	Tam = 67	Tam = 66 Mean	Tam = 64
	Ful = 84	Ful = 87	Ana = NR[a]	Ana = 68	Ana = 89	Let = NR

Trial		FIRST[5-7]	FALCON[8]	Milla-Santos[11]	North American[9]	TARGET[10]	PO25[12,13]
Measurable disease at baseline, %		Ana = 85	Ana = 90	Tam = NR[a]	Tam = 77	Tam = 87	Tam = NR
Metastatic disease at baseline		Ful = 88	Ful = 81	Ana = 100	Ana = 99	Ana = 99	Let = 93
		Ana = 86	Ana = 83	Tam = 100	Tam = 99	Tam = 100	Tam = 92
Endocrine naive participants, %		74.6	99.4	100	80	89	82
HR status, %	**HR+**	100	100	100	89	45	66
	ER+	97	99	100	85	43	NR
	PgR+	80	77	NR	69	26	NR
	HER-ve	47	99.8	NR	NR	NR	NR

This table draws on information presented in CS Tables 26, 27 and 28 pp. 87-89
[a] The Milla-Santos publication does indicate that patients were required to have bi-dimensional measurable lesions or evaluable lytic bone metastases.
Ana, anastrozole; ER+, oestrogen receptor positive; Ful, fulvestrant; HER-ve, human epidermal growth factor receptor negative; HR, hormone receptor; Let, letrozole n, number; NR, not reported; PgR+, progesterone receptor positive; Tam, tamoxifen.

Some aspects of the clinical characteristics appear broadly similar between the trial populations (e.g. age), whereas others were not sufficiently reported across the studies to make a judgement about how similar the populations were (performance status, HER2 status, Prior surgery &/or radiotherapy, Race and disease-free interval). As previously noted, the CS states that eligibility was not restricted to populations known to be HER2 negative because HER2 receptor testing was not routinely conducted until the mid-2000s. This means that HER2-positive patients may have been included in the comparator studies and if HER2 positive patients were included and they responded less well to treatment this would disadvantage the comparator studies.

The CS does not present a 'bottom-line statement' following the assessment of heterogeneity, however as an NMA was conducted, the ERG presumes that the company judged the studies were sufficiently similar to combine. The CS does state that studies were similar with respect to age of participants, patient performance status, largely similar in race, comparable in terms of metastatic sites of the disease and the majority of patients (>70%) were endocrine treatment naïve. However, the population in PO25 may not have been as similar to the other studies (because a third of patients were not HR+).

CS p. 90 presents further considerations for NMA and at this point explains that the Milla-Santos trial was excluded from the final network (because it was the only trial to use the higher 40 mg dose of tamoxifen, which is not approved by the EMA and because its inclusion led to heterogeneity in the NMA of both the OS and PFS outcomes, which may have been because these were calculated only for patients with clinical benefit and not for all patients). Furthermore, for the OS outcome only, OS results for the North American and TARGET trials combined were available, and hence combined OS results from these trials were considered in the OS analysis. From the description provided in the CS, it also seems that the North American and TARGET trial data were combined for the PFS analysis, although this is not explicitly stated.

ERG summary on the heterogeneity of trials:

- There are some differences between the trials, both in terms of methodology and participants.
- The exclusion of the Milla-Santos trial from the network seems appropriate due to the use of the higher dose of tamoxifen in this trial and because OS and PFS were not calculated for the full trial population in this trial.
- The inclusion of FIRST, FALCON, North American, TARGET and PO25 trials appears appropriate despite some evidence of heterogeneity in trial participants between the trials, but this could potentially be accounted for by using a random effects model.

3.1.7.4 NMA statistical methods

The methods of the NMA are presented in CS section 4.10.1 (pp. 90 - 99).

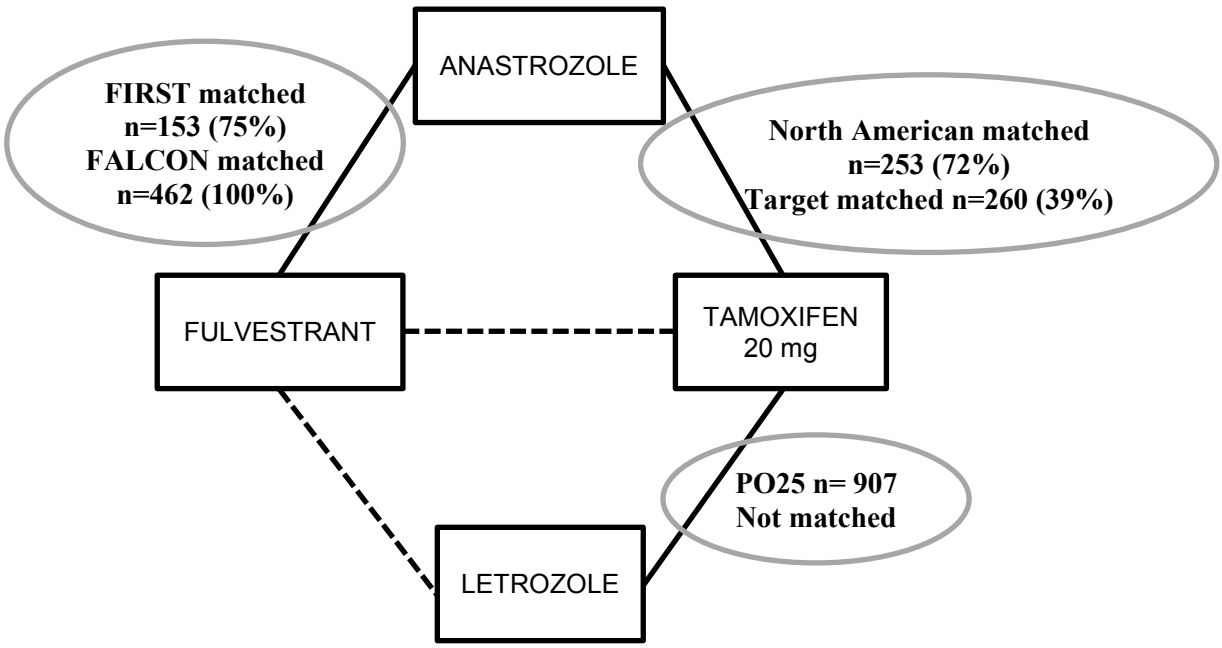
The CS states that the inclusion and exclusion criteria from the FALCON trial were applied to each treatment arm of the FIRST and NorthAmTarget trials for which patient level data were available. The reason the CS gives for this approach was so that the FIRST and NorthAmTarget trials would better match the FALCON trial population (CS pp. 90 - 91). Although not explicitly stated the ERG presumes that the reason studies were matched to FALCON (instead of another study) was because this is the pivotal phase III trial for the proposed new indication for fulvestrant. No details of the matching methodology used were presented in the CS, so the ERG and NICE sought clarification from the company. In response to clarification question A8, the company explained that criteria were applied so that only data for ER+/PgR+ patients plus endocrine treatment naive patients would be

included. The ERG assumed that the matching process would decrease the sample size of the FIRST and NorthAmTarget trials, but this was not commented on in the CS and patient demographics or clinical characteristics for these trials following the matching process were not presented. The ERG and NICE therefore asked the company to provide this information in clarification question A9. The company were able to supply information regarding the number of study participants retained after matching and this is summarised below (Table 10 and Figure 3). As can be seen the effect of matching in decreasing the numbers of participants included in the NMA was most pronounced for the TARGET trial where only 39% of participants met the matching criteria. The company do not comment on this but the ERG believes that this is because for 55% of participants in TARGET had unknown ER and unknown PgR status.[10]

Table 10 Patient numbers in the NMA studies before and after matching to the FALCON trial.

	Trial									
	FALCON		FIRST		North American		TARGET		NorthAm-Target	
Treatment arm	Ful	Ana	Ful	Ana	Ana	Tam	Ana	Tam	Ana	Tam
ITT population, n	230	232	102	103	171	182	340	328	511	510
Matched to FALCON, n (%)	230 (100)	232 (100)	73 (72)	80 (78)	119 (70)	134 (74)	132 (39)	128 (39)	251 (49)	262 (51)

This table draws on information presented in the company's written response to clarification question A9, Table 3. Note trial PO25 is not included because only aggregate data were available.
Ana, anastrozole; Ful, fulvestrant; ITT, intention-to-treat; Let, letrozole; n, number; Tam, tamoxifen



Interventions are shown in rectangular boxes, available trial evidence is shown in oval shapes. Solid lines indicate direct comparisons, dashed lines indicate indirect comparisons. Numbers and proportion of participants remaining after matching are provided for the FIRST, North American and Target studies.

Figure 3 Network of final set of studies and patient numbers after matching

As noted above, although a matching process with the FALCON trial was undertaken, the CS does not report the demographic and clinical characteristics of the matched populations. The ERG and NICE therefore sought clarification from the company (clarification question A9) and in response, baseline characteristics for the matched trial populations were provided. Where possible the ERG has compared the baseline characteristics for the matched trial populations and those for the whole trial populations reported in CS Tables 26-28. Where the ERG is confident that the definition of characteristics correspond (e.g. age, visceral disease, measurable disease) the baseline characteristics of the matched and whole trial population data are very similar. As expected, the matching process increased homogeneity between the FALCON and the FIRST and NorthAmTarget trials but heterogeneity remained with the PO25 trial for which only aggregate level data were available (Table 11).

The ERG is not aware of any published methodological guidance that addresses the issue of matching individual patient data (IPD) from one trial (in this case FALCON) to IPD from other studies (in this case FIRST and NorthAmTarget). Whilst it is clear that the matching process allows for the exclusion of participants [redacted]

[redacted] to create a more homogeneous population in the NMA the ERG is concerned about potential disadvantages, for example if matching creates scope for bias as randomisation has been broken. For this reason the ERG and NICE asked the company in clarification question A12 to provide results using all study data from FIRST and NorthAmTarget (i.e. to conduct the analysis without undertaking the matching process). The company declined to do this because approximately a third of the patients in the resulting network (560/1688) would be outside the scope for the appraisal. The ERG has concluded that, the known advantages of matching in [redacted] reducing heterogeneity in the NMA (at least for the trials that could be matched) are likely to outweigh potential disadvantages. A similar conclusion was reached in a previous STA for fulvestrant (TA239[21]) in which only a subgroup of one trial met the decision problem. The ERG for that STA believed that the advantages of decreased heterogeneity outweighed the disadvantages of reduced power.

Table 11 Baseline characteristics of participants in the FIRST and NorthAmTarget studies after matching in comparison to the unmatched PO25 study.

Characteristic n (%) unless stated otherwise	**FALCON** baseline		**FIRST** (matched to FALCON)		**NorthAmTarget** (matched to FALCON)		**PO25** baseline (no IPD, unmatched)	
	Ful n=230	Ana n=232	Ful match n=73	Ana match n=80	Ana match n=251	Tam match n=262	Let n=453	Tam n=454
Median age, years	64	62	67	69	67	66	65	64
ER+ and/or PgR+	220 (96) 10 un[a]	225 (97) 7 un[a]	73 (100)	80 (100)	251 (100)	262 (100)	294 (65) 156 un	305 (67) 149 un
Visceral disease	135 (59)	119 (51)	33 (45)	43 (54)	103 (41)	132 (50)	194 (43)	208 (46)
Bone only disease	24 (10)	24 (10)	2 (3)	2 (3)	53 (21)	50 (19)	69 (15)	72 (16)
Soft tissue only disease	8 (4)	6 (3)	0	0	53 (21)	45 (17)	113 (25)	116 (25)
No prior chemo	151 (66)	151 (65)	63 (86)	68 (85)	191 (76)	198 (76)	320 (71)	301 (66)
Prior chemo for ABC	36 (16)	43 (19)	0	0	0	0	40 (9)	48 (11)
Prior adjuvant chemo	43 (19)	40 (17)	10 (14)	12 (15)	60 (24)	65 (25)	93 (21)	105 (23)
Prior endocrine therapy[b]	2 (1)	1 (0.4)	0	0	0	0	84 (19)[c]	83 (18)[c]
Measurable disease	193 (84)	196 (84)	69 (95)	78 (98)	195 (78)	208 (79)	-	-
Locally advanced	28 (12)	32 (14)	19 (26)	18 (23)	-	-	145 (32)	146 (32)

This table draws on information presented in the company's written response to clarification question A9, Tables 4,5,6 and 9.

Grey shading indicates the characteristics that were matched. +ve, positive; ABC, advanced breast cancer; Ana, anastrozole; ER, oestrogen receptor; Ful, fulvestrant; IPD, individual patient data, Let, letrozole; n, number; PgR, progesterone receptor; Tam, tamoxifen; un, unknown

[a] The patients noted as being unknown are, according to the published paper ER+ and PgR unknown. Therefore the ERG believes that all FALCON participants are HR+; [b] Adjuvant endocrine therapy for early disease; [c] labelled as prior adjuvant anti-oestrogen therapy in the PO25 trial.

After the inclusion and exclusion criteria of FALCON had been applied to FIRST and NorthAmTarget, Kaplan-Meier (KM) plots of PFS and OS were produced for the matched subgroups of participants. For PO25 the published KM plots for the whole study population were digitised and then patient-level data were reconstructed using a published algorithm.[22]

The OS and PFS data were examined to determine whether there was a constant relative treatment effect over time by visual inspection of the KM plots for PFS (CS Figure 23, p. 92) and OS (CS Figure 24, p. 93), and visual inspection of log cumulative hazard plots for PFS (CS Figure 25, p. 98) and OS (CS Figure 26, p. 99) for each trial. The OS KM plots for the arms of the PO25 trial and the NorthAmTarget trial cross, suggesting that a constant relative treatment effect is unlikely in these studies. In the log cumulative hazard plots, a constant relative treatment effect (i.e. proportional hazards) could be assumed if the two lines for each trial run parallel to each other, but this is not the case for all studies.

The company therefore concluded that methods for NMA that rely on the assumption of proportional hazards being true would be inappropriate. The method used for NMA is one developed by Ouwens et al.[23] In this method the differences in the shape and scale parameters of the parametric survival function used to model PFS or OS between the intervention and each comparator over time are synthesised, and used both for the indirect comparison and to extrapolate the PFS and OS curves beyond the end of trial follow-up (see Section 4.3.5). The parametric distributions used to model the KM data were the Weibull, Gompertz, log-logistic, lognormal and generalised gamma. Although not explicitly stated in CS Section 4.10.1 (pp. 90 - 99), the ERG assumes that the analysis took a Bayesian approach using a Markov Chain Monte Carlo method implemented using the WinBUGs software package (as described by Ouwens et al.[23]).

The shape and scale parameters were calculated for the baseline (reference), which was anastrozole. These baseline parameters were then used as the anchor to obtain the estimates for the shape and scale of the other interventions in the network (i.e. fulvestrant, letrozole and tamoxifen).

If the shape parameter is regarded as fixed between treatment arms, this effectively assumes a proportional treatment effect. This ‘no shape arm’ model was tested in sensitivity analysis for all but the generalised gamma model (which, as a three parameter model, was more complex and therefore not included).

A fixed-effect meta-analysis was undertaken. The rationale for not including a random effects model was the limited number of trials in each network. Whilst the ERG agrees that the number of trials is limited, as noted earlier there is some evidence of heterogeneity in trial participants between the trials, which the ERG thought could potentially be accounted for by using a random effects model. The ERG and NICE therefore asked the company to provide results from a random effects NMA (clarification question A10). In response to clarification question A10, the company provided a more detailed explanation of the reasons why a random effects NMA could not be undertaken. Due to the presence of the pooled NorthAmTarget dataset, the only connection in the network where there are two or more trials is the fulvestrant-anastrozole comparison informed by the FALCON and FIRST trials (as shown in Figure 2). The company cites a recent (2016) paper by Friede et al.[24] which states that, in the Bayesian framework, if the number of studies is small then the choice of prior for the between-trial standard deviation is critical. The company goes on to state that an attempt was made to identify an informative prior (as detailed in the response to clarification question A10) but this proved a "*difficult question to answer*" and therefore they concluded, as before, that the more robust approach was to use a fixed effect meta-analysis.

The ERG accepts that there are few trials in the network and that, with the methodology the company have used for the NMA, a random-effects NMA is not possible, the ERG nevertheless is concerned that the potential uncertainty around the effect estimates may not be adequately represented.

The final consideration regarding the NMA is that for the PO25 trial IPD were not available and thus this trial population could not be matched to the FALCON inclusion and exclusion criteria. Furthermore, crossovers between treatments occurred in this trial which may have confounded the survival analysis and there is now a general agreement that the efficacy and safety of anastrozole and letrozole are equivalent [e.g. NICE CG81[2] states "All aromatase inhibitors appear to be equally effective in terms of primary outcome (overall survival)"]. For these reasons a scenario analysis in the economic model assumes the efficacy of letrozole is equivalent to anastrozole by using the anastrozole curves for letrozole (i.e. efficacy data from the PO25 trial is not used). The ERG had an additional concern regarding whether the data for TTP and OS came from the whole PO25 population or the HR+ subgroup (66%) and clarification was requested on this by the ERG and NICE. The company confirmed in their response to clarification question A6 that data from the full study population were used. Because of the differences between the PO25 study and the others in the network, and the general agreement that the efficacy of anastrozole and letrozole are equivalent, the ERG and NICE requested in clarification question A13 that an analysis omitting study PO25 from

the network be conducted and the company complied with this request (results are discussed in section 3.3).

3.1.7.5 ERG summary of the company's approach to evidence synthesis

The ERG agrees that, in the absence of RCTs comparing fulvestrant with the other comparators of interest, letrozole and tamoxifen, conducting an NMA to enable indirect comparisons between fulvestrant versus letrozole and fulvestrant versus tamoxifen is appropriate.

The ERG believes that the company has identified appropriate published data sources for the NMA. Six trials are included: two RCTs, FIRST and FALCON, of fulvestrant versus anastrozole; three RCTs, of anastrozole versus tamoxifen; and one RCT of letrozole versus tamoxifen. The selection of outcomes for analysis (PFS and OS) is reasonable.

It was difficult to determine the potential for bias in the four trials providing evidence anastrozole versus tamoxifen and letrozole versus tamoxifen because many of the details necessary to determine risk of bias were not reported in the published papers.

There was evidence of differences between the trials both in terms of methodology and participants. The ERG agrees that the exclusion of the Milla-Santos trial from the network is appropriate.

The availability of IPD enabled data from the FIRST and NorthAmTarget trials to be matched to the pivotal FALCON trial population. This enabled participants from the FIRST and NorthAmTarget trials [redacted] to be excluded from the network creating a more homogeneous population in the NMA. Matching was not possible for the PO25 study because only aggregate data were available.

The company used appropriate methods to determine whether the assumption of proportional hazards was true. A constant relative treatment effect was unlikely for some of the studies and therefore a method was used that did not rely on the assumption of proportional hazards.

A fixed-effect meta-analysis was undertaken. The ERG accepts the company explanation that a random-effects NMA was not possible (predominantly due to the low number of trials).

However, this may mean that the potential uncertainty around effect estimates is not adequately represented.

3.2 Summary statement of company's approach

The ERG's quality assessment of the company's SLR in the CS is summarised in Table 14. Processes for inclusion or exclusion of studies were conducted by two independent reviewers (CS p. 37), while extraction of included studies was carried out in parallel by two independent reviewers and any discrepancies between them were reconciled by a third independent reviewer (CS p. 41). Included studies were subject to critical appraisal. Overall, the ERG considers the study selection, data extraction and critical appraisal processes to have been adequate, following standard accepted review methodology.

The ERG concludes that the submitted evidence reflects the decision problem defined in the CS and that the overall risk of systematic error in the systematic review appears to be low.

Table 12 Quality assessment (CRD criteria) of CS review

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	1. Yes. Inclusion and exclusion criteria are clearly stated.
2. Is there evidence of a substantial effort to search for all relevant research? i.e. all studies identified	2. Yes. There was a substantial effort to search for all relevant studies and the restriction of the evidence to English Language only is unlikely to have resulted in any missed studies.
3. Is the validity of included studies adequately assessed?	3. Yes. Quality assessment of all of the included trials (including the four comparator trials from the NMA), was assessed using the NICE criteria. Generally, the ERG assessment agreed with the company assessment of the fulvestrant trials, with differences mainly due to insufficient reporting of details, preventing a judgement to be made. This was also the case for the quality assessment for the comparator trials included in the NMA.

4. Is sufficient detail of the individual studies presented?	4. Yes. Methodology, patient characteristics and outcomes of the included studies are generally presented in sufficient detail, although the ERG extracted some additional information from the trial publications. Most of the information for the fulvestrant trials was presented in a separate format, making an overview difficult. The ERG presents combined tables to aid with the interpretation of the two trials and their results.
5. Are the primary studies summarised appropriately?	5. Yes. The primary studies are summarised appropriately for both the fulvestrant trials and the NMA trials, with the majority of details provided in tables and figures in the main body of the CS.

3.3 Summary of submitted evidence

In this section the ERG focuses on the main outcomes of the included phase II FIRST trial and the phase III FALCON trial presented in the CS, supplemented with data from other sources (e.g. trial publications and clinical study reports) if necessary. The outcomes from the NMA are also included in this section.

Where evidence feeds into the economic model this is indicated and cross-references are provided to the economic section of the ERG report.

3.3.1 Summary of PFS (FALCON, primary outcome) and TTP (FIRST, secondary outcome)

The CS presents the PFS results for the FALCON trial (which was the primary outcome for this trial, CS p. 70) and TTP results for the FIRST trial (where TTP was a secondary outcome, CS p. 68). These analyses were undertaken when approximately 306 progression events had occurred in FALCON, and when 75% of patients had discontinued (failed) study treatment in FIRST. In both trials the proportion of events occurring in the fulvestrant arm was lower than that in the anastrozole arm (Table 13) over the study period (approximately 36 months since randomisation in the FALCON trial and approximately 42 months since randomisation in the FIRST trial).

Median PFS in the FALCON trial was 2.8 months longer in the fulvestrant arm than the anastrozole arm. Neither of the clinical experts the ERG consulted felt that this was a clinically significant increase and indicated that much larger increases could be obtained from other new drugs. The improvement in PFS with fulvestrant was statistically significant [HR = 0.797, 95% CI 0.637 to 0.999, p = 0.0486].

Median TTP in the FIRST trial was 10.3 months longer in the fulvestrant arm than the anastrozole arm. The improvement in TTP with fulvestrant would be considered clinically significant and was also statistically significant (HR 0.66, 95% CI 0.47 to 0.92, p = 0.01) (Figure 5).

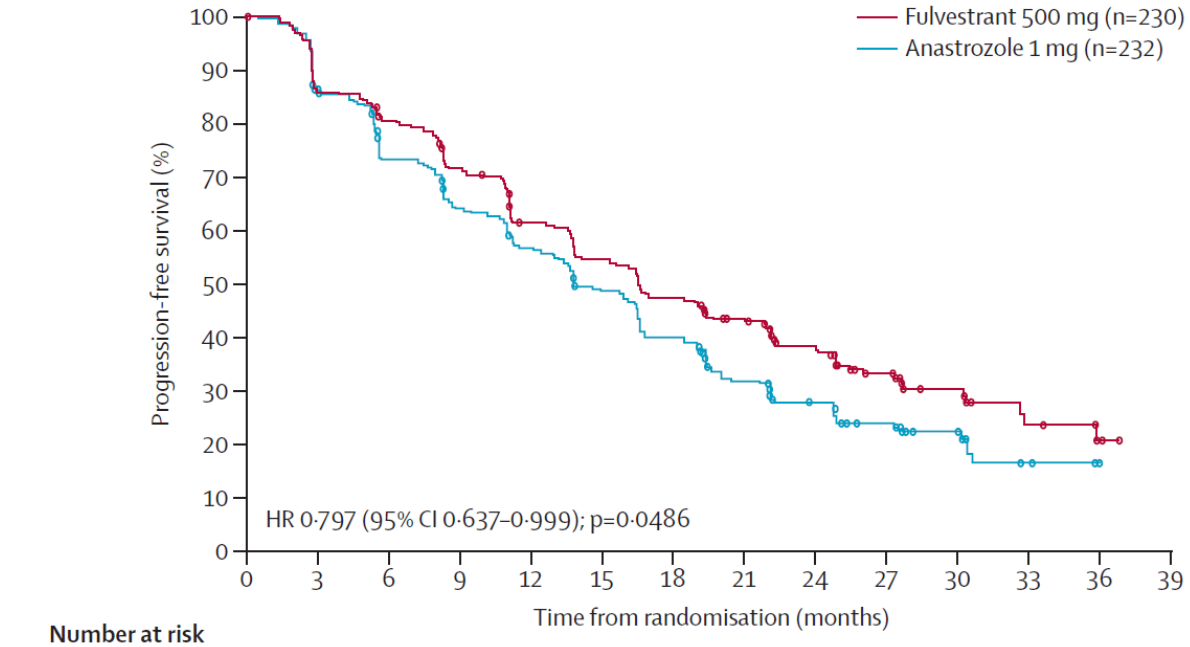
Table 13 PFS results for the FALCON trial and time to progression results for the FIRST trial

	FALCON (PFS)[a]		**FIRST (TTP)[a]**	
	Fulvestrant (n=230)	**Anastrozole (n=232)**	**Fulvestrant (n=102)**	**Anastrozole (n=103)**
Events, n (%)	143[b] (62)[b]	166[b] (72)[b]	63[b] (61.8)	79[b] (76.7)
HR, (95% CI) p-value	0.797, (0.637 to 0.999) 0.0486		0.66, (0.47 to 0.92) 0.01	
Median PFS (FALCON) or median TTP (FIRST) (95% CI), months	16.6 (13.83 to 20.99)	13.8 (11.99 to 16.59)	23.4	13.1

CI, confidence interval; HR, hazard ratio; n, number; PFS, Progression-free survival; TTP, Time to progression

[a] Median duration of follow-up for PFS in the FALCON study was not reported. Median follow-up for TTP in the FIRST study was 18.8 months in the fulvestrant group and 12.9 months in the anastrozole group.

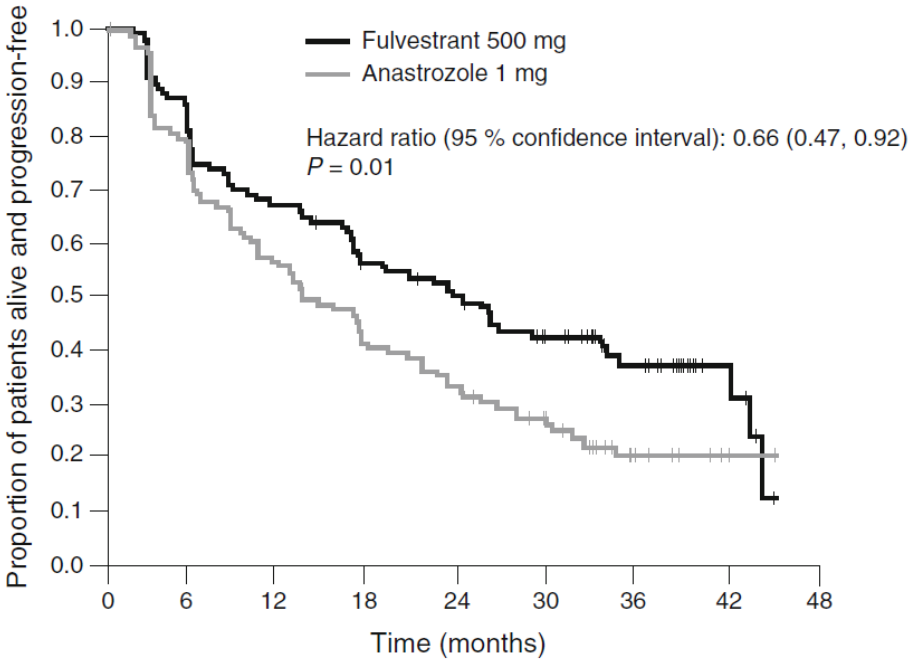
[b] These data were not reported in the CS but were obtained from the published papers for FALCON[8] and FIRST.[5]



Number at risk														
Fulvestrant 500 mg	230	187	171	150	124	110	96	81	63	44	24	11	2	0
Anastrozole 1 mg	232	194	162	139	120	102	84	60	45	31	22	10	0	0

A circle represents a censored observation

Figure 4 Kaplan-Meier plot of PFS in the FALCON trial (CS Figure 14, p. 71)



Patients at risk									
Fulvestrant 500 mg	102	74	65	52	45	34	20	6	0
Anastrozole 1 mg	103	69	55	39	30	21	8	2	0

After the primary data cut-off, progression was determined by investigator opinion

Figure 5 Kaplan-Meier plot of TTP in the overall FIRST population (CS Figure 12, p. 68)

KM plots of PFS for FALCON, the matched populations for FIRST and NorthAmTarget, and the full population for PO25 (for which only aggregate data were available) are presented in CS Figure 23. The ERG notes that HRs for the matched PFS data were not presented. PFS is included in the economic model (ERG report section 4.3.5.1).

The ERG notes that the degree of benefit seen with fulvestrant in the FIRST trial (median TTP 10.3 months longer in the fulvestrant arm than in the anastrozole arm) was greater than that observed in the FALCON trial (median PFS 2.8 months longer in the fulvestrant arm than in the anastrozole arm). The CS does not comment on this difference or provide any reasons for it. The ERG has checked to ensure that it is not due to differences in exposure to prior endocrine therapy (the same pattern is observed after matching the FIRST trial data to the key FALCON trial inclusion criteria prior to use in the NMA), nor due to differences in TTP/PFS outcomes in the anastrozole arms of the trials which appear to be broadly similar, nor due a difference in the proportion of events at the time of data analysis between the trials as this is also broadly similar. There is a key difference in the methodology of the two trials that may have had an impact on outcomes, which is that the FIRST trial was not a blinded study, whereas the FALCON trial was conducted with double-blinding. Finally, in the FALCON study publication[8] (but not in the CS) a suggestion is made, based on findings from subgroup analyses, that an enhanced treatment effect with fulvestrant might be seen in patients with non-visceral disease compared to those with visceral disease, but the authors of the paper caution that this observation requires further study. The company's decision problem, in line with the NICE scope[1] for this appraisal, indicates that if the evidence allows, subgroups of people with visceral disease and people with non-visceral disease will be considered. Analyses of subgroups are presented in section 3.3.6 but the CS does not discuss the outcome of these in any detail.

As described earlier (ERG report section 3.1.7), the method used for the NMA synthesises the differences in the shape and scale parameters of the parametric survival function used to model PFS between the intervention and each comparator over time. The baseline (reference) treatment is anastrozole and this is used as the anchor from which the estimates of the shape and scale for the other interventions are then obtained. As shown in Table 14, there were statistically significant differences in the scale parameter for fulvestrant and tamoxifen when compared against anastrozole for four of the five parametric distributions (Weilbull, log-logistic, lognormal and generalised gamma). Statistically significant differences were also seen in the shape parameter for fulvestrant and tamoxifen for the lognormal distribution when compared against anastrozole. Note that a positive estimate of

a difference in log scale indicates that the treatment is better than the reference and conversely, a negative estimate of a difference in log scale indicates that the treatment is worse than the reference. If both the limits of the 95% CI have the same sign this indicates that the difference between the treatment and reference is statistically significant. The ERG has added grey shading in Table 14 to indicate where the statistically significant differences are. Grey shading indicates fulvestrant is statistically significantly better than anastrozole and tamoxifen is statistically significantly worse than anastrozole.

Table 14 Fixed effect NMA PFS results: baseline parametric distribution parameters and difference from baseline for treatment alternatives versus (FALCON) anastrozole (CS Table 29 p. 101)

Weibull	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)						
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant						
Letrozole						
Tamoxifen						
Gompertz	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)						
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant						
Letrozole						
Tamoxifen						
Log-logistic	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)						
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant						
Letrozole						
Tamoxifen						
Lognormal	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)						
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant						
Letrozole						
Tamoxifen						

Generalised gamma	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Common parameter	Estimate	L95%	U95%	-	-	-
Q	[redacted]					

Abbreviations: L95%, lower limit of the 95% confidence interval; PFS, progression-free survival; U95%, upper limit of the 95% confidence interval

The ERG and NICE asked the company to provide the results of pairwise comparisons (clarification question A10). The company provided these results and the comparison between the fixed-effect NMA and fixed-effect pairwise comparisons (generalised gamma model) indicates the results are almost identical (Table 15).

Table 15 Comparison of PFS results obtained from NMA and pairwise meta-analysis

Intervention	**Ref**		**Scale**	**L95%**	**U95%**	**Shape**	**L95%**	**U95%**
Fulvestrant	Ana	NMA	[redacted]					
		Pairwise	[redacted]					
Letrozole	Ana	NMA	[redacted]					
		Pairwise	[redacted]					
Tamoxifen	Ana	NMA	[redacted]					
		Pairwise	[redacted]					

This table draws on information presented in CS Table 29 and the company's written response to clarification question A10, Table 11.

Ana, anastrozole; L95%, lower limit of the 95% confidence interval; NMA, network meta-analysis; Ref, reference; U95%, upper limit of the 95% confidence interval

The ERG and NICE also asked the company to provide the results obtained from a network that omits study PO25 (clarification question A13). The company provided results of the fixed -effects meta-analyses obtained when excluding the PO25 trial (again using the ganeralised gamma model) and these results were almost identical to those reported with PO25 included in the NMA (see Clarification Responses to question A13).

3.3.2 Summary of OS (secondary outcome)

OS was a secondary outcome of the FALCON trial planned at trial inception. In contrast, in the FIRST trial, OS was added in a protocol amendment as a secondary outcome to see whether the improvement observed in TTP would translate into an improvement in OS.

The OS data for the FALCON trial are immature and consequently, at the time of data analysis, it was not possible to calculate a median OS (Table 16). Although the proportion of deaths in the fulvestrant arm is slightly lower than in the anastrozole arm (29% vs 32% respectively[8]), the 95% CI for the HR spans 1 and there is no statistically significant difference between survival in the fulvestrant and anastrozole arms at the time of the primary efficacy analysis for PFS (Figure 6), which occurred approximately 36 months after the start of randomisation. The CS states that the next survival analysis will be performed when approximately 50% of patients have died (CS p. 59). [redacted]

The analysis of OS in the FIRST trial was performed when approximately 65% of deaths had occurred. At the data cut-off, the proportion of patients who had died was lower in the fulvestrant arm than in the anastrozole arm (61.8% versus 71.8% respectively,[7] Table 16). The improvement in the fulvestrant group was statistically significant (HR 0.70, 95% CI 0.50 to 0.98, p=0.04) with a median survival of 54.1 months in comparison to 48.4 months in the anastrozole arm (Figure 7). A limitation of this result is that it comes from an analysis that was not originally specified and some patients (n=35) did not contribute data to this outcome.

Table 16 OS results for the FALCON and FIRST trials

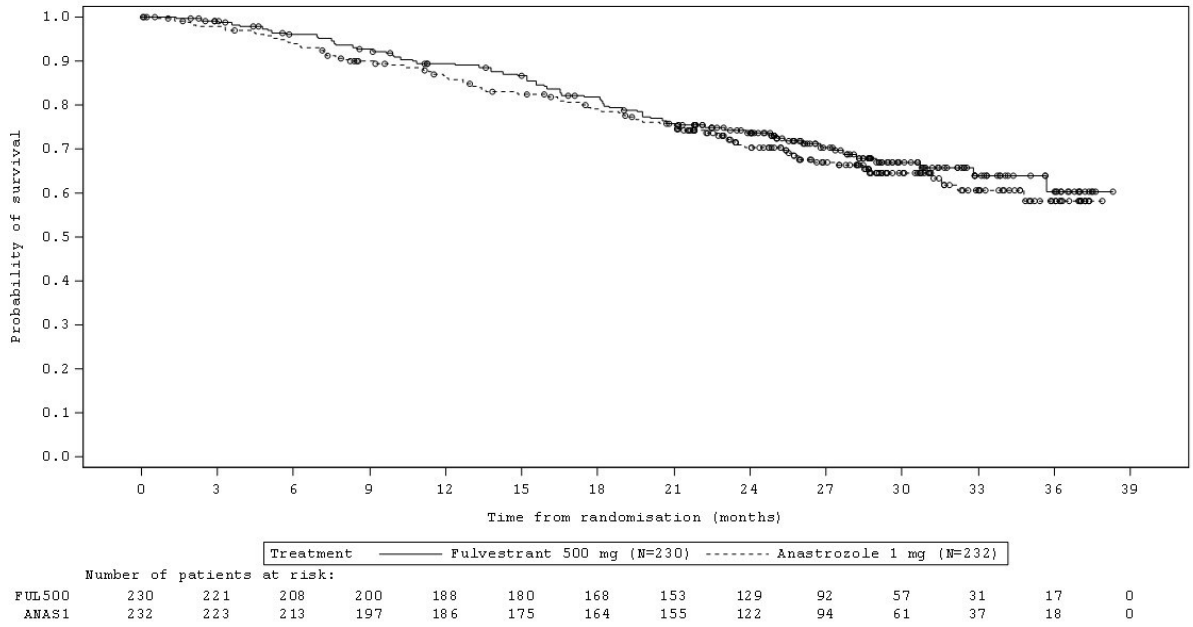
	FALCON		FIRST	
	Fulvestrant (n=230)	**Anastrozole (n=232)**	**Fulvestrant (n=102)**	**Anastrozole (n=103)**
Events, n (%)	67 (29%)[a]	75 (32%)[a]	63 (61.8%)[b]	74 (71.8%)[b]
HR, (95% CI)	0.875 (0.629 to 1.217)		0.70 (0.5 to 0.98)	
p-value	0.4277		0.04	
Median OS (95% CI), months	NC[c]	NC[c]	54.1 (NR)	48.4 (NR)

CI, confidence interval; HR, hazard ratio; n, number; NC, Not calculated; NR, Not reported; OS, Overall survival;

[a] These data were not presented in the CS so have been obtained from the published paper.[8]

[b] The CS presents rounded percentage values only so these data come from the published paper[7]

[c] Median overall survival could not be calculated because of insufficient follow-up time (31% maturity).



Note: A circle represents a censored observation
ANAS1: Anastrozole 1 mg; FUL500: fulvestrant 500 mg; OS: Overall survival; PFS: Progression-free survival

Figure 6 Kaplan-Meier plot of OS in the FALCON trial at the time of the PFS analysis (CS Figure 15, p. 72)

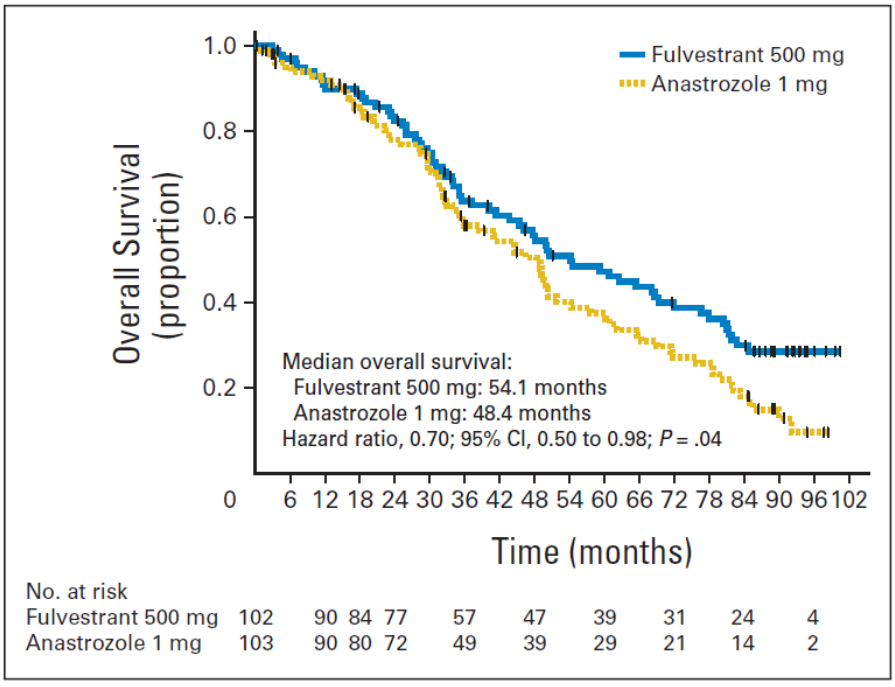


Figure 7 Kaplan-Meier plot of OS in the FIRST population (CS Figure 13 p. 69)

Using the same methodology described above for PFS, an indication of the effectiveness of fulvestrant and anastrozole in comparison to the other comparators letrozole and tamoxifen

was obtained by NMA using data from clinical trials identified by the company's systematic review and matched (where IPD were available) to include ER+/PgR+ participants plus endocrine treatment naive participants. KM plots of OS for FALCON, the matched populations for FIRST and NorthAmTarget, and the full population for PO25 (for which only aggregate data were available) are presented in CS Figure 24. The ERG notes that HRs for the matched OS data were not presented. Furthermore it should also be borne in mind that i) data from the FALCON trial are immature (and extend to approximately 36 months after baseline) and ii) OS analysis for the matched FIRST data extend to approximately 96 months, therefore the majority of the long-term OS data for fulvestrant come from the FIRST trial. OS is included in the economic model (ERG report section 4.3.5.1).

As shown in Table 17, there was a statistically significant difference in the scale parameter for letrozole when compared against anastrozole for the Gompertz distribution and in the shape parameter for four of the five distributions (Weibull, Gompertz, loglogistic and generalised gamma) when compared against anastrozole. The ERG has added grey shading to Table 17 to indicate where the statistically significant differences are. Grey shading indicates where letrozole is statistically significantly different in comparison to anastrozole.

Table 17 Fixed effect network meta-analysis OS results: baseline parametric distribution parameters and difference from baseline for treatment alternatives versus (FALCON) anastrozole (CS Table 30, p. 105)

Weibull	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					
Gompertz	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]					
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]					
Letrozole	[redacted]					
Tamoxifen	[redacted]					

Log-logistic	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)						
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant						
Letrozole						
Tamoxifen						
Lognormal	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)						
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant						
Letrozole						
Tamoxifen						
Generalised gamma	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)						
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant						
Letrozole						
Tamoxifen						
Common parameter	Estimate	L95%	U95%	-	-	-
Q						

Abbreviations: L95%, lower limit of the 95% confidence interval; OS, overall survival; U95%, upper limit of the 95% confidence interval

The company provided results of pairwise comparisons for OS in response to ERG and NICE clarification question A10. The comparison between the fixed-effect NMA and fixed-effect pairwise comparisons (Weibull model) indicates the results are almost identical (Table 18).

Table 18 Comparison of OS results obtained from NMA and pairwise meta-analysis

Intervention	**Ref**		**Scale**	**L95%**	**U95%**	**Shape**	**L95%**	**U95%**
Fulvestrant	Ana	NMA						
		Pairwise						
Letrozole	Ana	NMA						
		Pairwise						
Tamoxifen	Ana	NMA						
		Pairwise						

This table draws on information presented in CS Table 30 and the company's written response to clarification question A10, Table 12.
Ana, anastrozole; L95%, lower limit of the 95% confidence interval; NMA, network meta-analysis; Ref, reference; U95%, upper limit of the 95% confidence interval

As stated earlier the ERG and NICE also asked the company to provide the results obtained from a network that omits study PO25 (clarification question A13). The company provided results of the fixed -effects meta-analyses obtained when excluding the PO25 trial (using the Weibull model) and these results were almost identical to those reported with PO25 included in the NMA (see Clarification Responses to question A13).

3.3.3 Summary of clinical benefit rate for the FALCON trial (secondary outcome) and the FIRST trial (primary outcome)

CBR was a secondary outcome of the FALCON trial (Table 19). Although a higher proportion of participants in the fulvestrant arm had a clinical benefit compared to the anastrozole arm (78% versus 74% respectively) the comparison of the CBR between the arms was not statistically significant (OR 1.25, 95% CI 0.82 to 1.93, p = 0.3045). There was an increase in the EDoCB (21.9 months for fulvestrant versus 17.5 months for anastrozole), but again the comparison between arms did not reach statistical significance (EDoCB ratio 1.26, 95% CI 0.99 to 1.59, p-value = 0.0561).

CBR was the primary outcome of the FIRST trial. However, it must be remembered that this trial was designed as a non-inferiority trial and was therefore not powered to detect a statistically significant difference in CBR. A higher proportion of participants in the fulvestrant arm had a clinical benefit compared to the anastrozole arm (72.5% versus 67% respectively) the comparison of the CBR between the arms was not statistically significant (OR 1.30, 95% CI 0.72 to 2.38, p = 0.386) (Table 19). A blinded independent review of the response data was carried out on 190 records (95 from each trial arm) and concordance was above 86% in both arms (88.4% concordance in the fulvestrant arm and 86.3% in the anastrozole arm). The CBRs calculated after blinded independent review (CBR 69.5% fulvestrant versus 66.3% anastrozole) were similar to those obtained from the investigator's evaluation (Table 19).

Table 19 CBR for the FALCON and FIRST trials (Full analysis sets)

	FALCON		FIRST	
	Fulvestrant (n=230)	**Anastrozole (n=232)**	**Fulvestrant (n=102)**	**Anastrozole (n=103)**
Clinical benefit, n (%)				
CR	7 (3%)[a]	8 (3%)[a]	0	1 (1.0)[b]
Partial response	86 (37%)[a]	82 (35%)[a]	32 (31.4)	32 (31.1)
Stable disease ≥24 weeks	87 (38%)[a]	82 (35%)[a]	42 (41.2)[b]	36 (35)
Total with clinical benefit	180 (78)	172 (74)	74 (72.5)	69 (67)
CBR odds ratio (95% CI), p-value	1.25 (0.82 to 1.93), 0.3045		1.30 (0.72 to 2.38), 0.386	
Absolute difference (95% CI)	NR		5.6% (-7.8 to 15.8%)[b]	
EDoCB, months	21.9	17.5	NR	NR
EDoCB ratio (95% CI), p-value	1.26 (0.99 to 1.59), 0.0561		NR	
No clinical benefit, n (%)				
Stable disease <24 weeks	9 (4)	22 (9)	15 (14.7)	12 (11.7)
Progression RECIST progression Death	30 (13) 27 (12) 3 (1)	33 (14) 28 (12) 5 (2)	10 (9.8)[b]	20 (19.4)[b]
Not evaluable	11 (5)	5 (2)	3 (2.9)	2 (1.9)
Total with no clinical benefit	50 (22)	60 (26)	28 (27.5)	34 (33)

This table draws on information presented in CS Table 18, p. 67; ; Table 20, p. 76.

CI, confidence interval; EDoCB, Expected duration of clinical benefit; n, number; RECIST, Response Evaluation Criteria in Solid Tumors

[a] These data are not presented in the CS but were available in the published paper by Robertson et al. 2016[8]

[b] There appeared to be several typographical errors in CS Table 18 p. 67 and some data had been rounded in the CS. These data are taken from Table 2 in the published paper by Robertson et al. 2009.[6]

3.3.4 Summary of other secondary outcomes reported for the FALCON and FIRST trials

Secondary outcomes reported by both the FALCON[8] and FIRST[6] trials were based on response to treatment (Table 20). The ORR (defined as the best overall response of CR or PR) was broadly the same in the fulvestrant and anastrozole groups in both trials, as were proportions of participants with stable and progressive disease. In the FALCON trial, although the median time to onset of response was longer in the fulvestrant arm (8.1 months versus 5.6 months in the anastrozole arm), the median DoR was numerically longer. The proportions of patients responding to treatment and the mean DoR in responding patients was used to calculate the EDoR according to the method described by Ellis and colleagues.[25] The EDoR was numerically higher for the fulvestrant arm than the anastrozole arm and the EDoR ratio favoured fulvestrant . A similar effect was seen with the EDoCB.

Table 20 Additional secondary outcomes for the FALCON (for patients with measurable disease at baseline) and FIRST (evaluable for response analysis set) trials

	FALCON		FIRST	
	Fulvestrant (n=193)	**Anastrozole (n=196)**	**Fulvestrant (n=89)**	**Anastrozole (n=93)**
ORR, n (%)	89 (46)	88 (45)	32 (36)	33 (36)
OR (95% CI) & p-value for ORR	1.07 (95% CI: 0.72-1.61) p=0.7290		1.021 (0.556-1.87[a]) p=0.95	
CR, n (%)	[redacted]	[redacted]	0	1 (1)
Partial response, n (%)	[redacted]	[redacted]	32 (36)	32 (34)
Stable disease, n (%)	[redacted]	[redacted]	45 (51)	41 (44)
Progressive disease, n (%)	[redacted]	[redacted]	9 (10)	18 (19)
Median time to onset of response, months	8.1	5.6	NR	NR
Median DoR, months	20.0 (15.9 to 27.63)	13.2 (10.64 to 16.72)	NC	14.2[c]
Mean DoR (days)	752.14 (SE 0.138)	506.88 (SE 0.097)	NR	NR
Expected DoR (EDoR), months	11.4	7.5	NR	NR
EDoR ratio (95% CI), p-value	1.52 (95% CI 1.03 to 2.26) p=0.0367[c]		NR	
Mean DoCB (days)	853.48 (SE: 0.083)	717.64 (SE 0.068)	NR	NR

	FALCON		FIRST	
	Fulvestrant (n=230)	**Anastrozole (n=232)**		
EDoCB months	22.1 (18.46 to 24.87)	19.1 (16.53 to 20.47)	NR	NR
EDoCB ratio (95% CI), p-value	1.26 (0.99-1.59) p=0.0561[d]		NR	

This table draws on information presented in CS Table 19, p. 70 and Table 20 p. 76.

DoCB, duration of clinical benefit; DoR, duration of response; EDoCB, expected duration of clinical benefit; EDoR, expected duration of response; n, number of participants; NR, not reported; OR, odds ratio; ORR, objective response rate.

[a] the CS reports upper limit of the 95% CI as 1.687 but the paper published in 2009[6] reports 1.87.

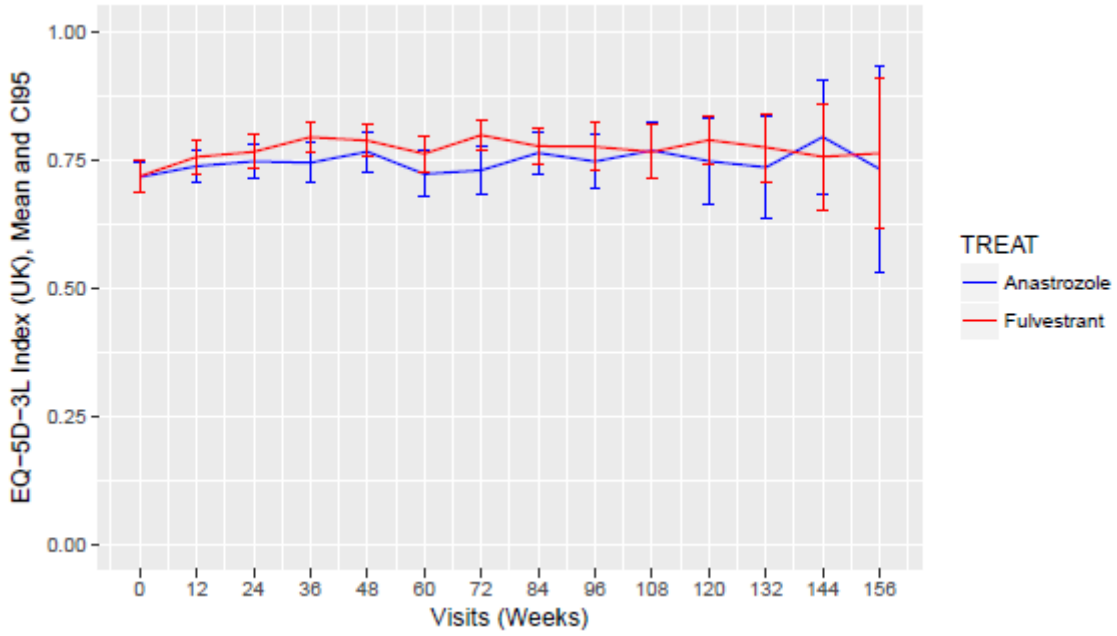
[b] these data were obtained from the FALCON CSR

[c] The CS reports 12 months but the paper published in 2009[6] reports 14.2 months

[d] The EDoR and EDoCB ratios presented in CS Table 20 (CS p. 76) match those presented in the response to clarification question A4, however the 95% CIs and p-values differ. The ERG has reported the values from the CS.

3.3.5 Summary of Health-related quality of life

As stated HRQoL was not measured in the FIRST trial.[6] In the FALCON trial[8] HRQoL was a secondary outcome. Two HRQoL questionnaires were utilised, the EQ-5D-3L and the FACT-B, and results from both are presented in the CS. Data collected using the EQ-5D-3L was used to inform HRQoL values, using the utility value set for the UK, in the economic model (see ERG report section 4.3.6). The CS reports that the results from the EQ-5D-3L questionnaire show that, over the 156 weeks of the study period, general health status was maintained across both treatment arms. These data are presented in a CS figure which is reproduced below (Figure 8). This figure did not indicate how many of the trial participants contributed data at each time point so NICE and the ERG requested clarification on this (clarification question A3). In response the company supplied a confidential reference which contains numerous tables and analyses. The ERG believes they have identified the correct patient numbers from this document and these have been added by the ERG to the figure.

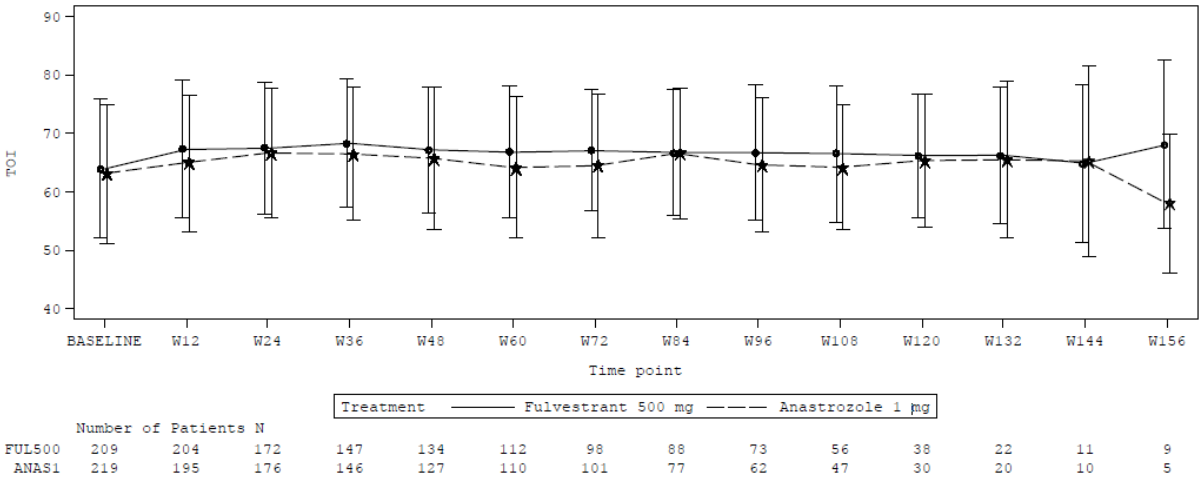


Number of observations per visit

Visits (weeks)	[redacted]													
Fulvestrant	[redacted]													
Anastrozole	[redacted]													

Figure 8 EQ-5D-3L Index (UK) per treatment and visit (CS Figure 17, p. 74)

The outcome measure from the FACT-B questionnaire was the TOI, which summarises three of the five subscales assessed by this questionnaire (physical well-being, functional well-being and breast cancer subscales). The CS reports (pp. 72 -73) that mean baseline TOI scores were high and comparable between the treatment arms and remained similar and high during treatment. The results are summarised in figure (CS Figure 16) which is reproduced below (Figure 9).



SOURCE: (AstraZeneca 2015a)
ANAS1, Anastrozole 1 mg; FUL500, fulvestrant 500 mg; TOI, Trial outcome index.

Figure 9 Mean TOI score across time points, by treatment group (CS Figure 16, p. 73)

3.3.6 Sub-group analyses results

As stated in Section 3.1.6 subgroup analyses (based on for the FIRST trial were not pre-planned. Results for these subgroups, which appear to be performed as defined by pre-defined covariates, are presented in forest plots (CS Figure 18 and Figure 19, pp. 77 to 78), which match the data in the published papers.[5,7] The CS states that the statistically significant difference in TTP reported for the FIRST trial population was maintained when adjusted for the pre-defined covariates (HR 0.64; 95% CI 0.46 to 0.90; p=0.01). The global interaction test was not statistically significant (p = 0.34). The treatment effect was consistent across the five subgroups (age, receptor status, visceral involvement, prior chemotherapy, measurable disease). The ERG notes that prior endocrine therapy was not included in the TTP subgroup analysis. Consistent results across six subgroups (age, receptor status, visceral involvement, prior chemotherapy, measurable disease, prior endocrine therapy) were also observed for OS. The FIRST trial's exploratory subgroup analysis suggesting that patients who had not received prior endocrine therapy received a greater OS benefit was the reason that the FALCON study focussed on endocrine therapy naive patients (although the CS p. 78 does caution that the endocrine therapy naive subgroup analysis was based on a very small sample size).

Subgroup analyses of PFS for the FALCON trial were pre-planned (albeit with some amendments prior to unblinding the data) and subgroup analysis for OS was added (prior to unblinding the data) as previously stated (Section3.1.6). PFS results for eight subgroups are presented in a forest plot (CS Figure 20, p. 79) and this matches the data in the published

paper.[8] For the subgroup analysis of OS, the geographic region subgroup is omitted (CS Figure 21, p. 80). The OS subgroup analysis is not presented in the published paper,[8] but the data match those reported in the FALCON CSR.[26] The subgroup analyses of PFS (breast cancer type, previous chemotherapy, geographic region, measurable disease, ER+ and PgR+, previous systemic ER containing HRT, bisphosphonate use, visceral disease) showed that the numerical improvement in PFS favouring fulvestrant was largely consistent across the subgroups. The largest numerical difference in the reported hazard ratios for PFS of subgroups was observed for the visceral disease versus no visceral disease at baseline. The analysis indicates that those with no visceral disease at baseline have a greater benefit than those with visceral disease at baseline. Consideration of subgroups of people with visceral disease and those with non-visceral disease (if evidence allows) was included in the company's decision problem. However, the company do not discuss this subgroup result in the CS. The published paper for the FALCON trial[8] points out that there is potential for an enhanced fulvestrant treatment effect in the non-visceral disease subgroup but indicates that the observation requires further study. Subgroup analysis was also conducted for the interim analysis of OS, in which the results were also consistent with the results for the whole study population. The CS states that a further analysis of OS will be conducted when approximately 50% of patients have died (CS p. 59). [redacted]

As already noted, for some subgroups the sample size is small and so caution is needed in interpreting these results.

3.3.7 Summary of adverse events

The CS presents an overview of the safety and tolerability of fulvestrant in CS section 4.12.1 (CS p. 119).

For the FALCON study, AEs are presented in the CS from the 11th April 2016 data cut off (the point of PFS analysis). At this point the median duration of exposure to fulvestrant was 14.7 months (range 0.9 to 37.7) and to anastrozole 13.9 months (range 0.2 to 36.0). The CS reports those events that occurred with a frequency of more than 5% in any treatment group (CS Table 39, p. 122).

Publications from the FIRST trial data provide safety data from three time points:

- At first data cut-off (10th January 2008)[6]
- At first follow-up (26th March 2010)[5]

- At the final assessment of OS (15th July 2014)[7]

The CS summarises data from the first two of these three time points and CS Table 38 (p. 121) summarises the data from the main study period and the follow-up period combined.

The combined data from the FIRST study and the data reported in the CS for the FALCON study have been used to populate Table 21.

The proportions of AEs and SAEs were similar between treatment groups. Due to differences in the length of follow-up and methods of recording AEs it is not possible to make comparisons between the two trials.

In the FALCON trial joint disorders and back pain were specified as AEs of special interest. These were reported by 26% of the fulvestrant group and 18% of the anastrozole group. In almost all cases the AEs of special interest were mild or moderate in severity (grade 1 or 2). The single exception was one patient (<1%) in the fulvestrant group who had grade 3 back pain.

Table 21 Summary of AEs reported in the CS for FALCON and FIRST

Parameter, n (%)	FALCON		FIRST	
	Fulvestrant (n=228)	**Anastrozole (n=232)**	**Fulvestrant (n=101)**	**Anastrozole (n=103)**
	At data cut-off (11/04/2016)		At final data cut-off (65% OS)	
Any AE	166 (73%)	173 (75%)		
Any SAE	30 (13%)	31 (13%)	24 (23.8%)	22 (21.4%)
Any SAE with outcome other than death			21 (20.8%)	18 (17.5%)
Any causally related SAE			2 (2.0)	0 (-)
Grade 3 or worse AEs	51 (22%)	41 (18%)		

Parameter, n (%)	AEs ≥5% in any treatment group[8]		Most commonly reported SAEs (≥2 patients)	
Alanine aminotransferase increased	16 (7%)	7 (3%)		
Anaemia	9 (4%)	20 (9%)		
Arthralgia	38 (17%)	24 (10%)		
Aspartate aminotransferase increased	12 (5%)	8 (3%)		

Atrial fibrillation			1 (1.0)	1 (1.0)
Back pain	21 (9%)	14 (6%)		
Cardiac failure			2 (2.0)	0 (-)
Constipation	13 (6%)	11 (5%)		
Cough	12 (5%)	8 (3%)		
Death			0 (-)	2 (1.9)
Decreased appetite			2 (2.0)	0 (-)
Dehydration			2 (2.0)	0 (-)
Diarrhoea	14 (6%)	13 (6%)		
Dyspnoea	9 (4%)	13 (6%)	2 (2.0)	0 (-)
Fatigue	26 (11%)	16 (7%)		
Femur fracture			1 (1.0)	2 (1.9)
Hot flush	26 (11%)	24 (10%)		
Hypertension	15 (7%)	21 (9%)		
Insomnia	15 (7%)	13 (6%)		
Myalgia	16 (7%)	8 (3%)		
Nausea	24 (11%)	24 (10%)		
Neuralgia			1 (1.0)	1 (1.0)
Oedema peripheral	9 (4%)	13 (6%)		
Pain in extremity	13 (6%)	10 (4%)		
Transient ischaemic attack			0 (-)	2 (1.9)

This table draws on information presented in CS Table 38, p. 121 and Table 39 p. 122.

AE, adverse event; n, number; OS, overall survival; SAE, serious adverse event

Discontinuations

In the FALCON study, 7% of the fulvestrant arm and 5% of the anastrozole arm discontinued because of AEs. The CS presents discontinuations by organ class in CS Table 40 (p. 123). For the FIRST study, information on discontinuation due to an AE is reported from the first data cut-off in the CS, with additional information being presented in the published paper from the first follow-up. In both studies the proportion of patients discontinuing due to an AE were similar in the fulvestrant and anastrozole groups (Table 22).

Table 22 Summary of study discontinuations due to an AE

	FALCON		**FIRST**		
Parameters, n (%)	**Fulvestrant (n=228)**	**Anastrozole (n=232)**	**Time-point**	**Fulvestrant (n=101)**	**Anastrozole (n=103)**
Discontinuation due to an AE	16 (7%)	11 (5%)	First data cut-off, 10/01/2008[6], CS p. 119	3 (3.0%)	3 (2.9%)
			First follow-up (26th March 2010)[5]	0	2 (1.9%)

AE, adverse event; CS, company submission; n, number

Deaths related to adverse events

In the FALCON trial 3% of deaths were considered to be related to AEs (6 in the fulvestrant group and 7 in the anastrozole group) at the 11th April 2016 data cut off (the point of PFS analysis). None of these deaths were considered to be causally related to study treatment. A similar proportion of deaths from the main study period and the follow-up period combined in the FIRST study were due to AEs [3 (3%) SAEs in the fulvestrant group and 5 (4.9) SAEs in the anastrozole group] (Table 23).

Table 23 Summary of deaths related to AEs

Parameters, n (%)	FALCON		FIRST	
	Fulvestrant (n=228)	**Anastrozole (n=232)**	**Fulvestrant (n=101)**	**Anastrozole (n=103)**
Deaths related to AEs	6 (3%)	7 (3%)	3 (3.0%)	5 (4.9%)

AE, adverse event; n, number

3.4 Summary

The systematic review of clinical effectiveness evidence in the CS identified two RCTs of fulvestrant as a treatment for people with untreated hormone-receptor positive locally advanced or metastatic breast cancer (FIRST and FALCON). Both trials compared fulvestrant to anastrozole.

The two RCTs were judged to be of good methodological quality although there was the potential for the FIRST trial to be at a high risk of bias due to the absence of blinding. Overall, both studies appear to have been well conducted. The main clinical efficacy outcomes reported in the CS are PFS, OS, CBR (response rates) and HRQoL. AE outcomes are also reported. Follow-up of participants from the FALCON study is continuing, particularly with regard to OS for which there are currently only interim results.

The company's SLR had broad inclusion criteria, enabling the identification of studies that could contribute to the wider evidence base where necessary. As there is no direct evidence comparing fulvestrant to either letrozole or tamoxifen it was necessary for the company to conduct an NMA. In addition to the two trials of fulvestrant versus anastrozole, the NMA included data from a further four trials: combined data from the North American and TARGET studies (these two trials were prospectively designed to allow for combined data

analysis) which compared anastrozole to tamoxifen, and the PO25 trial which compared letrozole to tamoxifen. A sixth trial (comparing anastrozole with 40 mg tamoxifen) was not included in the final network because it used the higher 40 mg tamoxifen dose which is not approved by the EMA and its inclusion caused heterogeneity in the NMA.

The additional RCTs contributing data to the NMA were judged to be of good methodological quality where judgements about the risk of bias could be made. However, the ERG found that for many items the risk of bias judgement was 'unclear' because the published papers did not report the necessary details.

The ERG found some evidence of heterogeneity in trial participants between the five trials that contributed to the final NMA. However, the company conducted a matching process, so that for the trials where IPD were available (FIRST and NorthAmTarget) only data for ER+/PgR+ patients plus endocrine treatment naive patients would be included in the NMA. Inevitably the matching process decreased the sample size of the FIRST and NorthAmTarget studies. The ERG is aware that a benefit of the matching process is that it allows for the exclusion of participants [redacted] creating a more homogeneous population for the NMA (except for study PO25 for which IPD were not available). Although, the ERG is uncertain about the potential disadvantages of this approach in terms of the effects on the original randomised trial arms (e.g. if it creates scope for bias as randomisation has been broken) the ERG has concluded that it is likely that the benefits outweigh potential disadvantages.

Two outcomes were analysed by NMA, PFS and OS. The PFS and OS data from the individual trials (after matching where applicable) were examined to determine whether the assumption of proportional hazards held. Visual inspection of both the KM plots and of log cumulative hazard plots suggested that a constant relative treatment effect in the studies was unlikely. Therefore the company concluded that methods of NMA reliant on the assumption of proportional hazards were inappropriate and instead used an alternative method developed by Ouwens et al.[23] In this method PFS and OS data can be both synthesized in the NMA and extrapolated beyond the available trial follow-up.

A fixed-effect NMA was undertaken because of the small number of studies and the difficulty in determining an appropriate informative prior for a random-effects analysis. The ERG accepts that the small number of trials available in the network is a limitation and is

concerned that the inability to conduct random-effects analyses means that the potential for uncertainty may be inadequately captured.

PFS was the primary outcome of the FALCON trial and TTP was a secondary outcome of the FIRST study (the FIRST study definition of TTP included deaths and hence is treated the same as PFS). In both studies a benefit was observed for the fulvestrant group: median PFS 2.8 months longer for the fulvestrant group in FALCON; median TTP 10.3 months longer for the fulvestrant group in FIRST. In both cases these improvements were statistically significant (FALCON HR = 0.797, 95% CI 0.637 to 0.999, p = 0.0486; FIRST HR = 0.66, 95% CI 0.47 to 0.92, p = 0.01). The fixed-effect NMA was conducted for five different parametric distributions. For four of these (Weibull, log-logistic, lognormal and generalised gamma) the difference in the scale parameter indicated that fulvestrant PFS is better than anastrozole and was statistically significant, whereas with tamoxifen PFS was statistically significantly worse than anastrozole. For the shape parameter a statistically significant difference was apparent only for the lognormal distribution indicating fulvestrant was better than anastrozole whereas tamoxifen was worse than anastrozole.

OS was a secondary outcome of both the FALCON and FIRST RCTs, in the case of the FIRST study the outcome was added in a protocol amendment after improvements in TTP had been observed. The OS data for FALCON are immature and median survival has not yet been reached. The slight difference in the proportion of deaths in favour of the fulvestrant arm (29% vs 32%) is not statistically significant. In the FIRST trial median survival in the fulvestrant arm was almost 6 months longer than that of the anastrozole arm (54.1 months versus 48.4 months) and this improvement with fulvestrant was statistically significant (HR 0.70, 95% CI 0.50 to 0.98, p=0.04). A fixed-effect NMA was conducted for five different parametric distributions. Although some statistically significant differences were observed for the comparison of letrozole versus anastrozole there were not statistically significant differences with any of the parametric distributions for the fulvestrant versus anastrozole comparison.

CBR was the primary outcome of the FIRST trial (powered for non-inferiority) and a secondary outcome of the FALCON trial. In both trials the CBR favoured fulvestrant (FIRST: fulvestrant 72.5% versus anastrozole 67%; FALCON: fulvestrant 78% versus anastrozole 74%).

Secondary outcomes reported by both trials were based on response to treatment. ORR (the best overall response of CR or PR) was broadly the same in the trial arms of both trials.

Other secondary outcomes based on response reported for the FALCON trial only (e.g. median DoR, EDoR, mean DoCB and EDoCB) were numerically in favour of fulvestrant and in the case of EDoR ratio, statistically significantly in favour of fulvestrant.

HRQoL was reported only from the FALCON trial using both the EQ-5D-3L and FACT-B questionnaires. Results from both questionnaires showed HRQoL was similar in the trial arms at the start of treatment and was maintained during treatment. Data from the EQ-5D-3L informed the economic model.

Subgroup analyses for both trials indicate that the TTP/PFS and OS results were consistent across the subgroups tested [FIRST: age, receptor status, visceral involvement, prior chemotherapy, measurable disease, prior endocrine therapy; FALCON: breast cancer type, previous chemotherapy, geographic region (not for interim OS subgroup analysis), measurable disease, receptor status, prior systemic ER containing HRT, bisphosphonate use, visceral disease]. Although the company decision problem includes provision for consideration of people with visceral disease and non-visceral disease the CS does not make any specific comments about this subgroup analysis.

The FIRST and FALCON trials reported similar proportions of AEs and SAEs between the study arms. Joint disorders and back pain were specified as AEs of special interest in the FALCON trial (reported by 26% of the fulvestrant group and 18% of the anastrozole group). Apart from one patient (<1%) in the fulvestrant group who had grade 3 back pain the AEs of special interest were mild or moderate in severity (grade 1 or 2). Discontinuations due to AEs were similar in the fulvestrant and anastrozole groups of the two trials. Some deaths due to adverse events were recorded but none were reported as being causally related to study treatment.

4 COST EFFECTIVENESS

4.1 Overview of company's economic evaluation

The company's submission to NICE includes:

i) a targeted review of published submissions made to national reimbursement and health technology assessment organisations of therapies for the treatment of locally advanced or metastatic breast cancer.

ii) a report of an economic evaluation undertaken for the NICE STA process. The cost effectiveness of fulvestrant is compared with anastrozole, letrozole and tamoxifen for post-menopausal women with HR+ locally advanced or metastatic breast cancer who have not previously been treated with any hormonal therapy.

4.2 Company's review of published economic evaluations

A targeted review was conducted by the company to identify HTAs of therapies for locally advanced or metastatic breast cancer. The review included a search of national reimbursement and technology assessment organisations. The websites were searched in May 2016 for any HTA in breast cancer and those related to advanced or metastatic breast cancer were included. The company did not include any additional inclusion or exclusion criteria. More details on the search strategies are provided in section 3.1.1.

The HTAs identified are shown in CS Appendix E. The company considered those published by NICE to be most relevant and therefore included these assessments in their review. They identified 10 NICE technology appraisals, relating to metastatic breast cancer. These are summarised in CS Table 43 and the methods and results of each submission are shown in CS Table 44. The company does not provide any discussion about the assessments identified, for example concerning their relevance to the current submission.

The ERG notes that five submissions relate to first-line therapy but none of the submissions relate to the same population as in the current submission. The ERG notes that the company has not searched for published cost-effectiveness literature. The ERG has therefore completed a search of published cost-effectiveness studies.

The ERG searched EMBASE and Pubmed database from 2010 (date of search in previous NICE appraisal for fulvestrant) for economic evaluations of anastrozole, letrozole, tamoxifen or fulvestrant in post-menopausal women with ER+ advanced or metastatic breast cancer. We excluded studies reported as abstracts or not in English. We identified two studies.[27,28]

Newman et al.[27] compared fulvestrant 250 mg with fulvestrant 500 mg for patients previously treated with an AI or antiestrogen therapy. Das et al.[28] compared fulvestrant 500 mg with nonsteroidal AIs (anastrozole and letrozole) in patients who had previously received hormonal therapy in the United Kingdom. The ERG notes that these studies are for a relevant population but are not for first-line treatment so may be of limited relevance to this appraisal.

4.3 Critical appraisal of the company's submitted economic evaluation

4.3.1 NICE reference case

The NICE reference case requirements have been considered in the ERG critical appraisal of the submitted economic evaluation in Table 24.

Table 24 NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	Yes	CS Table 1
Comparator: As listed in the scope developed by NICE	Yes	CS Table 1
Perspective on costs: NHS and PSS	Yes	CS Table 46
Evidence on resource use and costs: Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	CS Table 46
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Yes	
Type of economic evaluation: Cost utility analysis with fully incremental analysis	Yes	
Synthesis of evidence on outcomes: Based on a systematic review	Yes	
Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	CS Table 46
Measuring and valuing health effects: Health effect should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life.	Yes	EQ-5D used for disease health states from the company's clinical trial
Source of data for measurement of health-related quality of life: Reported directly by patients and/or carers.	Yes	
Source of preference data: Representative sample of the UK population	Yes	
Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes	
Discount rate: 3.5% pa for costs and health effects	Yes	CS Table 46

As shown in Table 24, the methods and data inputs used in the company's economic evaluation conform to NICE methodological guidance.

4.3.2 Model Structure

The company presented a cohort-based partitioned survival model with three mutually exclusive health states: PFS, PD and death. A schematic of the model was presented in CS Figure 39 which showed the proportion of patients in the three mutually exclusive health states over the model time-horizon. However, the company's model schema did not reflect the direction of the patients' flow across the three mutually exclusive health states. To address this, the ERG produced a diagram of the three-state model structure (shown in Figure 10) to illustrate the patient flow in a transparent and intuitive manner. A lifetime horizon of 30 years was applied in the base case model. The CS justified the time-frame by stating that at the end of this time horizon <1% of the population were alive. A cycle length of four weeks was used in the model, which, as stated in the CS, is the shortest time-period to observe any change in the disease symptoms and was consistent with the follow-up visit schedule in the FALCON trial. A half-cycle correction was applied correctly and costs and health effects were discounted at 3.5% per annum as outlined in the NICE reference case.[18] The perspective adopted was that of the NHS and PSS. The model was constructed in Microsoft Excel 2010.

The CS stated that this model structure was chosen as the health states are in line with the clinical pathway and the model structure is consistent with the approaches used in earlier NICE appraisals for ABC as well as other cancers. The model accurately represents the clinical pathway of patients' transition through the course of their treatment for advanced/metastatic breast cancer by assuming that patients with disease progression cannot transition back to progression-free health state.

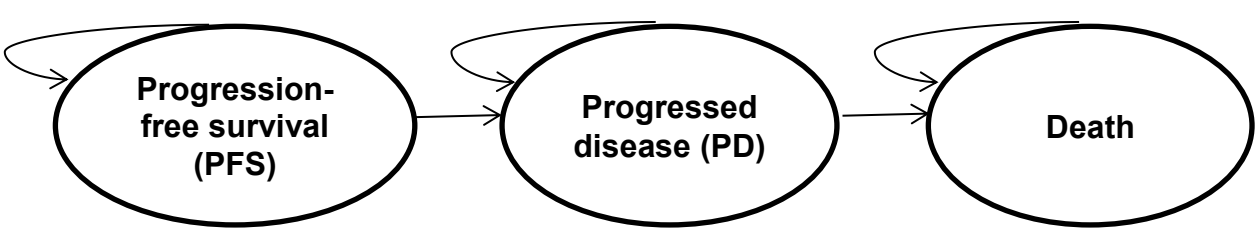


Figure 10 Model structure (illustration adapted by the ERG)

To inform the clinical parameters of PFS and OS within the economic model, the CS used the results from the NMA, as discussed earlier in section 3.3. Long term data for these parameters were extrapolated by fitting parametric survival curves (see more details in section 4.3.5). The model derived the proportion of patients in the PD state as the difference between the PFS and OS curves. Patients received treatment until disease progression. All patients were assumed to receive subsequent treatments and these subsequent treatments were only assumed to impact costs. AEs were included as a one-off event in the first treatment cycle within the company's analyses to account for the AEs associated costs and quality of life whilst on treatment. The model included costs associated with disease management, treatment acquisition, treatment administration, subsequent therapy and AEs and incorporated quality-adjusted life years (QALYs) by assigning utility values to the health states (further details are discussed in sections 4.3.6 and 4.3.7).

Overall, the ERG considers the model approach to be appropriate and consistent with the clinical pathway of patients with advanced or metastatic cancer. The CS presents sufficient justification for the company's methodological and structural choices in CS Section 5.2.

4.3.3 Population

The economic evaluation includes the population defined in the company's decision problem as postmenopausal people with locally advanced or metastatic HR+ breast cancer who have not received endocrine therapy. This corresponds with the final scope issued by NICE[1] [redacted] The patient population is also consistent with the patient population included in the FALCON trial.

4.3.4 Interventions and comparators

The cost-effectiveness model compares fulvestrant to anastrozole, letrozole and tamoxifen, as specified by the NICE scope[1] and the company's decision problem. Fulvestrant currently has a marketing authorisation for the treatment of patients on or after adjuvant anti-oestrogen therapy, or disease progression on therapy with an anti-oestrogen therapy. [redacted] The recommended dose is 500 mg administered IM into the buttocks as two injections, twice in the first month and then monthly thereafter. This dosage was used in the FIRST and FALCON trials. The ERG considers that the intervention in the decision problem reflects the anticipated use in UK clinical practice.

The comparators listed in the NICE scope[1] and the company's decision problem are aromatose inhibitors (anastrozole and letrozole) and tamoxifen. The use of tamoxifen is restricted to the instance where AIs are not tolerated or are contra-indicated. Anastrozole, letrozole and tamoxifen are available as oral medication taken daily by patients. The ERG's clinical advisors agreed that the comparators in the NICE scope were appropriate and were routinely used in the UK NHS.

4.3.5 Treatment effectiveness and extrapolation

As described in section 4.3.2, the economic model comprises three health states. In the company's base case analysis, patients were modelled to move through these mutually exclusive states over four-weekly cycles for a life time horizon. Patients were modelled to discontinue the first-line therapy and move to the PD state when the disease progressed.

The company identified six relevant studies of first-line pharmacological therapies for post-menopausal women with HR+, locally advanced or metastatic breast cancer through their SLR. The SLR has been summarised and critiqued in section 3.1 of the ERG report. The studies are: the FALCON[8] and FIRST[5] trials of fulvestrant versus anastrozole, the North American[9] and TARGET[10] trials of anastrozole versus tamoxifen (20 mg), the Milla-Santos et al.[11] trial of anastrozole versus tamoxifen (40 mg) and the PO25 trial[12] of letrozole versus tamoxifen (20 mg). These studies enabled indirect treatment comparison of fulvestrant and the other first line interventions tamoxifen and the AIs, anastrozole, and letrozole.

The company modelled clinical outcomes using a fixed-effect NMA. The key outcomes, PFS and OS were estimated from extrapolated survival curves. Incidence rates of AEs specific to each treatment group were used to estimate associated costs and disutilities for the corresponding cohort in the company's model. In this section, we summarise and discuss the methods used by the company to estimate the effectiveness outcomes of PFS, OS and time to treatment discontinuation (TTD) as well as AE rates for fulvestrant and the above-mentioned comparators.

4.3.5.1 Survival outcomes

As stated above the company identified six studies from its SLR for analysis in the model. Given the absence of head-to-head trials between fulvestrant and the comparators tamoxifen and letrozole, the company analysed these studies using indirect treatment comparison. The Milla-Santos[11] trial was ultimately dropped from the company's meta-analysis because it included comparison of a higher dose (40 mg) of tamoxifen than the

other pooled studies and its inclusion led to heterogeneity in the NMA of both the OS and PFS outcomes. The company combined individual patient level data from the North American and TARGET trials, and these two trials are jointly referred to as NorthAmTarget. A detailed description and critique of the company's approach to evidence synthesis can be found in section 3.1.7 of the ERG report.

The CS reports an attempt to match patients in each treatment arm of all relevant studies to the FALCON trial population. This was not possible for PO25 as patient-level data had to be reconstructed from a published article on the trial. The methodology of the matching process is discussed in detail in section 3.1.7 of this report. The KM plots of PFS and OS for the four studies (FALCON, FIRST, NorthAmTarget, and PO25) included in the economic model are reported in the CS (CS Figures 23 and 24, respectively) and reproduced below (Figure 11 and Figure 12). Plots for the FALCON, FIRST, and NorthAmTarget trials are for the matched data and not the full data set. In the absence of individual patient level data for PO25, the CS reports that KM data were digitised to permit the estimation of survival functions.

Figure 11 PFS KM plots from FALCON and studies identified in the SLR (CS Figure 23, p. 92)

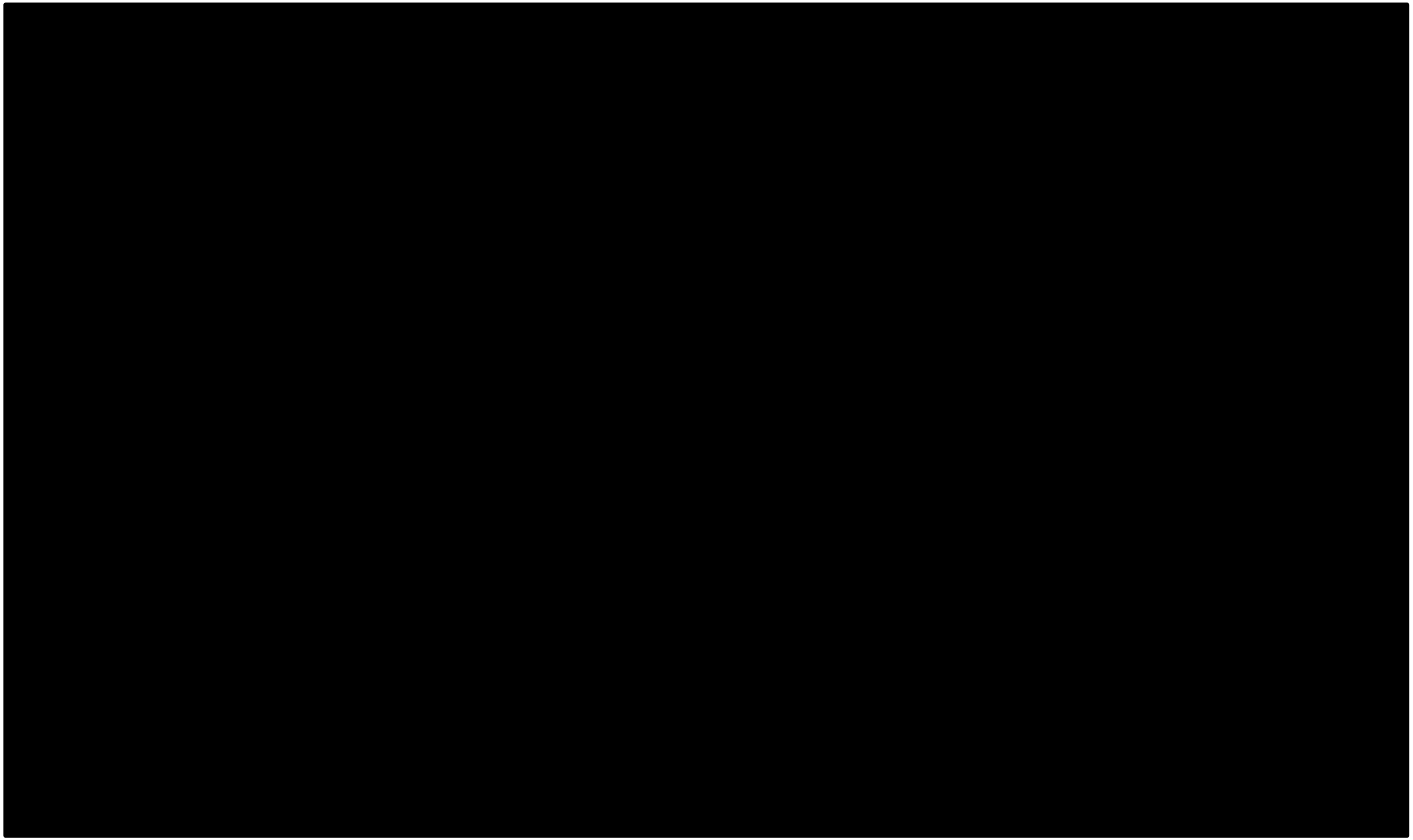
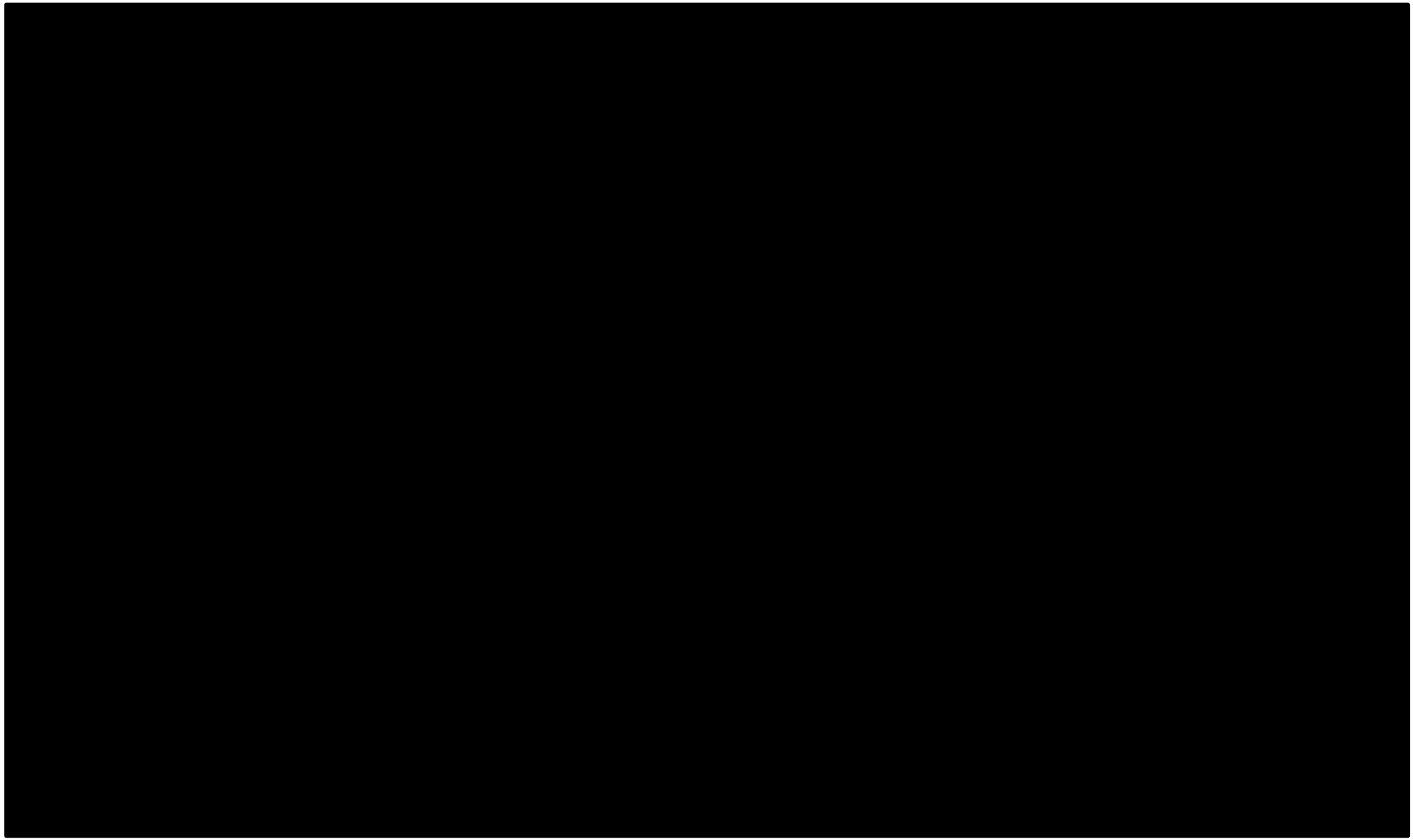


Figure 12 OS KM plots from FALCON and studies identified in the SLR (CS Figure 24, p. 93)



The company states that visual inspection of KM plots for PFS showed that treatment arms remained separated over the trial period. KM plots for OS depict late separation (21 months) for the FIRST trial and crossing plots for the PO25 trial and the NorthAmTarget trial. We agree with the company that, based on visual inspection, some of the treatment arms particularly for the KM plots of OS (NorthAmTarget and PO25) cross or separate beyond the median survival time. This suggests that NMA methods, which rely on the assumption of proportional hazards, may not be suitable for analysing the studies.

The CS further estimates the log cumulative hazard plots for PFS and OS for the four trials, to further investigate the violation of proportional hazards. These hazard functions are presented in CS Figures 25 and 26. Like the KM plots, visual inspection seems to suggest that the assumption of proportional hazards is violated: it can be observed that for OS, the treatment arms of the PO25 and NorthAm Target trial crossed. The log cumulative hazard arms in the FALCON, FIRST and NorthAmTarget trials cross for PFS, while for OS, arms cross for the NorthAmTarget trials. The CS further argues that using HRs as outcomes for the analysis places a restriction on the choice of distributions (such as log-normal and log-logistic distributions) that can be used to extrapolate PFS and OS. The company therefore sought alternative methods suitable for assessing NMA to extrapolate the treatment effect. The CS implements a method developed by Ouwens et al.[23] The Ouwens et al. method is premised on the fact that survival distributions, such as the Weibull or Gompertz, commonly used to extrapolate outcomes for cost-effectiveness analysis, can be described by two parameters (shape and scale). Further, applying a constant HR implies that treatment only affects the scale parameter. The Ouwens et al. method can be applied to both IPD and data derived from published KM curves such as the PO25 trial. A previous NICE appraisal for fulvestrant for previously treated patients with ABC reports the use of the Ouwens et al. method.[21] The ERG finds this method appropriate for implementing NMA, given the violation of the proportional hazards assumption.

The CS argues in favour of a fixed-effect NMA for PFS and OS rather than the random-effects model. The company's preference for a fixed-effect NMA has been critiqued in section 3.1.7 of this report. The CS describes two types of fixed-effect analyses. The first scenario is the 'All-shapes' model which permits the modelling of parametric survival distributions with the estimation of their shape and scale parameters, since it does not rely on the assumption of

proportional hazards. It forms the basis of the base case survival curves used in the cost-effectiveness model and tabulated results from the CS are reported in section 3.3.1 of the ERG report. The second scenario is the 'No shape arm' model, which assumes proportional treatment effects between treatment arms. The ERG believes the choice of the 'all shapes' model for the base case analysis is reasonable. The ERG queried the inclusion of the PO25 trial in the analysis (see section 3.1.3 of this report) and the company has provided cost-effectiveness results excluding this trial in its clarification response (Question A13, Table 25). The ERG has conducted a scenario analysis that excludes the PO25 trial data and the results are shown in this report section 4.4.

PFS extrapolation

The company extrapolated KM curves for all the selected parametric distributions (Weibull, Gompertz, log-logistic, lognormal and generalised gamma). The ERG verified that the extrapolated curves reported in the CS corresponded to those used in the economic model. Extrapolated curves for all distributions were simultaneously plotted along with observed data from each of the meta-analysed studies. See Figure 13 to Figure 16 below (CS Figures 29-32).

Figure 13 FALCON PFS study fit with fixed effects 'all shapes' network meta-analysis model (CS Figure 29, p. 110)

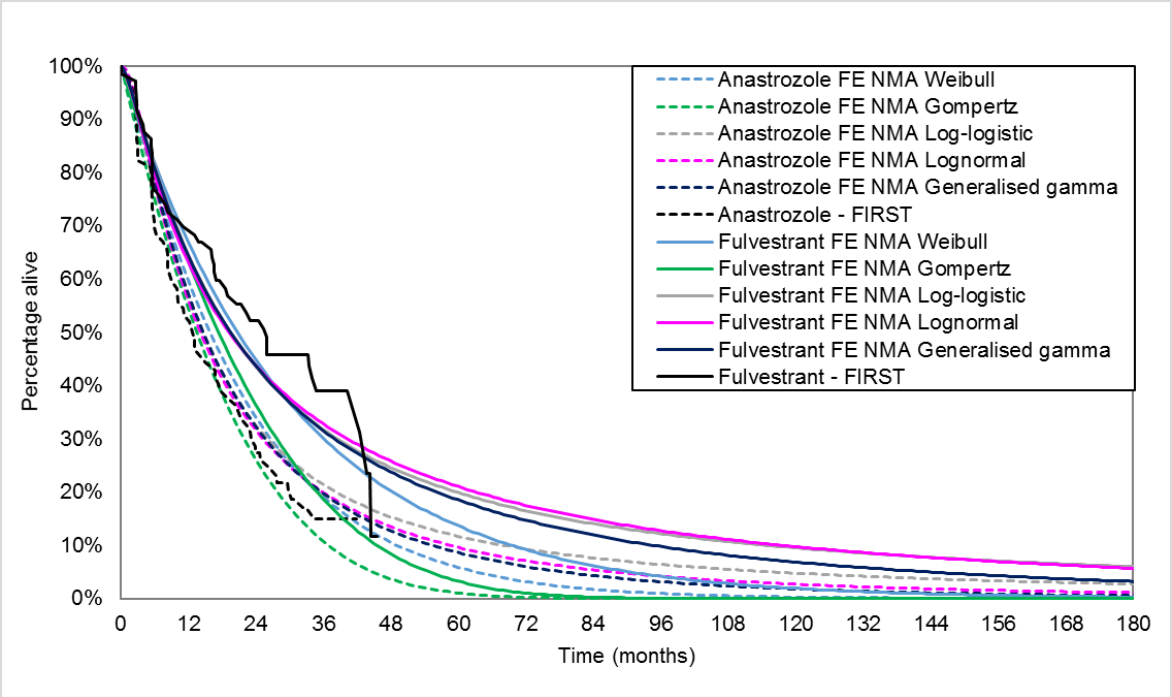


Figure 14 FIRST PFS study fit with fixed effects 'all shapes' network meta-analysis model adjusted for between-study differences (CS Figure 30, p. 110)

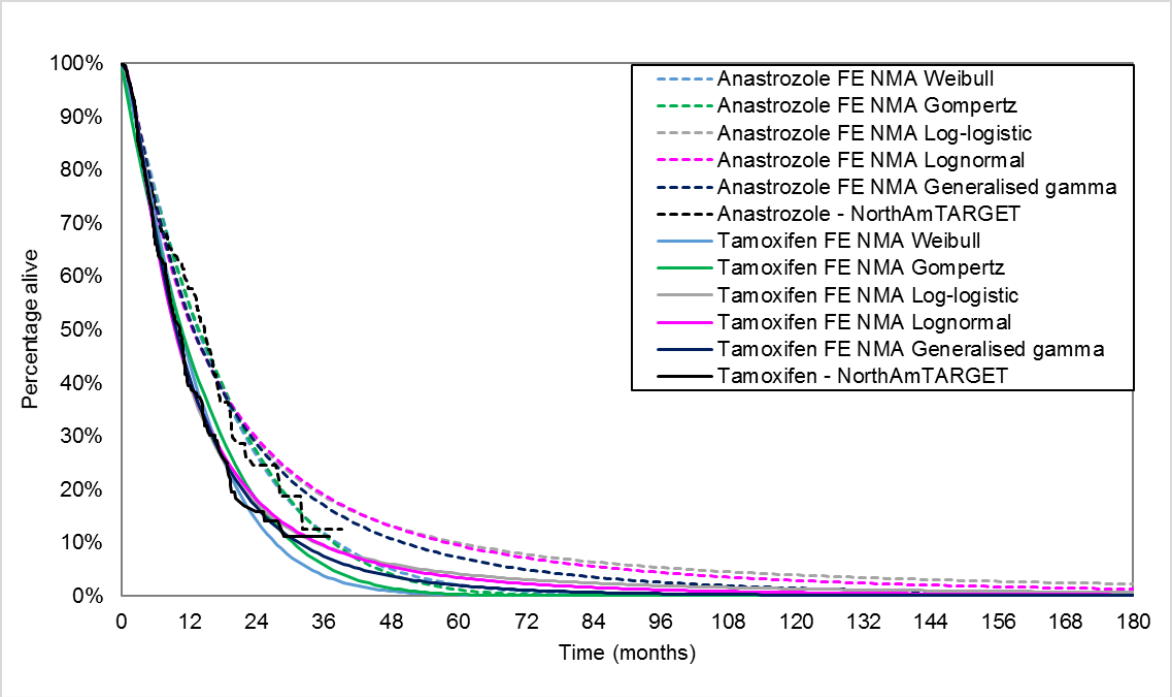


Figure 15 NorthAmTarget PFS study fit with fixed effects 'all shapes' network meta-analysis model adjusted for between-study differences (CS Figure 31, p. 111)

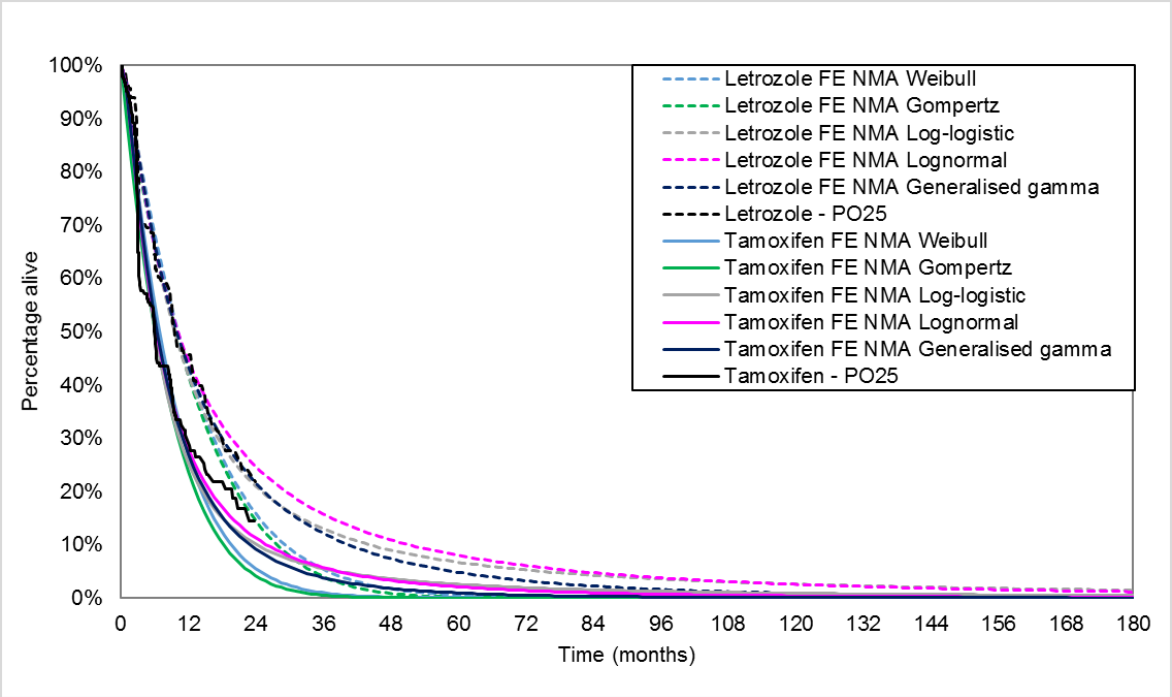


Figure 16 PO25 PFS study fit with fixed effects 'all shapes' network meta-analysis model adjusted for between-study differences (CS Figure 32, p. 111)

The ERG notes that the PFS curves in figures 12 to 15 are different for the same intervention. The ERG understands that the company has fitted the four curves to the observed data from the trials separately to give outputs for their Akaike and Bayesian Information Criteria statistics, but this is not stated explicitly in the CS.

The CS reports Akaike and Bayesian Information Criteria statistics for PFS (Table 25). The Bayesian information criterion (BIC) and the Akaike information criterion (AIC) are closely related statistics commonly used for model or distribution selection. The distribution with the lowest AIC or BIC value represents the best fit to the observed survival data. One limitation of the AIC and BIC is that they cannot be extended to make predictions of fitness beyond the observed data. The CS reports that visual inspection and expert opinion have been used to assess the different extrapolations of the survival data. Based on the company's clinical experts, 1-5% of patients treated with anastrozole are estimated to still be progression-free after 10 years (see Table 26). The company chose the generalised gamma distribution as the most appropriate fit, based on visual inspection and the opinion of the company's clinical experts[29], although AIC and BIC (Table 25) placed the distribution at second best after the log-logistic distribution. Other distributions (log-logistic, lognormal, Weibull and Gompertz) were tested in

sensitivity analyses (Table 99 of the CS) which shows that the choice of distribution did not impact significantly on the ICER.

We note that the results from the company's AIC / BIC statistics seem inconclusive as certain distributions perform better for one trial and worse for others. For instance, the Weibull distribution which was one of the least favourable according to AIC and BIC criteria had a better fit to the tail of the FALCON KM plot for fulvestrant than the log-logistic, generalised gamma and log-normal. Advice from our clinical expert confirmed the PFS estimates in Table 26. We note that the fit in Figure 13 against the FALCON study is reasonable. The ERG, therefore, considered the company's choice of the generalised gamma distribution was reasonable for modelling PFS.

Table 25 AIC and BIC statistics for PFS based on fixed effects NMA model (CS Table 31, p. 109)

Distribution	AIC	AIC rank	BIC	BIC rank
Log-logistic	8624.747	1	8703.403	1
Generalised gamma	8627.055	2	8711.329	2
Lognormal	8636.065	3	8714.721	3
Weibull	8687.484	4	8766.140	4
Gompertz	8720.786	5	8799.441	5

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; NMA, network meta-analysis; PFS, progression-free survival.

Table 26 KOL opinion on PFS at 1, 2, 5 and 10 years (CS Table 32, p. 112)

	1 year	2 years	5 years	10 years
KOL estimate	50-60%	30-40%	5-10%	1-5%

Abbreviation: KOL, key opinion leader.

OS extrapolation

KM curves were also extrapolated for OS for the same parametric distributions as for PFS. Extrapolated curves for all the distributions were simultaneously plotted along with the observed data (using the matched subgroup as stated earlier) from each of the meta-analysed studies and are shown in Figure 17 to Figure 20 (CS Figures 34 -37). Similarly, we ascertained that extrapolated curves reported in the CS corresponded to those used in the economic model.

Figure 17 FALCON OS study fit with fixed effects 'all shapes' network meta-analysis model (CS Figure 34, p. 115)

[redacted]

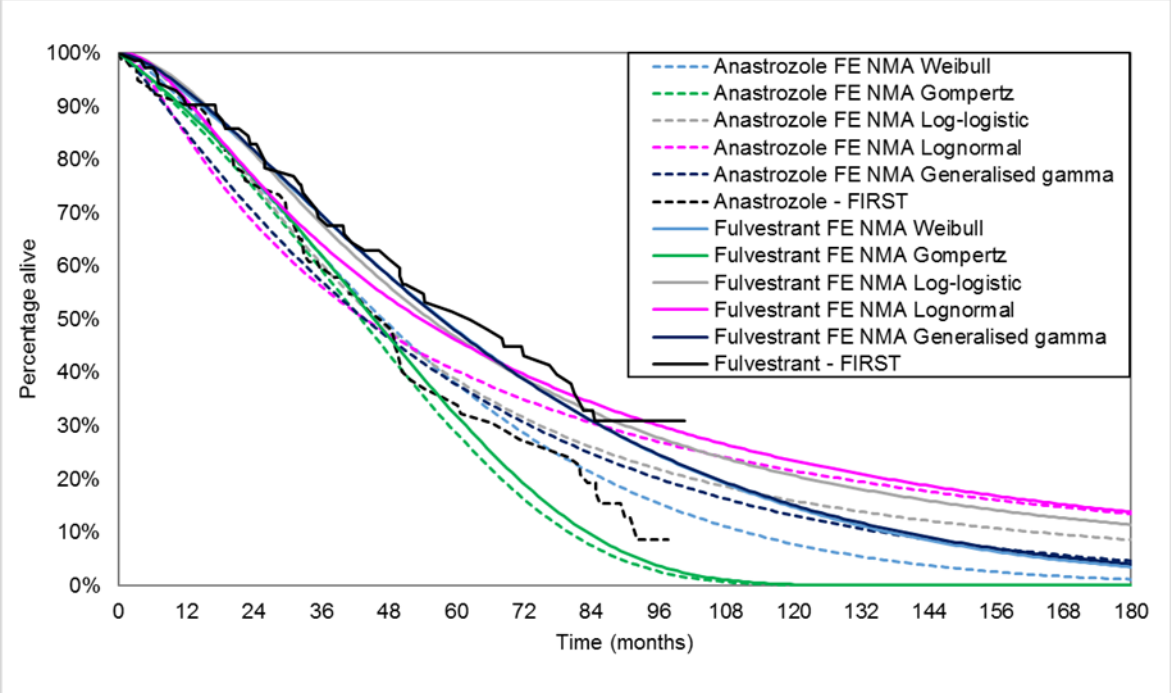


Figure 18 FIRST OS study fit with fixed effects 'all shapes' network meta-analysis model (CS Figure 35, p. 115)

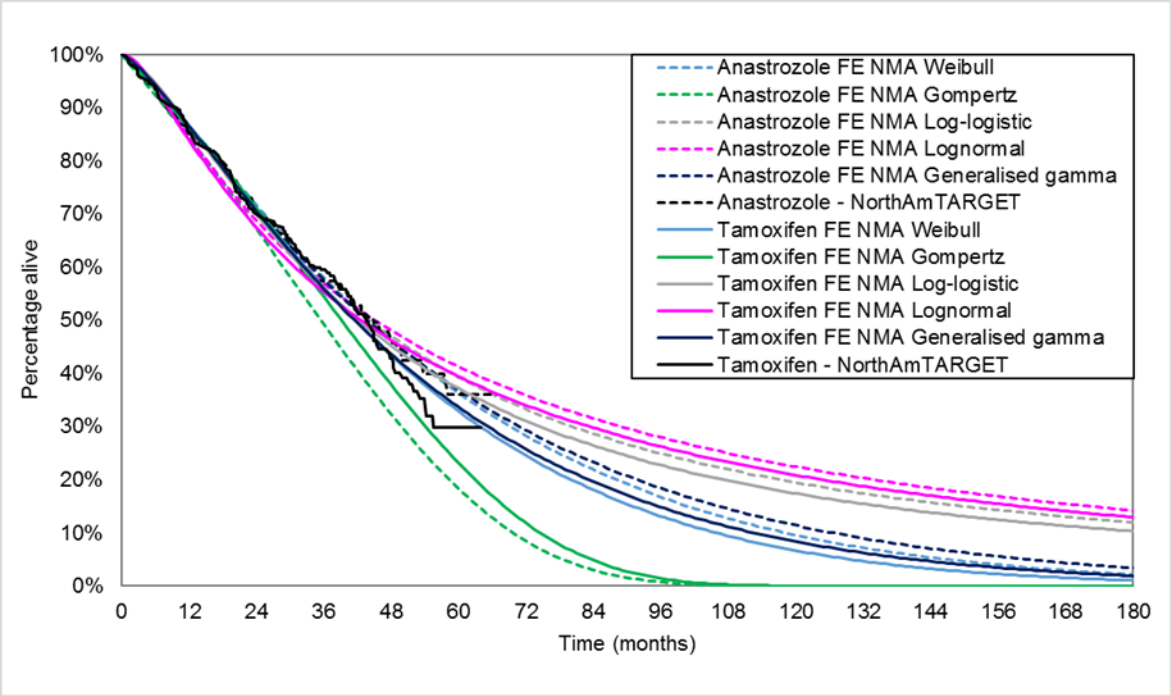


Figure 19 NorthAmTarget OS study fit with fixed effects 'all shapes' network meta-analysis model (CS Figure 36, p. 116)

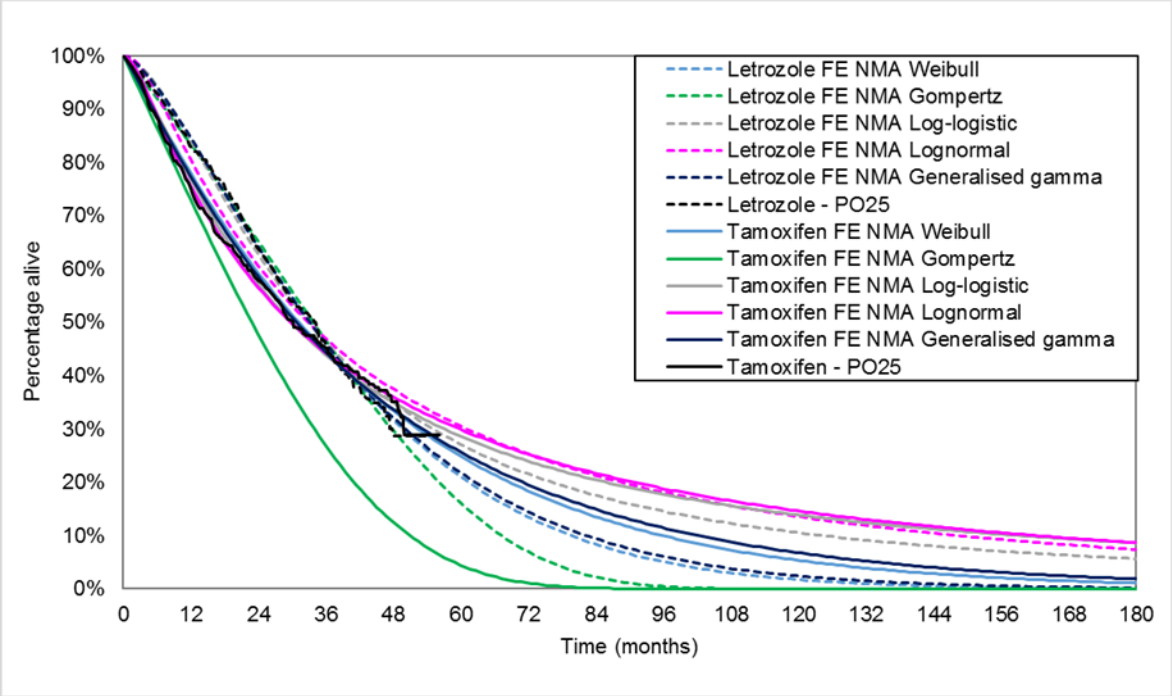


Figure 20 PO25 OS study fit with fixed effects 'all shapes' network meta-analysis model (CS Figure 37, p. 116)

The CS based its choice of the Weibull distribution as the best fit on visual inspection, AIC and BIC (Table 27) and clinical expert opinion[29] (Table 28). Advice from our clinical expert confirmed the estimates of OS for anastrozole (Table 28). The OS in the FALCON study (Figure 17) is immature as median survival had not been reached by the time of this submission; therefore the OS in the company model for fulvestrant is largely based on the FIRST trial. Therefore Figure 18 provides better insight regarding the suitability of the distributions explored.

The company carried out a sensitivity analysis using the gamma distribution (CS Table 98). The company considered that only the generalised gamma or the Weibull distribution was appropriate based upon the long-term extrapolations for these distributions compared to expert clinical opinion for anastrozole. The ERG carried out further analysis to explore the Gompertz, log-logistic and lognormal distributions (see section 4.4.1 for details). Based on our additional analysis, we consider that the choice of distribution does not have a significant effect on the ICER, except for the Gompertz distribution which does not provide a good fit to the FIRST study. We consider that the company's choice of distribution is reasonable based on the explanation in the CS.

Table 27 AIC and BIC statistics for OS based on NMA (CS Table 34, p. 114)

Distribution	AIC	AIC rank	BIC	BIC rank
Weibull	10499.131	1	10577.848	1
Generalised gamma	10500.300	2	10584.640	2
Gompertz	10508.995	3	10587.713	3
Log-logistic	10513.882	4	10592.599	4
Lognormal	10552.618	5	10631.335	5

AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; NMA, network meta-analysis; PFS, progression-free survival.

Table 28 KOL opinion on OS at 1, 2, 5 and 10 years (CS Table 35, p. 117)

	1 year	2 years	5 years	10 years
KOL estimate	75-85%	55-70%	20-30%	5-10%

KOL, key opinion leader.

Response rate and other outcomes

The CBR, EDoR, ORR and other outcomes are discussed in section 3.3.3 of this report. These outcomes have no direct implication on progression or survival in the company's economic model. This seems to be because any impact on patients' survival is implicitly built into survival data

Time to treatment discontinuation

The model structure assumes that treatment duration is until objective disease progression, when patients switch over to second line treatment. CS Figures 43 and 44 compare the time to treatment discontinuation (TTD) and PFS curves for anastrozole and fulvestrant respectively in the FALCON trial. The curves are reasonably similar for anastrozole but there is a separation on the curves for fulvestrant. The company's approach in modelling was to use PFS as a proxy for TTD. We note that the company did not attempt to extrapolate TTD beyond the trial period. This limits the conclusions that can be drawn from CS Figures 43 and 44 and PFS may not be a good proxy for TTD with fulvestrant.

Adverse events

Only the FIRST and FALCON trials provided comprehensive individual patient level data on AEs. The North American trial reported certain AEs such as diarrhea, fatigue and nausea (see Table 41 of the CS). The CS reports that the incidence rates for AEs for fulvestrant and anastrozole were sourced from the FALCON trial, while rates for letrozole and tamoxifen were sourced from the literature. The company has given the paucity of data as the reason for not performing an indirect comparison of AE data (see page 146 of the CS). The company acknowledges that, as a result, the analysis may suffer some bias due to difference in follow-up periods and patient characteristics across the treatment groups.

AE rates for all four pharmacological agents are reported in CS Table 49 which is reproduced below (Table 29). The company model applies these event rates on a one-off basis, rather than as monthly rates applied throughout the time horizon of the model. The CS provides justification for this approach (CS section 5.3.2). The ERG is of the view that this approach is acceptable, given that the AEs are not expected to last beyond one year. While the CS states that events of grade ≥ 3 and experienced by 2% or more of patients in the treatment groups of interest are to be modelled for costs and utility impacts, we found that some AEs outside this definition were included in the model (e.g. Bilirubin increased). In the company's clarification response

(Question B2), it admits that such events should have been excluded. The ERG considered that this error was not likely to have a significant impact on the model outcomes. The ERG also spotted discrepancies regarding the rates reported in the CS and those used in the model (AST increased for tamoxifen), as well as differences in the rate reported in the CS and that reported in the literature and the CS/company model (dyspnoea for letrozole). The company acknowledged these errors in its clarification responses (Question B3). The ERG's view is that these errors have only a minor impact on the model results.

Table 29 Incidence rates of adverse events used in the model (CS Table 49, p. 147)

Adverse event	Fulvestrant	Anastrozole	Letrozole	Tamoxifen
Source:	FALCON[26]	FALCON[26]	Finn 2016[30]	Paridaens 2008[31]
Sample size (n)	228	232	222	189
ALT increased	1.3%	0.0%	0.0%	4.2%
AST increased	1.3%	0.4%	0.0%	1.6%
Hypertension	1.8%	1.7%	0.0%	3.2%
Pleural effusion	2.2%	0.4%	0.0%	0.0%
Pain, bone	0.4%	0.4%	0.0%	5.8%
Pain, other	1.3%	0.9%	1.4%	3.2%
Dyspnoea	0.0%	0.9%	0.5%	2.6%
Bilirubin increased	0.0%	0.4%	0.0%	1.6%

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase.

Implications of survival parameters for cost-effectiveness

To predict the proportion of patients flowing from state to state per cycle throughout the modelled time horizon, the company estimated shape and scale parameters (and an additional Q parameter for the generalised gamma distribution) of PFS and OS from the fixed-effects NMA model. An 'All shapes' version of these parameters was then used in the company's health economic model for their base case cost-effectiveness results. The CS reports these parameter values in CS Table 73. We pointed out to the company that the values in CS Table 73 for PFS were not used in the model and this was acknowledged as a transcript error in the company's clarification response (Question B7). The actual model values are shown in CS Table 29 and in this report in Table 17.

One-way deterministic sensitivity analysis helped identify the top 10 parameters which cause the most significant change in the incremental cost-effectiveness ratio (ICER) for pair-wise comparisons between fulvestrant and the comparators. These analyses are discussed in section 4.3.10 of the ERG report. Choice of parameter inputs for OS are key model drivers of the cost effectiveness results.

4.3.5.2 Summary of ERG views on treatment effectiveness and extrapolation

One limitation with the comparison between anastrozole and fulvestrant stems from the immature OS data. Overall, the FIRST and FALCON trials seem to have been well conducted. The lack of individual patient level data from the PO25 trial makes it disparate in comparison with the FIRST and FALCON trials and not best suited for inclusion in the NMA. There are minor errors in the estimation of AE costs but these are unlikely to affect the conclusion from the results in a significant way. In general, we consider that the company's choice of base case distributions for extrapolating PFS and OS, are reasonable. As will be shown later, the results of cost-effectiveness are sensitive to survival outcomes, particularly for the OS scale and shape parameters, suggesting that longer term data from the FALCON could potential have a significant effect on the model results and more analysis might be needed to draw firm conclusions on the cost-effectiveness of anastrozole.

4.3.6 Health-related quality of life

Review of health-related quality of life

The company conducted a structured review to identify health state utility values for the economic evaluation. The EMBASE database was searched using the search strategy shown in CS Table 52. The search was for studies published between October 2013 and June 2016. The company chose this start date on the basis that this was the date of the search in the latest NICE Technology Appraisal for breast cancer. In their letter of clarification (Question B4), the company stated that this refers to the submission for trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane (TA371).[32] Other more recent appraisals for breast cancer such as TA424 (pertuzumab for neoadjuvant treatment of HER2-positive breast cancer),[33] TA421 (everolimus with exemestane for advanced breast cancer after endocrine therapy),[34] TA423 (erbulin for locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens)[35] and the ongoing technology appraisal for palbociclib in combination with an aromatase inhibitor[36] did not identify any further utility studies.

The inclusion criteria included quality of life studies in patients with advanced or metastatic breast cancer. The search identified 354 studies. Titles and abstracts were screened and studies were excluded if they did not mention EQ-5D or QALYs, were not about breast cancer, were not written in English or were posters or conference abstracts that did not provide utility values. Thirteen studies that contained primary sources of utility data were identified. Of these studies eleven studies were excluded for not using EQ-5D to measure utilities or were published prior to 2013. A PRISMA flow diagram that shows the exclusion process is shown in CS Table 42.

Two studies were included in the review: Fukuda et al.[37] and Eyles et al.[38] A summary of these studies is shown in Table 30 (CS Table 53). Of these studies, the company suggests that the study by Fukuda et al.[37] is the most relevant as it was a randomised trial with a large sample of comparable patients with HER2 negative metastatic breast cancer receiving first-line therapy. EQ-5D values were calculated for up to 36 months and also post-progression. However, the CS notes that 57% of patients had received prior endocrine therapy.

Table 30 Metastatic cancer utility studies

Study [country]	Population / disease area (sample size)	Study design /intervention	Population, method of elicitation and valuation technique / tariff	Health states and/or treatment description	Mean
Fukuda et al. (2015)[37] Takashima et al. (2016)[39] [Japan]	HER2 negative metastatic breast cancer, resistant to endocrine therapy (57% previous endocrine treatment after recurrence)	Randomised open-label phase III trial 1L taxane (docetaxel or paclitaxel) vs. S-1	Patients EQ-5D-3L (pre-treatment, 3 months after randomisation, every 6 months thereafter) Tariff:Japanese	Mean EQ-5D scores up to 60 months (S-1)	0.748
				Mean EQ-5D scores up to 60 months (taxanes)	0.741
				During 1L – mean EQ-5D up to 36 months (S-1)	0.810
				During 1L – mean EQ-5D up to 36 months (taxanes)	0.781
				Post-progression period (S-1)	0.729

	Age (years), median (IQR): S-1 59.0 (53–65) and taxane 58.5 (51–65)			Post-progression period (taxanes)	0.703
Eyles et al. (2015) [England][38]	Metastatic breast cancer, stable disease Age (years): 37–65 Years since diagnosis, mean: 2.76 (0.5–7) Life expectancy: >6 months ECOG: 0–2 (n=19)	Feasibility study Mindfulness-based stress reduction for self-management of anxiety, depression, QoL, and fatigue	Patients EQ-5D-3L (baseline, during treatment [4 and 8 weeks] and follow-up [16 and 24 weeks]) Tariff: NR	Baseline	0.74
				End of follow-up	0.72
				End of follow-up (extreme outlier removed)	0.76

Abbreviation: 1L, first line; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EQ-5D, EuroQol-5 Dimension; HER2: Human epidermal growth factor; IQR, interquartile range; NR, not reported; QoL, quality of life; SD, standard deviation; SG, standard gamble; TTO, time trade off; VAS, visual analogue scale.

The ERG considers the company's search to not be fully up-to-date and therefore we have updated the search until June 2017. We found four more potentially relevant primary studies that reported EQ-5D values in patients with advanced or metastatic breast cancer.[40-43] Three studies[40-42] were reported as conference abstracts and the details of these studies are shown in Table 31. The other study was a more detailed description of the study by Fukuda et al.,[43] shown in Table 30.

Table 31 Metastatic cancer utility studies identified in ERG update searches

Study [country]	Population / disease area (sample size)	Study design /intervention	Population, method of elicitation and valuation technique / tariff	Health states and/or treatment description	Mean
Lambert-Obry (2016)[42]	Postmenopausal women with ER+/HER2 negative locally advanced or metastatic breast cancer	Retrospective non-interventional study	EQ-5D 5L and WPAI questionnaire (at recruitment and at 3 and 6 months after recruitment)	First-line progression-free EQ-5D	0.73
				First-line progressed disease EQ-5D	0.62
Loibl (2016)[41]	HR+, HER2 negative metastatic breast cancer	Randomised trial (PALOMA-3) of palbociclib plus fulvestrant versus fulvestrant alone	EQ-5D 3L and EQ-5D VAS (at baseline and then on day 1 of each cycle until cycle 4 and then every alternate cycle until end of treatment)	Palbociclib plus fulvestrant EQ-5D	0.73
				Fulvestrant only EQ-5D	0.71
Mitra (2016)[40]	HR+/HER2 negative advanced or metastatic breast cancer	Multicenter real world study	EQ-5D 3L, EQ-5D VAS	EQ-5D all patients	0.73
				EQ-5D, 1st line	0.77
				EQ-5D 2nd line	0.69
				EQ-5D, 3rd and subsequent line	0.69

Abbreviation: EQ-5D, EuroQol-5 Dimension; HER2: Human epidermal growth factor; HR+: Hormone-receptor positive; IQR, interquartile range; VAS, visual analogue scale.

The company also reviewed utility values used in previous NICE breast cancer appraisals and details of these are shown in CS Table 54 - 55. The CS reports that four primary studies are used in the NICE Technology Appraisals for ABC and all these studies used the standard gamble to elicit utilities from either the general public or from medical personnel. These studies do not meet the NICE reference case criteria, as HRQoL have not been directly measured from patients. The most common utility study used in previous technology appraisals was by Lloyd et al.[44] but this study has been criticized by previous ERG reports for other STA appraisals for not

meeting the NICE reference case and that the utility values derived may not be reflective of patients with breast cancer.

Health-related quality of life from clinical trials

The FALCON trial[8] collected HRQoL data including the EQ-5D 3L, using the UK tariff (section 3.3.5). The questionnaire was administered at baseline and every 12 weeks until disease progression or treatment discontinuation. For patients whose disease had progressed, the questionnaire was administered three months after disease progression and then at 6-monthly intervals. Health state utility values for progression-free and progressed disease are shown in Table 32 (CS Table 50) for patients treated with fulvestrant, anastrozole and all patients. The CS states that the mean EQ-5D values were similar across treatments with overlapping 95% CIs. For this reason, the company used the same utility values for both treatments. The ERG agrees that it is reasonable to use the same utility values for patients receiving fulvestrant and anastrozole.

Table 32 Health state utility values from the FALCON trial

Treatment	Health state		ITT	
		n	Mean	95% CI
Overall	Progression-free	449	0.75	[0.73, 0.77]
	Progressed disease	232	0.69	[0.65, 0.72]
Fulvestrant	Progression-free	225	0.76	[0.73, 0.78]
	Progressed disease	104	0.69	[0.63, 0.74]
Anastrozole	Progression-free	224	0.74	[0.71, 0.76]
	Progressed disease	128	0.69	[0.63, 0.74]

Abbreviations: CI, confidence interval; ITT, intention-to-treat.

The company uses the utility values from the FALCON trial for all patients for the health state utility values in the economic model. However the company adjusted these values using repeated measures mixed effects regression models (MMRMs) "*in order to take account of the repeated measures per patient, and estimate the association between utilities and clinical events in the FALCON study"*. The company included two mixed models: MMRM (1) included only a coefficient for disease progression, while MMRM (2) included coefficients for patient characteristics. The company preferred MMRM (1) because the coefficients used in MMRM (2) were not statistically significant. The ERG agrees with this choice and presumes that the values

from MMRM (1) are equivalent to those for the mean unadjusted utility values shown in Table 32, as there is only one coefficient for progression. The utility value used for the progression-free health state in the model is 0.7511 and for the progressed state is 0.6913.

The company has also provided the utility values at different time points from baseline (CS Figure 65 and 67). The CS comments that the utility values collected in the FALCON trial are higher than those used in previous appraisals but they are preferred because they align with the NICE reference case in the use of EQ-5D data collected in a patient population as specified in the decision problem. Further the CS comments that utility values have face validity as the utility estimates are lower than the EQ-5D population norms for this age and sex group (Kind et al.[45]).

The ERG agrees with company's use of the health state utilities from the FALCON trial in the economic model and considers that the utility values collected are an improvement on the data used in previous technology appraisals for advanced and metastatic breast cancer. As noted above, the utility values have been collected in the same patient group as specified in the NICE scope[1] and the methodology used is consistent with the NICE reference case. Further, the ERG considers that the utility values are consistent with those collected by Fukuda et al.,[37] in terms of the difference between the utility values for progression-free and progressed health states.

Adverse event disutilities

The company includes disutility for AEs. These are applied to grade 3/4 AEs and applied for the duration of the AE. The disutility values were taken from previous NICE submissions, as shown in Table 33 (CS Table 57).

Table 33 Disutilities associated with AEs

Adverse event	Utility decrement per event	Duration (days)	Source
ALT increased	-0.050	28.0*	Boehringer Ingelheim Ltd. (2014) [46]
AST increased	0.000	0.000	
Hypertension	-0.153	8.0	Swinburn et al. (2010)[47]
Pleural effusion	-0.371	3.0	Swinburn et al. (2010)[47]
Pain, bone	-0.069	17.0	Doyle et al. (2008)[48]
Pain, other	-0.069	17.0	Doyle et al. (2008)[48]
Dyspnoea	-0.05[b]	12.7	Doyle et al. (2008)[48]
Bilirubin increased	0.000	0.000	

CS Table 57
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
*Assumption
[b] Value corrected in company clarification response

In a clarification response (Question B5), the company noted that the disutility value for dyspnoea should be 0.05, rather than the initial value of -0.103, and that there is a mistake in the disutility values for pleural effusion, which had been confused with palmar-plantar erythrodysesthesia in the study by Swinburn and colleagues.[47] They have been unable to identify an alternative published value for pleural effusion.

The ERG considers the company's approach to including disutilities for AEs in the economic model is reasonable and notes that the effect of AE disutilities on the model results is negligible due to the low frequency of SAEs.

4.3.7 Resource use and costs

The economic evaluation includes costs for disease management, treatment acquisition, treatment administration, subsequent therapy and AEs. Unit costs for health care resources were taken from National Reference Costs[49] and PSSRU Unit costs of health and social care.[50] The company did not conduct a review of resource use in ABC.

Treatment cost and resource use

The dosing schedules for fulvestrant and its comparators are shown in Table 34 (CS Table 63). The dosing information is taken from the British National Formulary (BNF).[51] The recommended dose for fulvestrant is 500 mg, administered twice in the first two weeks and monthly thereafter. Fulvestrant is administered in the outpatient setting by IM injection into the buttocks. The dosing schedule is consistent with that used in the FALCON trial. The unit cost for fulvestrant is £522.41 per dose. Anastrozole, letrozole and tamoxifen are oral treatments and all cost less than £2 per 4 week treatment cycle. In the model, patients are treated until disease progression, on the basis that the treatment discontinuation and disease progression curves were similar.

Table 34 Treatment dosing, administration and drug acquisition costs

		Fulvestrant (first 4 weeks)	Fulvestrant (after first 4 weeks)	Anastrozole	Letrozole	Tamoxifen
Label information	**Administration method**	IV	IV	Oral	Oral	Oral
	Dose per administration (mg)	500	500	1.0	2.5	2.5
	Administration frequency	2 per 4 weeks	1 per 4 weeks	1 per day	1 per day	1 per day
Package information	**Formulation (mg)**	250	250	1.0	2.5	20
	Pack size	2	2	28	28	30
	Cost per pack (£)	£522.41	£522.41	£0.75	£1.52	£1.62
Dosing required in model	**Required dose (mg)**	500	500	1.0	2.5	20
	Vials/ capsules per administration	1	1	0.04	0.04	0.03
Relative dose intensity/ compliance		1.00	0.99	0.99	1.00*	1.00*
Drug cost per 4-week cycle		£1,044.82	£522.41	£0.75	£1.52	£1.51
Administration cost 1st cycle		£370.35	-	£196.64	£196.64	£196.64
Administration cost subsequent cycles		-	£73.74	£27.93	£27.93	£27.93

CS Table 63
Abbreviations: IV, intravenous. *Assumption (data not available)

The approach for calculating administration costs is based on the previous NICE appraisal for fulvestrant (TA239).[21] The administration costs differ between the first four-week cycle and subsequent cycles. The treatment-related administration costs for fulvestrant 500 mg in the first

month is £370.35, which includes an initial visit with the oncologist for the initial dose (£199.64), the administration of fulvestrant by a clinical nurse (£99.97), plus the average cost of administrating the dose two weeks later, assuming 32% are administered in the primary care setting and 68% are administered in the secondary care outpatient setting (£18.75). The cost for administering fulvestrant in subsequent cycles is £73.74. One of our clinical experts stated that all patients in their locality would be administered in the hospital setting and that it may be a challenge persuading primary care to take on treatment delivery. The ERG has run an analysis assuming that all patients receiving fulvestrant are treated in the outpatient setting and none receive the treatment in primary care (section 4.4).

Anastrozole, letrozole and tamoxifen are oral medications and the only administration costs are the cost of prescription each month (after the first month) and this was assumed to be a telephone consultation with general practitioner lasting 7.1 minutes (£27.93). The initial cycle includes a visit with the oncologist (£199.64).

Disease management costs

Disease management costs are included in the model for the progression-free and progressed health states and for a one-off cost of terminal care. The company did not collect health care resource use data for the FIRST or FALCON trials. Health-state costs are taken from the NICE clinical guidelines for ABC (CG81)[2] using the resources specified for 'Package 1' and 'Package 2'. Unit costs have been inflated to 2015-6 using the PSSRU Hospital and Community Health Services (HCHS) indices.[50] The resource use and unit costs are shown for the progression-free and progressed health states in Table 35 and Table 36 respectively (CS Table 60 - 61).

Table 35 Costs of progression-free health state

Items	Resource usage per 4 weeks	Frequency	Unit cost (£) inflated to 2015/16	Total cost per month	Source*
Community nurse (home visit - 20 minutes)	2	1 per 2 weeks	£14.67	£29.34	PSSRU 2015/16
GP contact (surgery visit – 11.7 minutes)	1	1 per month	£46.02	£46.02	PSSRU 2015/16
Clinical nurse specialist (1 hour)	1	1 hour every month	£108.00	£108.00	PSSRU 2015/16
Total progression-free cost per 4 weeks				£183.36	Calculation

Abbreviation: GP, General Practitioner.

*PSSRU 2015 used to provide duration of appointment time; PSSRU 2016 used to provide unit costs.

Table 36 Costs of progressed disease health state

Resource	Resource usage per 4 weeks	Frequency	Unit cost (£)	Total cost per 4 weeks (£)	Source*
Community nurse (home visit 20 minutes)	4	1 per week	£14.67	£58.67	PSSRU 2015/16
Consultation with a GP (home visit)	2	1 per 2 weeks	£65.00	£130.00	PSSRU 2015/16
Clinical nurse specialist (duration 1 hour)	4	1 per week	£108.00	£432.00	PSSRU 2015/16
NHS community occupational therapist	2	1 per 2 weeks	£42.00	£84.00	PSSRU 2015/16
Total progressed disease cost per 4 weeks				£704.67	Calculation

Abbreviations: GP, General Practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

*PSSRU 2015 used to provide duration of appointment time; PSSRU 2016 used to provide unit costs.

The ERG notes that the resources described in the NICE clinical guidelines refer to patients receiving chemotherapy, rather than patients receiving endocrine therapy and therefore do not appropriately estimate the resource used in this submission. For example, our clinical experts stated that patients treated with endocrine therapy would not receive home visits from a nurse. Furthermore they stated that patients would see a medical oncologist regularly (every three months) and this resource has not been included in the model. The ERG considers that the resources would be more consistent with previous clinical trials for AIs (such as Karnon et al.[52]) and provides an analysis with alternative resource use in section 4.4.

Terminal care costs

Terminal care costs are included in the model for patients with progressed disease for the end of patients' life and consist of time spent either in the hospital, hospice or at home. Based on NICE clinical guidance CG81,[2] the company assumes that 40% of patients died at the hospital, 10% at a hospice and 50% at home. The unit costs from CG81 were inflated to 2015/16 costs using the HCHS index.[50] The total terminal care cost per patient in the model is £4,379.03.

Subsequent therapy

The economic model includes subsequent lines of treatment for patients whose disease progresses. Second-line and third-line therapies include further endocrine therapy (fulvestrant, anastrozole, letrozole, exemestane, tamoxifen), targeted therapies (everolimus plus exemstane), chemotherapy (docetaxel, capecitabine, paclitaxel, erbulin) or no treatment. The proportions of patients receiving subsequent therapies and the treatment durations are based upon Kurosky et al.,[53] a retrospective cohort study of postmenopausal patients with metastatic ER+, HER2 negative breast cancer in the UK.

The proportions of patients receiving second-line and third-line therapy are shown in Table 37 (CS Table 66). It was assumed in the model that all patients that initiated first-line treatment received second-line treatment and 54.41% of patients who received second-line treatment received third-line treatment.

Table 37 Proportion of patients using subsequent treatments in the second- and third-line settings

From primary treatment to →→→ / Setting	Endocrine therapy (%)	Targeted therapy (%)	Chemotherapy (%)	No treatment (%)	Total (%)
Second-line	54.35%	8.08%	37.57%	0.00%	100.00%
Third-line	24.02%	0.00%	30.39%	45.59%	100.00%

Based on Kurosky et al.,[53] patients on endocrine therapy were assumed to receive treatment for 9.16 months for second-line and 6.17 months for third-line.

Dosing schedules, unit costs and administration costs for the chemotherapy treatment and the targeted therapies are shown in CS Table 68-69. A weighted cycle cost was calculated for the first and subsequent cycles for second-line and third-line treatment for the endocrine therapies, targeted therapies and chemotherapies (CS Table 70). It was assumed that patients starting on fulvestrant would not receive fulvestrant as a second-line or third-line therapy. For all other initial therapies subsequent treatment options would be the same. The weighted average costs of the subsequent therapies are shown in CS Table 71.

The ERG notes that in the population in the Kurosky retrospective study about a third of patients were initially diagnosed at early stage breast cancer and of these the majority received surgery and adjuvant endocrine therapy. Furthermore, only 49.3% of patients received endocrine therapy as first-line therapy. The ERG consulted their clinical advisors on the proportion of patients receiving endocrine therapy as subsequent therapy. Their view was that the proportion of patients receiving endocrine therapy as second-line treatment would be higher and in the region of 67-80% with fewer patients receiving chemotherapy. The ERG has conducted an analysis varying the proportions of patients receiving subsequent treatment in section 4.4.

Adverse event costs

The costs of treating treatment-related AEs are shown in CS Table 72. The costs are taken from National Reference costs 2015-16[49] and the cost codes are based upon those reported in previous NICE appraisals.

4.3.8 Model validation

In line with the recommendations developed by a task force of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM)[54] for model quality assurance, the ERG checked the economic model for transparency and validity. These are discussed below.

Model transparency

The CS clearly described the model structure, parameter values and their sources, data identification methods, and assumptions used in the model. The model was technically transparent and the visual basic code used within the model was accessible. In general, the technical report and the model described the analyses clearly and provided adequate information to assess the model. The CS clearly presented the results of the NMA but did not present the WinBUGS code used to derive those results.

Model validation

To validate the economic model, the company stated that the model was reviewed by their internal health economists. They undertook an assessment of the face-validity of the model, and conducted a third-party validation of the model calculations and the data sources. Extreme value and log tests were also conducted by the company to examine if the model behaved as expected and that the results obtained were logical.

The ERG checked the model for internal as well as external validity. The step-by-step approach used for this purpose is discussed below.

- *Face validity*

The company conducted an extensive review of the existing NICE appraisals in advanced/metastatic breast cancer in May 2016 to inform their modelling approaches. They also conducted a structured review of utility studies in June 2016 to inform the quality of life parameters. The opinions of seven UK clinical experts were used to validate the extrapolation of PFS and OS within the company's analyses. The CS compared the long-term predicted model outcomes for PFS and OS with the corresponding clinical expert opinion as shown in Table 38. The modelled outcomes appeared comparable with the expert opinion.

Table 38 Comparison of predicted model outcomes with those of clinical opinions

Outcomes	Time-frame			
	1 year	2 years	5 years	10 years
PFS				
KOL opinion (anastrozole)	50-60%	30-40%	5-10%	1-5%
Modelled PFS (anastrozole)	52.2%	25.7%	4.6%	0.6%
Modelled PFS (letrozole)	59.3%	30.8%	5.8%	0.7%
OS				
KOL opinion (anastrozole)	75-85%	55-70%	20-30%	5-10%
Modelled OS (anastrozole)	86.0%	69.6%	30.7%	5.5%
Modelled OS (letrozole)	91.5%	74.5%	23.2%	0.7%

Source: CS Table 108 & 109. KOL: Key Opinion Leader; PFS: Progression-free survival; OS: overall survival.

The company did not provide any further details if the third-party constituted experts from clinical and/or health economic backgrounds. The CS also did not explicitly document the steps taken to validate the model calculations and the data sources. Therefore, the ERG is unable to comment on these. Further, no information was presented to ascertain if the model assumptions were validated by clinicians or experts.

- *Internal validity*

Internal validity checks consist of two main steps: checking the individual equations within the model; and verifying their accurate implementation in code.[54]

Although the company cited a number of internal validity checks, they did not present any formal checklist for quality assurance of the model used by their health economists. Below is a summary of the checks conducted by the ERG to assess the internal validity of the model:

i. Individual equations were checked for their mathematical correctness. However, due to time constraints, the ERG focused primarily on the equations defining survival functions, patient transition in different health states, costs, QALYs, and overall results. Within the costs calculations, the ERG identified errors in estimating the discounted costs. The company rectified these errors and submitted new sets of base case results in the clarification response (Clarification response Appendix Table 30). The ERG were able to reproduce the new sets of base case results of the CS.

ii. The visual basic programming code within the model was checked and appeared to be correct, except for a few minor errors in the model. These errors affected cosmetic features of the model and did not have any impact on the overall model calculations or results.

iii. The ERG checked for consistency of the parameters reported in the technical document and those utilised within the model. There were minor reporting errors in CS Table 77 which the company rectified in their clarification response (Clarification response A13.1(c) Table 26).

iv. The ERG conducted a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed. The list of the tests conducted is presented in Appendix 1.

Based on the checks conducted as stated above, the company's model had a few calculation errors, although the overall technicalities of the model appeared to be correct. Rectifying the calculation errors did not have significant impact on the overall base case model results.

- *External validity*

The company presented comparisons of the modelled outcomes for PFS and OS with the results of a systematic review and previous HTA assessments, shown in CS Table 79 and Table 80, respectively. These are reproduced below in Table 39. The results obtained from the model appeared to be comparable with the existing evidence.

Table 39 Comparison of the modelled outcomes with other sources

Treatment	Median PFS (months)		
	Model outcomes	**Systematic literature review**	**Previous HTA assessments**
Fulvestrant	16.56	Range: 16.6 – 25.9	NA
Anastrozole	11.96	Range: 12.9 – 14.8	NA
Letrozole	14.72	9.60	14.5
Tamoxifen	9.20	Range: 5.9 – 10.4	NA

Treatment	Median OS (months)		
	Model outcomes	Systematic literature review	Previous HTA assessments
Fulvestrant	47.84	62.5	NA
Anastrozole	39.56	Range: 44.9 – 46.5	NA
Letrozole	38.64	34	33.3
Tamoxifen	36.80	Range: 30.3 – 43.6	NA

Source: CS Table 79 & 80; HTA: Health Technology Assessment; NA: Not available; PFS: Progression-free survival; OS: Overall Survival

In addition to the above analyses, the ERG compared the predicted OS data for fulvestrant and anastrozole with the observed data from the FIRST trial (using the matched population alone) as shown in Figure 21. The graph shows that the predicted OS data provided a reasonable comparison of the observed data in the FIRST trial.

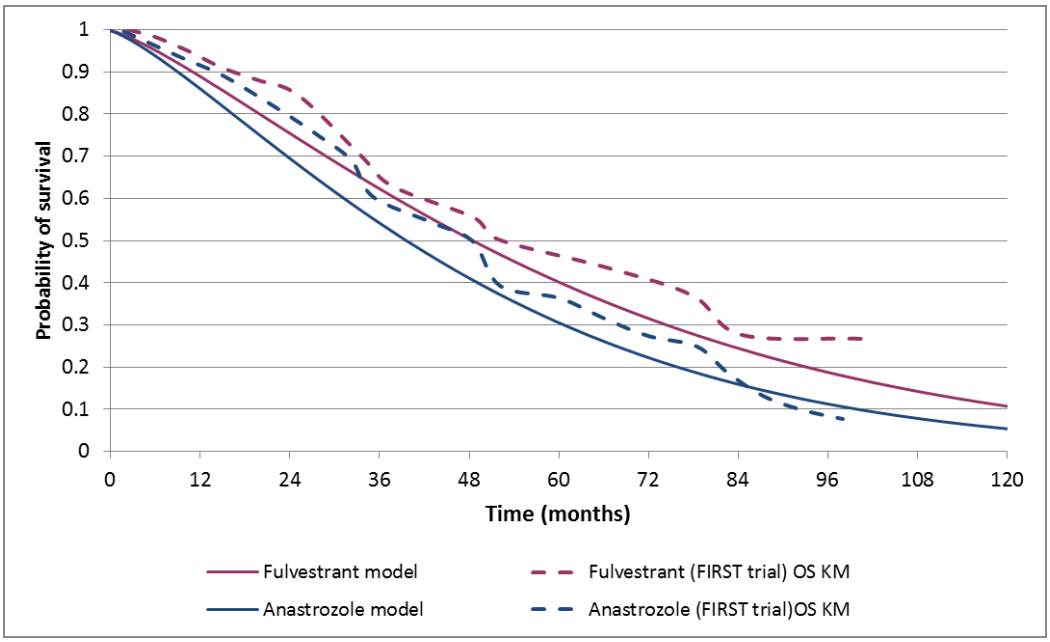


Figure 21 Comparison of predicted OS data against the observed data from the FIRST trial (using the matched patients only)

- *Cross validity and predictive validity*

Cross validation checks, which involve assessing different mathematical models addressing the same decision problem, were not relevant from the perspective of this technology appraisal as there are no existing models with the same decision problem for the same drug. Fulvestrant is a *de novo* intervention for post-menopausal people with locally advanced or metastatic HR+ breast cancer who had not received endocrine therapy. The ERG did not perform any checks on predictive validity of the economic model.

4.3.9 Cost effectiveness results

The company presented base case results in terms of total costs, life years gained, QALYs and incremental cost per QALY. Results were presented as pair-wise comparisons of fulvestrant versus anastrozole, letrozole and tamoxifen (CS Table 74 – 76) along with an incremental analysis of fulvestrant versus AIs (CS Table 77). As mentioned in section 4.3.8, the company rectified a few calculation errors for the costs in the economic model and submitted new sets of results for the base case analyses with the clarification response. The results presented in the following sections of this appraisal are based on the corrected economic model.

Results of the incremental analysis of fulvestrant versus comparators are summarised below in Table 40. The results are presented in order of increasing costs. Letrozole was associated with lowest overall costs. Tamoxifen was dominated as it was associated with comparatively higher costs and lower QALYs when compared against anastrozole in the incremental analysis; thereby resulting in an incremental ICER of £34,099 for fulvestrant versus anastrozole.

Table 40 Results of incremental analysis (based on corrected economic model)

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
Letrozole	£26,221	2.46	--	--	--
Anastrozole	£30,572	2.68	£4,351	0.22	£19,702
Tamoxifen	£32,328	2.47	£1,756	-0.21	Dominated
Fulvestrant	£49,431	3.23	£18,859	0.55	£34,099

This table draws on information presented in the Table 30 in the appendix to the company's written response to clarification questions.

No sub-group analysis was conducted as part of the submission. This was considered appropriate and aligned with the final NICE scope.

4.3.10 Assessment of uncertainty

In accordance with the NICE final scope,[1] the company assessed methodological, structural and parameter uncertainties associated with the base-case analyses by conducting a range of deterministic sensitivity-, probabilistic sensitivity- and scenario- analyses, details of which are discussed below.

Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) was conducted on a number of key parameter groups. The parameters and their ranges are shown in Table 41. In general, the choice of parameters included and the ranges for variation appeared to be reasonable, although the ERG viewed that it would have been more appropriate to use a range of 95% confidence intervals for the health state utilities.

Table 41 Parameters and their ranges used for deterministic sensitivity analyses

Parameters	Range
Parametric survival distribution parameters	95% confidence interval
Disease management costs	20% of the mean values
Terminal care/ end of life costs	20% of the mean values
Treatment acquisition and administration (per 4 weeks)	20% of the mean values
Health state utilities	10% of the mean values
Discount rates	0% to 6%

The company produced tornado plots for the 10 most sensitive parameters for each of the comparisons. The ERG observed that, unlike those presented in the CS, the tornado plots programmed in the model excluded the parameters for parametric survival distributions. We were, therefore, unable to reproduce the same sets of top 10 sensitive parameters by running the 'Update DSA' button within the economic model as reported in the CS Figure 51-53. Owing to this limitation, we reproduced the results of the DSA for fulvestrant versus comparators in Table 42, Table 43 and Table 44 based on the corrected model for the parameters that were reported in CS Tables 94-96.

Table 42 Results of DSA - fulvestrant versus anastrozole (based on corrected model)

Parameter	Base case (ICER)	Lower value (ICER)	Upper value (ICER)
(OS) fulvestrant: Weibull scale parameter	£34,099	£338,729	£23,236
Health state utilities: PF	£34,099	£42,187	£28,613
Discount rate - Outcomes	£34,099	£27,193	£39,387
Treatment acquisition costs per 4 weeks: fulvestrant	£34,099	£28,371	£39,827
Discount rate - Costs	£34,099	£38,592	£31,660
(OS) anastrozole: Weibull scale parameter	£34,099	£36,757	£31,584
(PFS) anastrozole: gamma scale parameter	£34,099	£31,560	£36,791
(OS) fulvestrant: Weibull shape parameter	£34,099	£31,031	£35,450

Abbreviations: ICER, incremental cost-effectiveness ratio; PF, progression-free; PFS, progression-free survival; OS, overall survival.

Table 43 Results of DSA - fulvestrant versus letrozole (based on corrected model)

Parameter	Base case (ICER)	Lower value (ICER)	Upper value (ICER)
(OS) letrozole: Weibull scale parameter	£29,991	£23,917	£94,487
(OS) fulvestrant: Weibull scale parameter	£29,991	£63,332	£22,677
(PFS) letrozole: gamma scale parameter	£29,991	£24,832	£37,963
Discount rate - Outcomes	£29,991	£23,213	£35,521
Treatment acquisition costs per 4 weeks: fulvestrant	£29,991	£25,897	£34,084
Discount rate - Costs	£29,991	£34,864	£27,352
Health state utilities: PD	£29,991	£31,608	£28,531
Health state utilities: PF	£29,991	£31,531	£28,594

Abbreviations: ICER, incremental cost-effectiveness ratio; PF, progression-free; PFS, progression-free survival; OS, overall survival.

Table 44 Results of DSA - fulvestrant versus tamoxifen (based on corrected model)

Parameter	Base case (ICER)	Lower value (ICER)	Upper value (ICER)
(OS) tamoxifen: Weibull scale parameter	£22,498	£19,408	£40,262
Health state utilities: PF	£22,498	£25,502	£20,495
Treatment acquisition costs per 4 weeks: fulvestrant	£22,498	£18,330	£26,665
Discount rate - Outcomes	£22,498	£17,981	£25,976
Discount rate - Costs	£22,498	£26,239	£20,495
(PFS) tamoxifen: gamma scale parameter	£22,498	£19,975	£25,710
(PFS) tamoxifen: gamma shape parameter	£22,498	£21,151	£24,158
(OS) fulvestrant: Weibull scale parameter	£22,498	£41,586	£18,470

Abbreviations: ICER, incremental cost-effectiveness ratio; PF, progression-free; PFS, progression-free survival; OS, overall survival.

None of the sensitivity analyses reduced the ICER for fulvestrant compared to the AIs (i.e. analstrozole and letrozole) to below £20,000 per QALY. When fulvestrant was compared to the AIs, the model results were most sensitive to the OS parameters. For example, the ICERs ranged from £23,236 per QALY for the lower value of the OS scale parameter to £338,729 per QALY for the upper value of the parameter for fulvestrant versus anastrozole. The ICERs were also sensitive to the PFS parameters and moderately sensitive to the health state utilities, discount rates and treatment acquisition costs for fulvestrant.

The results of the DSA show that the OS parameters had the most influence on the base case model results with a wide range in the ICERs obtained from using the upper and lower values for this parameter. This indicated a considerable amount of uncertainty in the model results.

Scenario analysis

The company analysed structural and methodology uncertainties by performing a range of scenario analyses. These analyses and their justifications, reproduced from CS Table 97, are presented in Table 45.

Table 45 List of scenario analyses conducted by the company

Variables	Base case	Scenario	Rationale
OS extrapolations	'All shapes' NMA model OS - Weibull	'All shapes' NMA model plausible extrapolations: OS - generalised gamma	To assess the impact of a range of survival estimates
PFS extrapolations	'All shapes' NMA model PFS - generalised gamma	'All shapes' NMA model: PFS - log-logistic PFS - lognormal PFS - Weibull PFS - Gompertz	To assess the impact of a range of survival estimates
OS and PFS extrapolations	'All shapes' NMA model: OS - Weibull PFS - generalised gamma	'No shape arm' NMA model: OS - Weibull PFS - Weibull PFS - Gompertz	To assess the impact of not adjusted for differences in shapes between treatment arms
OS and PFS extrapolations	'All shapes' NMA model: OS - Weibull PFS - generalised gamma	Assume equivalent efficacy between AIs 'All shapes' NMA model (anastrozole curves used for letrozole): OS - Weibull PFS - generalised gamma	To assess the impact of commonly held clinical opinion that AIs have equal efficacy
Utility values	FALCON MMRM (1)	FALCON summary statistics; FALCON MMRM (1) and Lloyd (2006); Lloyd (2006)	To assess the impact of using alternative data sources for health state utility values
Time horizon	30	5; 10; 15; 20; 25; 35	To assess the impact of varying the time horizon.
Discount rate	3.5% for both costs and outcomes	1.5% for both costs and outcomes	NICE guidelines

Variables	Base case	Scenario	Rationale
AEs	AE costs and disutilities	No AE costs and disutilities	To assess the impact of inclusion of AE costs and disutilities on cost-effectiveness results
Treatment administration costs	Inclusion of administration costs for oral treatments	Exclusion of administration costs for all comparator therapies	To assess the impact that oral treatments are self-administered by the patient
Subsequent treatment costs and end of life care	Exclusion of fulvestrant as a subsequent treatment option for patients on first-line fulvestrant	Same subsequent treatment costs for all patients Exclusion of subsequent treatment costs altogether	To assess the impact of subsequent treatment overall and whether patients initially treated with fulvestrant will receive it again as a subsequent therapy

Source: CS Table 97

Results of the scenario analyses are presented in CS Table 98 – 99, 102 – 107. The ERG re-ran all the scenarios with the corrected model and have updated the results below in Table 46.

Table 46 Summary of the scenario analyses (based on the corrected economic model)

Parameters		Base case ICER	Scenario ICER
Scenario 1: OS generalised gamma; PFS: generalised gamma			
Fulvestrant vs	Letrozole	£29,991	£28,665
	Anastrozole	£34,099	£33,387
	Tamoxifen	£22,498	£22,183
Scenario 2: OS Weibull; PFS: various distributions			
OS Weibull; PFS Weibull			
Fulvestrant vs	Letrozole	£29,991	£28,488
	Anastrozole	£34,099	£33,079
	Tamoxifen	£22,498	£23,050
OS Weibull; PFS Gompertz			
Fulvestrant vs	Letrozole	£29,991	£30,267
	Anastrozole	£34,099	£33,551
	Tamoxifen	£22,498	£24,442
OS Weibull; PFS log-logistic			
Fulvestrant vs	Letrozole	£29,991	£31,458
	Anastrozole	£34,099	£35,252
	Tamoxifen	£22,498	£22,625
OS Weibull; PFS lognormal			
Fulvestrant vs	Letrozole	£29,991	£32,048
	Anastrozole	£34,099	£33,986
	Tamoxifen	£22,498	£22,233

Scenario 3: 'No shape arm' with OS			
		Base case (all shape model)	Base case (no shape model)
Fulvestrant vs	Letrozole	£29,991	--
	Anastrozole	£34,099	--
	Tamoxifen	£22,498	--
OS: Weibull; PFS: Weibull			
Fulvestrant vs	Letrozole	£29,991	£37,358
	Anastrozole	£34,099	£33,710
	Tamoxifen	£22,498	£25,036
OS: Weibull; PFS: Gompertz			
Fulvestrant vs	Letrozole	£29,991	£36,293
	Anastrozole	£34,099	£33,687
	Tamoxifen	£22,498	£25,210
OS: Weibull; PFS: Log-logistic			
Fulvestrant vs	Letrozole	£29,991	£46,189
	Anastrozole	£34,099	£39,664
	Tamoxifen	£22,498	£29,001
OS: Weibull; PFS: Lognormal			
Fulvestrant vs	Letrozole	£29,991	£45,356
	Anastrozole	£34,099	£38,753
	Tamoxifen	£22,498	£29,308
Scenario 4: Assuming equal efficacy between AIs using the anastrozole parametric survival models			
OS: Weibull; PFS: generalised gamma			
Fulvestrant vs	Letrozole	£29,991	£34,140
	Anastrozole	£34,099	£34,099
	Tamoxifen	£22,498	£22,498
OS: Weibull; PFS: Weibull			
Fulvestrant vs	Letrozole	£29,991	£33,123
	Anastrozole	£34,099	£33,079
	Tamoxifen	£22,498	£23,050
OS: Weibull; PFS: Gompertz			
Fulvestrant vs	Letrozole	£29,991	£33,597
	Anastrozole	£34,099	£33,551
	Tamoxifen	£22,498	£24,442
OS: Weibull; PFS: Log-logistic			
Fulvestrant vs	Letrozole	£29,991	£35,284
	Anastrozole	£34,099	£35,252
	Tamoxifen	£22,498	£22,625
OS: Weibull; PFS: Log-normal			
Fulvestrant vs	Letrozole	£29,991	£34,022
	Anastrozole	£34,099	£33,986
	Tamoxifen	£22,498	£22,233

Scenario 5: Utility values			
FALCON summary statistics			
Fulvestrant vs	Letrozole	£29,991	£30,042
	Anastrozole	£34,099	£34,151
	Tamoxifen	£22,498	£22,530
FALCON study MMRM model (1) and Lloyd (2006)			
Fulvestrant vs	Letrozole	£29,991	£35,211
	Anastrozole	£34,099	£34,516
	Tamoxifen	£22,498	£21,390
Lloyd (2006)			
Fulvestrant vs	Letrozole	£29,991	£34,921
	Anastrozole	£34,099	£34,281
	Tamoxifen	£22,498	£21,256
Scenario 6: Different time horizons			
5 years			
Fulvestrant vs	Letrozole	£29,991	£80,244
	Anastrozole	£34,099	£61,423
	Tamoxifen	£22,498	£35,472
10 years			
Fulvestrant vs	Letrozole	£29,991	£33,750
	Anastrozole	£34,099	£38,457
	Tamoxifen	£22,498	£24,245
15 years			
Fulvestrant vs	Letrozole	£29,991	£30,575
	Anastrozole	£34,099	£34,986
	Tamoxifen	£22,498	£22,815
20 years			
Fulvestrant vs	Letrozole	£29,991	£30,132
	Anastrozole	£34,099	£34,344
	Tamoxifen	£22,498	£22,580
25 years			
Fulvestrant vs	Letrozole	£29,991	£30,032
	Anastrozole	£34,099	£34,171
	Tamoxifen	£22,498	£22,521
35 years			
Fulvestrant vs	Letrozole	£29,991	£29,973
	Anastrozole	£34,099	£34,067
	Tamoxifen	£22,498	£22,487
Scenario 7: Discount rates of 1.5% for both costs and outcomes			
Fulvestrant vs	Letrozole	£29,991	£28,223
	Anastrozole	£34,099	£32,179
	Tamoxifen	£22,498	£21,609
Scenario 8: Exclusion of AE costs and dis-utilities			
Fulvestrant vs	Letrozole	£29,991	£29,861
	Anastrozole	£34,099	£33,990
	Tamoxifen	£22,498	£22,756

Scenario 9: Zero administration costs for comparator (oral) treatments			
Fulvestrant vs	Letrozole	£29,991	£31,039
	Anastrozole	£34,099	£35,424
	Tamoxifen	£22,498	£23,235
Scenario 10: Different assumptions regarding subsequent treatment costs			
Same subsequent treatment costs for all treatments			
Fulvestrant vs	Letrozole	£29,991	£30,377
	Anastrozole	£34,099	£34,639
	Tamoxifen	£22,498	£22,890
Exclusion of subsequent treatment costs			
Fulvestrant vs	Letrozole	£29,991	£30,799
	Anastrozole	£34,099	£35,232
	Tamoxifen	£22,498	£24,217

In scenario 1, the company changed the OS distribution for the generalised gamma distribution alone. The ERG felt that, for completeness, the company should have also presented results for all the other distributions (Gompertz, log-logistic, lognormal). This is explored in the ERG additional analyses in section 4.4.

In scenario 2, assigning various distributions to PFS resulted in the ICER of fulvestrant vs anastrozole to vary between £33,079 and £35,252 per QALY compared to the base case ICER of £34,099 per QALY. The ICER of fulvestrant vs letrozole ranged between £28,488 and £32,048 per QALY, and that of fulvestrant vs tamoxifen was between £22,233 and £24,442 per QALY respectively.

In scenario 3, using the 'no shape arm' model with the generalised-gamma distribution for PFS extrapolation provided implausible results as in this scenario; all the patients started the model in the PD health state and PFS was equal to zero. This distribution was excluded in the 'no shape arm' model because of the *"complexity in the interpretation of setting two of the three-parameter generalised gamma model equal".* (CS Section 4.10.1, Page 96; and clarification response to question B9). Assigning other distributions to the PFS (Weibull, Gompertz, log-logistic and lognormal) resulted in the ICER of fulvestrant vs anastrozole varying between £33,687 and £39,664 per QALY.

When anastrozole and letrozole were assumed to have equal efficacy (scenario 4), the ICER of fulvestrant vs letrozole was similar to fulvestrant vs. anastrozole and ranged between £33,123 and £35,284 per QALY for different distributions for PFS.

In scenario 5, the CS explored the impact of using three sets of utility values on the base case results. Of these sets, the values obtained from the combination of the FALCON study MMRM model (1) and Lloyd 2006 had the most influence on the base case results, particularly on the ICER of fulvestrant vs letrozole which increased by £5,220 from the base case value. The ICER for fulvestrant vs anastrozole increased slightly by £417, whilst the ICER for fulvestrant vs tamoxifen decreased by £1,108 compared to the base case results.

Using a lower time-horizon increased the ICERs relative to the base case values and vice-versa (scenario 6); using lower discount rates (scenario 7) and excluding AE costs and dis-utilities (scenario 8) lowered the ICERs of fulvestrant vs the comparators compared to the base case results.

Including zero administration costs (scenario 9), the same subsequent treatment costs for all comparators and excluding subsequent costs (scenario 10) increased the ICERs of fulvestrant vs comparators marginally, compared to the base case results.

In summary, the results from the above analyses indicate that alternative scenarios provided broadly similar results to the base case.

Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) on their base case analysis to assess parametric uncertainty (CS section 5.8.1). The PSA was well-conducted and accounted for uncertainty around most of the input parameters. The parameters, together with the chosen distribution alongside their rationale, are reproduced from CS Table 87 in Table 47 below.

Table 47 List of parameters and associated distributions included in the PSA

Parameter	Distribution	Comment
Survival distributions	Cholesky decomposition	Decomposition of a Hermitian, positive-definite matrix into the product of a lower triangular matrix and its conjugate transpose
Survival curve (shape, scale, and covariate parameters)	Multinomial normal	Incorporates the covariance between parameters estimated in a survival regression analysis
Costs	Gamma	Likely skewed nature of health care costs, and their constraint to positive values
AE rates (incidence)	Beta	Bounded between 0 and 1
Distribution of subsequent treatments	Dirichlet distribution	Normalised sum of independent gamma variables
Duration of subsequent treatment	Gamma	Bounded between 0 and infinity, and skewed
Utilities	Beta	Constrained to values between minus infinity and 1. Modelled as a disutility
AE disutilities	Lognormal	Bounded between 0 and infinity, and skewed

Source: CS Table 87; AE: Adverse Event

The CS presented the results of the PSA for 10,000 simulations; the ERG ran these simulations in the corrected model which took approximately 40 minutes to run. We considered the distributions assigned to the parameters along with the justifications provided to be appropriate. Patient age, discount rates, model time horizon and acquisition costs of fulvestrant and the comparator drugs were not varied in these analyses.

The results of the PSA were tabulated in CS Table 88 – 91 and diagrammatically presented as scatter-plots (CS Figure 46 - 48) and cost-effectiveness acceptability curves (CEACs) (CS Figure 49 - 50). The point estimates from the average PSA results from the corrected model were close to the results obtained from the deterministic analysis as summarized in Table 48.

Table 48 Comparison of the point estimates obtained from the deterministic and PSA analyses (based on corrected model)

Intervention vs comparator	Deterministic ICER (£/QALY)	Probabilistic ICER (£/QALY)
Fulvestrant vs Anastrozole	£34,099	£33,762
Fulvestrant vs Letrozole	£29,991	£31,264
Fulvestrant vs Tamoxifen	£22,498	£22,815

The probability of the treatments being cost-effective at different willingness-to-pay thresholds (WTP) are tabulated in Table 49 and the CEACs are reproduced from the company's model in Figure 22. At a WTP threshold of £30,000 per QALY, the probability of fulvestrant being cost-effective is 26.5%; whereas the probabilities are 37.4% for anastrozole; and 33.3% and 2.9% for letrozole and tamoxifen, respectively.

Table 49 Probability of the treatments being cost-effective at different WTP thresholds (based on corrected model)

WTP threshold (per QALY)	Probability of being cost-effective (%)			
	Fulvestrant	Anastrozole	Letrozole	Tamoxifen
£20,000	1.1%	46.4%	51.5%	1.0%
£30,000	**26.5%**	**37.4%**	**33.3%**	**2.9%**
£50,000	67.8%	14.5%	14.0%	3.8%

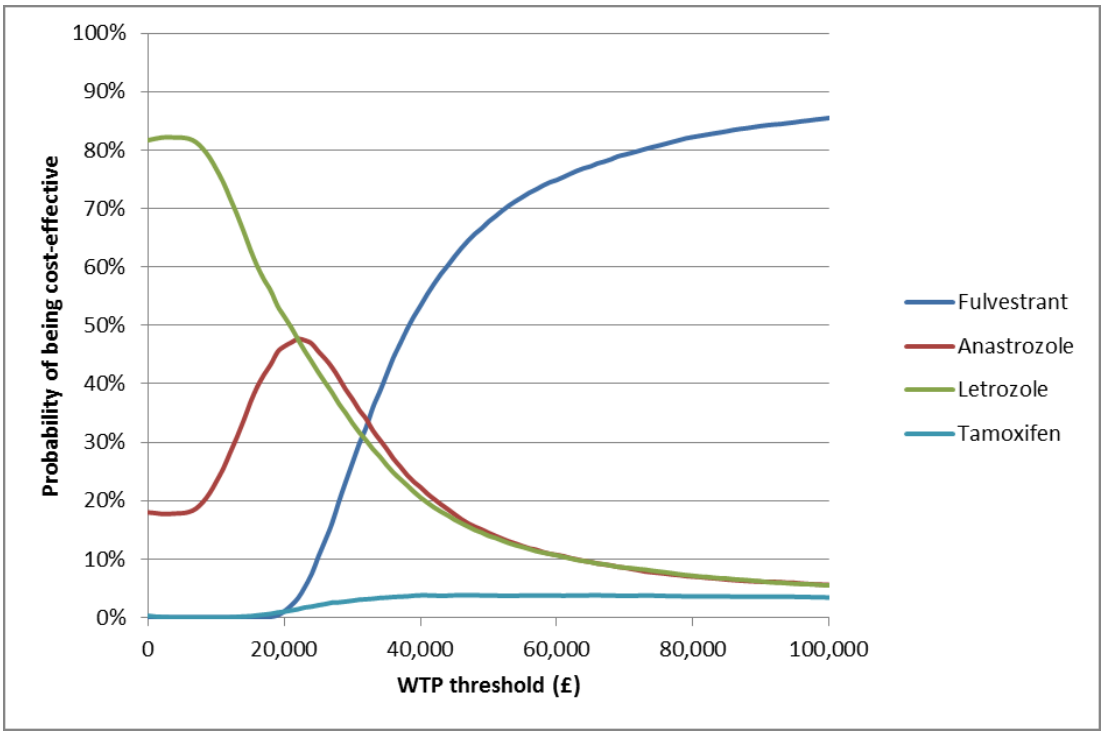


Figure 22 Cost-effectiveness acceptability curves for all the treatments (based on corrected model)

4.4 Additional work undertaken by the ERG

There were a few areas where the ERG considered the CS base case to be limited. In this section, we detail the ERG's further exploration of these issues and uncertainties which have been highlighted in the review and critique of the CS base case analyses, in the earlier sections of this report. A summary of the ERG's exploratory analyses are presented in Table 50, along with their justifications, and how these analyses changed the parameters from the CS base case. We then combine some of these analyses to form the ERG base case, which we regard as the most representative analysis for the cost-effectiveness of fulvestrant compared to anastrozole, letrozole and tamoxifen for treating advanced or metastatic breast cancer.

Table 50 Summary of the ERG's exploratory analyses

ERG scenario	Analysis description in the CS base case	ERG's analysis	Justification
1.	Clinical efficacy: OS extrapolation using Weibull distribution	OS extrapolation using Gompertz, log-logistic and log-normal distribution	The CS explored all the distributions for PFS but not for OS extrapolation. Hence, the ERG extrapolated OS with the remaining distributions for completeness.
2.	Deterministic sensitivity analyses for OS shape parameter	More detailed analysis of variation of ICER with changes in OS scale parameter	There remains uncertainty around the OS parameters, given the immature FALCON OS data
3.	Resource use associated with PFS and PD health states per cycle within disease management costs were derived from NICE clinical guidance -81 and PSSRU	Using resource use of PFS and PD from the study by Karnon et al..[52]	The resources described in the NICE CG refer to patients receiving chemotherapy, not patients receiving endocrine therapy.
4.	The proportions of patients receiving subsequent 2nd treatment are: Endocrine therapy: 54.35%; Chemotherapy: 37.57% ; Targeted treatment: 8.08%	The proportions of patients receiving 2nd line treatment are: Endocrine therapy: 67%; Chemotherapy: 25.92%; Targeted therapy: 8.08%	Based on ERG clinical expert opinion and ERG assumption.
5.	Inclusion of PO25 trial from the NMA to obtain PFS and OS estimates	Exclusion of PO25 trial from the NMA to obtain PFS and OS estimates	PO25 trial population differs from the other trial in the NMA and letrozole is widely accepted to be of equal efficacy as that of anastrozole.
6	Administration of fulvestrant in the outpatient setting for 67% of patients and in the primary care setting for 33%	Fulvestrant administered to all patients in the outpatient setting	Based on clinical expert opinion
7	ERG base case	Combining ERG scenarios 3, 4, 5 and 6	As stated above

Further discussion and results of all the above exploratory analyses are presented in the following sub-sections.

4.4.1 ERG Scenario 1: Extrapolation of OS curve: assigning different distributions for the 'all shapes model' (based on the corrected model)

The results obtained from assigning different distributions to extrapolate the OS curve are presented in Table 51.

Table 51 ERG scenario 1: OS extrapolation using different distributions for the 'all shapes model'

Parameters		Base case ICER (OS: Weibull)	Scenario ICER
Scenario 1: OS Gompertz; PFS: generalised gamma			
Fulvestrant vs	Letrozole	£29,991	fulvestrant dominated
	Anastrozole	£34,099	£59,953
	Tamoxifen	£22,498	£75,229
Scenario 2: OS log-logistic; PFS: generalised gamma			
Fulvestrant vs	Letrozole	£29,991	£29,628
	Anastrozole	£34,099	£35,128
	Tamoxifen	£22,498	£22,677
Scenario 2: OS log-normal; PFS: generalised gamma			
Fulvestrant vs	Letrozole	£29,991	£33,834
	Anastrozole	£34,099	£34,896
	Tamoxifen	£22,498	£22,976

Using the Gompertz distribution to extrapolate the OS curve changes the direction of the base case results. Fulvestrant is dominated when compared with letrozole, as letrozole is less expensive and more effective with higher QALYs, thereby resulting in a negative ICER in the south-west quadrant of the cost-effectiveness plane. Further, the ICERs increase significantly when fulvestrant is compared against anastrozole and tamoxifen. However, the ERG notes that the Gompertz distribution provides a poor fit to the observed data so results from this distribution should be treated with caution. Extrapolating the OS curve by assigning log-logistic and log-normal distributions has minimal impact on the ICERs for fulvestrant vs comparators, compared to the base case ICERs.

4.4.2 ERG Scenario 2: Changes to the OS scale parameter for fulvestrant

The company model results were most sensitive to changes in treatment effectiveness by varying the OS scale parameter (see section 4.3.10). As shown in Table 42, varying the OS scale parameter between the lower and upper 95% confidence intervals resulted in the ICER for fulvestrant vs. anastrozole varying between £23,236 and £338,729 per QALY (Incremental scale parameter for fulvestrant varied between [redacted] and [redacted]).

The ERG considers that there remains uncertainty around the OS scale parameters due to the immature OS data from the FALCON trial. The long-term OS data from this trial was not available to be included in the NMA. The ERG considers that the survival benefit for fulvestrant compared to anastrozole is likely to be lower from the FALCON trial than observed in the FIRST trial. Therefore, when data from the FALCON trial becomes available, the treatment benefit for fulvestrant may be lower than estimated in the NMA. The ERG varies the OS scale parameter in scenario 2 between its mean value and the upper 95% confidence interval to illustrate the effect of changes to the treatment benefit. The results are shown for four scale parameters (incremental values from [redacted]) in Table 52.

Table 52 ERG scenario 2: Effect of changes of the fulvestrant OS scale parameter

Parameters		Base case ICER (OS: Weibull)	Scenario ICER
Scenario 2: Fulvestrant Incremental scale parameter [redacted]			
Fulvestrant vs	Letrozole	£29,991	£33,475
	Anastrozole	£34,099	£40,761
	Tamoxifen	£22,498	£24,432
Scenario 2: Fulvestrant Incremental scale parameter [redacted]			
Fulvestrant vs	Letrozole	£29,991	£38,326
	Anastrozole	£34,099	£52,405
	Tamoxifen	£22,498	£27,146
Scenario 2: Fulvestrant Incremental scale parameter [redacted]			
Fulvestrant vs	Letrozole	£29,991	£45,842
	Anastrozole	£34,099	£79,337
	Tamoxifen	£22,498	£31,404
Scenario 2: Fulvestrant Incremental scale parameter [redacted]			
Fulvestrant vs	Letrozole	£29,991	£59,000
	Anastrozole	£34,099	£208,231
	Tamoxifen	£22,498	£39,027

These illustrative results indicate that even with a relatively small change to the OS scale parameter to [redacted], produces an ICER of £40,761 per QALY for fulvestrant vs. anastrozole.

4.4.3 ERG Scenario 3: Change in resource use for disease management costs (based on the corrected model)

To address the ERG's concerns in relation to the estimation of disease management costs for PFS and PD states (as outlined in section 4.3.7), the ERG calculated the base case results by estimating resource use for these health states from the study by Karnon et al.[52] This study conducted a trial-based cost-effectiveness analysis of letrozole (first-line) with the option of second-line tamoxifen vs tamoxifen (first-line) with the option of second-line letrozole in postmenopausal advanced breast cancer patients. The proportion of patients receiving interventions in each health state was estimated based on a three month period. For the purpose of this appraisal, we converted these proportions for a four week period as shown in Table 53 and updated the unit costs for these resources.

The revised estimated cost for both PFS and PD health states is £90.91 per cycle. The incremental results from this scenario analysis are presented in Table 54.

Table 53 Resource use and unit costs for PFS and PD health states based on Karnon et al.

	Proportion of patients per 4 weeks	Unit cost (£)	Total cost (£)	Source
Outpatient visits				
Oncologist	0.29	162.84	47.22	NHS reference costs 2015-16 (Non-admitted face to face attendance Follow-up Medical oncology code 370)[49]
GP	0.18	46.02	8.28	PSSRU 2015/16[50]
Radiographer	0.08	46	3.68	PSSRU 2015/16[50]
Lab tests				
Biochemical	0.28	1.18	0.33	NHS reference costs 2015-16 DAPS04[49]
Blood tests	0.27	3.1	0.84	NHS reference costs 2015-16 DAPS05[49]
Bone scintography	0.18	75.89	13.66	Cost updated from Karnon et al.[52] using PSSRU HCHS indices[50]
Ultrasound	0.06	53.45	3.21	NHS reference costs 2015-16 (Imaging codes Ultrasound scan RD40Z-FD43Z)[49]
Chest x-ray	0.14	15.10	2.11	Cost updated from Karnon et al.[52] using PSSRU HCHS indices[50]

Bone x-ray	0.08	24.58	1.97	Cost updated from Karnon et al.[52] using PSSRU HCHS indices[50]
Hospitalisation				
General medicine	0.01	246.58	2.47	Cost updated from Karnon et al.[52] using PSSRU HCHS indices[50]
Oncology	0.01	713.81	7.14	NHS reference costs 2015-16 (Non elective short stay codes Malignancy of bone or connective tissue HD40D – HD40H) [49]

Table 54 Incremental results of the ERG's scenario 3 for revised health state costs

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
Letrozole	£11,098	2.46	--	--	--
Anastrozole	£11,388	2.68	£290	0.22	£1,314
Tamoxifen	£11,895	2.47	£507	-0.21	Dominated*
Fulvestrant	£29,133	3.23	£17,745	0.55	£32,084

For the incremental analyses, the treatment strategies were placed in order of increasing total costs. Letrozole was used as the baseline comparator as it is associated with the lowest total costs. The decrease in total costs for all the treatments compared to that of the base case analyses occurred due to the lower disease management costs associated with the PFS and PD states. The ICER of fulvestrant vs anastrozole was £32,084 per QALY compared to the base case ICER of £34,099 per QALY. Tamoxifen was dominated when compared with anastrozole as it was associated with higher incremental costs and lower incremental QALYs.

4.4.4 ERG Scenario 4: Change in the proportion of patients receiving subsequent treatments for second-line

In this scenario analysis the ERG changed the proportion of patients receiving second line treatments to address the views of our clinical experts, as previously outlined in section 4.3.7. Our clinical experts suggested that 67-80% of the patients would receive endocrine therapy as second-line treatment. One of our experts considered that 20% of the patients would have targeted therapy in combination with endocrine therapy or chemotherapy, whilst the other considered that fewer would have chemotherapy than estimated by the CS. Owing to limited information on the proportion of patients receiving these combination therapies, the ERG pragmatically assumed the proportions of patients for the subsequent therapies as shown in Table 55. The results of this analysis are presented in Table 56.

Table 55 ERG's assumptions related to the proportion of patients receiving second-line treatments

Proportion of patients (%)	Endocrine therapy	Chemotherapy	Targeted therapy
Baseline	54.35%	37.57%	8.08%
Scenario	67.00%	24.92%	8.08%

Table 56 Incremental results from ERG scenario 4 for changing proportion of patients receiving second-line endocrine therapy

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
Letrozole	£26,188	2.46	--	--	--
Anastrozole	£30,539	2.68	£4,351	0.22	£19,702
Tamoxifen	£32,286	2.47	£1,737	-0.21	Dominated*
Fulvestrant	£49,369	3.23	£18,830	0.55	£34,046

*Tamoxifen is more expensive and less effective compared to anastrozole.

The change in the proportion of patients receiving second-line treatments results in an ICER for fulvestrant vs anastrozole of £34,046 per QALY, a decrement of £53 compared to the company's base case ICER of £34,099 per QALY. This indicates that varying the proportion of patients receiving subsequent therapies as second-line does not influence the base case results.

4.4.5 ERG Scenario 5: Excluding PO25 trial from the NMA network to obtain PFS and OS estimates for 'all shapes model'

This scenario uses the fixed-effects NMA results without the PO25 trial for both PFS and OS for the 'all shapes model' and assumes that anastrozole and letrozole have similar efficacy. The incremental results are presented in Table 57. The parameters used for the parametric distributions for this scenario are described in the company's clarification response (Clarification Question A13).

Table 57 Incremental results from ERG Scenario 5 obtained from excluding PO25 trial from the fixed-effects NMA for both PFS and OS for the 'all shape model'

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
Letrozole	£30,541	2.68	--	--	--
Anastrozole	£30,561	2.68	--	--	--
Tamoxifen	£32,323	2.47	£1,762	-0.21	Dominated
Fulvestrant	£49,435	3.23	£18,874	0.55	£34,113

As letrozole and anastrozole are assumed to be of equal efficacy, incremental results are obtained by using anastrozole as the base-case.

When compared with anastrozole, tamoxifen is associated with an additional cost of £1,762 but lower QALYs of -0.21, thereby making tamoxifen a dominated strategy. The incremental ICER of fulvestrant vs anastrozole is £34,113, thereby indicating that exclusion of PO25 trial had almost no impact on the base case ICER of £34,099 per QALY.

4.4.6 ERG Scenario 6: Change in administration cost for fulvestrant

One of our clinical experts stated that all patients in his locality would be treated in the outpatients setting and none in the primary care setting. Furthermore, this expert considered that it would be difficult to persuade primary care to administer fulvestrant. We therefore included a scenario where all patients received fulvestrant in the outpatient setting.
The administration cost for fulvestrant for treatments in the first four weeks are £399.58 and in subsequent months are £99.97 using this assumption. The incremental results are presented in Table 58.

Table 58 Incremental results from ERG Scenario 6 with a change in the administration cost for fulvestrant

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
Letrozole	£26,221	2.46	--	--	--
Anastrozole	£30,572	2.68	£4,351	0.22	£19,702
Tamoxifen	£32,328	2.47	£1,756	-0.21	Dominated
Fulvestrant	£50,203	3.23	£19,632	0.54	£35,496

When compared with anastrozole, tamoxifen is a dominated strategy. The incremental ICER of fulvestrant vs anastrozole is £35,496 per QALY, i.e. an increase of £1,397 on the base case ICER of £34,099 per QALY.

4.4.7 ERG base case

The assumptions for the ERG base case are listed below and results of this analysis are presented in Table 59. We consider this scenario to be most representative analysis of the available evidence for the cost-effectiveness of fulvestrant.

- Resource use for PFS and PS health states are based on the study by Karnon et al[52] as shown in ERG scenario 3
- Revised proportion of patients receiving second-line treatment, shown in ERG scenario 4
- Exclusion of PO25 trial from the NMA network and assuming similar efficacy for letrozole and anastrozole, shown in ERG scenario 5.
- All patients receiving fulvestrant administered in an outpatient setting, shown in ERG scenario 6.

Table 59 Incremental results of the ERG base case

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
Letrozole	£11,336	2.68	--	--	--
Anastrozole	£11,356	2.68	--	--	--
Tamoxifen	£11,852	2.47	£496	-0.21	Dominated
Fulvestrant	£29,866	3.23	£18,510	0.54	£33,455

The ERG base case incremental ICER for fulvestrant vs anstrozole is £33,455 per QALY gained Letrozole and anastrozole were assumed to be of equal efficacy, so the incremental analysis was estimated using anastrozole as the baseline comparator. Tamoxifen is dominated when compared with anastrozole as it is more expensive and less effective.

The ERG also conducted a PSA for 10,000 simulations of our base case. A comparison of the results obtained from the deterministic base case and the point estimates from the average PSA are presented in Table 60.

Table 60 Comparison of the point estimates obtained from the deterministic and PSA analyses of the ERG base case

Intervention vs comparator	Deterministic ICER (£/QALY)	Probabilistic ICER (£/QALY)
Fulvestrant vs Anastrozole	£33,455	£32,956
Fulvestrant vs Letrozole	£33,495	£32,983
Fulvestrant vs Tamoxifen	£23,687	£23,999

The ERG set anastrozole to have equal efficacy to that of letrozole, however we note that this produces PSA results for anastrozole and letrozole that have the same QALYs for each simulation, rather than simulating anastrozole and letrozole independently. We were unclear how to change the PSA calculations in the model to simulate anastrozole and letrozole independently as these calculations are not intuitive and have not been clearly explained.

4.5 Conclusions of cost effectiveness

The company used a model structure commonly used for economic models of cancer treatments with health states for progression-free survival, progression and death. The ERG considers the model structure to appropriate for the decision problem and the clinical pathway of advanced or metastatic breast cancer. The company used methods for the economic evaluation that are consistent with NICE methodological guidelines. The population, intervention and comparators used in the economic evaluation are consistent with the NICE scope.[1]

The company compares fulvestrant with anastrozole, letrozole and tamoxifen using an NMA that produces output in the form of parametric distributions of survival curves for PFS and OS. These curves are used directly in the economic model. The ERG considers that the distributions chosen by the company for PFS and OS are appropriate and provide a reasonable fit to the observed data. The ERG notes that using alternative parametric distributions for PFS and OS do not have significant impact on the model results, with the exception of the Gompertz distribution for OS (which the ERG considers to provide a poor fit to the observed data).

The ERG notes that the OS data from the FALCON trial are immature. Therefore OS for fulvestrant vs, anastrozole is largely based upon the FIRST trial. The ERG notes that the gain in PFS for fulvestrant compared to anastrozole was significantly lower in the FALCON trial than in

the FIRST trial and therefore suggests that it is likely that the OS benefit will also be lower in the FALCON trial than in the FIRST trial. Given the sensitivity of the model results to changes in OS, the ERG therefore considers there is some uncertainty in the cost-effectiveness estimates and the ICERs are likely to be higher when the full results of the FALCON trial become available.

5 End of life

The company do not consider fulvestrant to be an 'End of Life medicine' in this indication (CS p. 128).

6 Innovation

The CS highlights the innovative nature of fulvestrant based on its unique mechanism of action to block oestrogen by targeting and degrading the ER (CS section 2.5 p. 25). The CS states that this unique mechanism of action could potentially delay acquired resistance and increase OS. The ERG notes that evidence regarding resistance is not presented in the CS and whilst a significant improvement in OS was observed in the FIRST trial (where 72% of patients were endocrine therapy-naive [redacted]), median OS has not yet been reached in the FALCON trial.

In comparison to the AIs and tamoxifen which are oral therapies, the IM administration route for fulvestrant may improve compliance. The CS points out that a therapy with an IM route of administration may benefit patients who have difficulty swallowing and those whose compliance with oral therapy may be limited (e.g. the elderly or those with psychiatric illness). The ERG agrees that this would be the case. The ERG sought clinical advice regarding whether the IM administration would be unsuitable for any patients. The advice received was that for very thin women with little muscle in the gluteal area the injections would be very painful.

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

The company identified one phase II RCT (the FIRST trial) and one phase II RCT (the FALCON trial) that are relevant to the decision problem. The two trials provide evidence on a total of 667 postmenopausal patients with hormone-receptor positive advanced breast cancer who were randomised to treatment with either fulvestrant or anastrozole. All participants in the FALCON

trial and 74.6% of participants in the FIRST trial were endocrine therapy naive. No head to head trials were identified comparing fulvestrant to either letrozole or tamoxifen.

The extent to which the benefits of fulvestrant in terms of TTP/PFS and OS exceed those of anastrozole are uncertain. For PFS the uncertainty is because the degree of PFS benefit seen with fulvestrant in the FIRST trial (median TTP 10.3 months longer with fulvestrant) is greater than that observed in the FALCON trial (median PFS 2.8 months longer with fulvestrant). For OS the uncertainty is because OS was added as an outcome after the TTP analysis for the FIRST trial. So although median survival in the fulvestrant arm of the FIRST trial was almost 6 months longer than that of the anastrozole arm, confirmation of this result is required from the FALCON trial, but median OS has not yet been reached in the FALCON trial so these results are not available.

To obtain an estimate of the comparative effectiveness of fulvestrant in comparison to anastrozole, letrozole and tamoxifen an NMA was conducted. The ERG found some evidence of heterogeneity between the trials. However, for the trials where there was IPD (FALCON, FIRST, NorthAmTarget) the company matched participants to inclusion criteria of the FALCON trial such that only ER+/PgR+ patients plus endocrine treatment naive patients would be included in the NMA. This created a more homogeneous population for the NMA (except for study P025 which could not be matched because the company did not have access to IPD for this study). The company undertook a fixed-effect NMA because the number of studies in final network was small (five studies, two of which were designed to allow for combined data analysis) and the methodological difficulties of conducting a random-effects NMA but this may mean that the results do not fully capture uncertainty.

7.2 Summary of cost effectiveness issues

The CS includes evidence on the cost effectiveness of fulvestrant compared to anastrozole, letrozole and tamoxifen in post-menopausal women with untreated hormone-receptor positive locally advanced or metastatic breast cancer. The model structure adopted for the economic evaluation is appropriate and consistent with the clinical disease pathway. The model contains health states of progression-free, progressed disease and death. Parametric survival curves are used for PFS and OS based upon the clinical evidence. The clinical evidence consists of an NMA of trials. The ERG considered that the parametric distributions chosen by the company to

model PFS and OS were appropriate and a reasonable fit to the observed data. However, the OS data for the FALCON trial are immature and so long-term OS data were not available to be included within the NMA.

The ERG considers that it is more appropriate to exclude the PO25 trial that compares letrozole and tamoxifen. When this trial is excluded, there is no clinical evidence to include in the NMA to compare letrozole with the other treatments. Based on clinical advice, we assume that the efficacy of letrozole is equal to that of anastrozole.

The CS models produce an ICER of £34,099 per QALY compared to anastrozole. The model results were particularly sensitive to changes in the OS parameter values. The company's probabilistic sensitivity analyses showed there is a probability of 1.1% and 26.5% of fulvestrant being cost-effective at a willingness to pay threshold of £20,000 and £30,000 per QALY respectively.

The ERG's base case analysis includes changes to the health state resources, the proportion of patients receiving second-line endocrine therapy, excluding the PO25 trial from the NMA and for all patients to receive fulvestrant administered in an outpatient care setting. The ERG's base case analysis produces an ICER of £33,455 per QALY compared to anastrozole.

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9 APPENDICES

Appendix 1: List of verification checks conducted by the ERG

Checks conducted	Model outcome
Does the model provide a brief background on the model structure and design?	Yes
Are the different components of the model well presented?	Yes
Is it possible to navigate through the model easily?	Yes
Are the inputs used in the model clearly referenced?	Yes
Is the model is transparent with respect to its layout and technicalities?	The model is easy to navigate through. However, use of array functions in calculations have made it quite laborious and time-consuming to tease out the model calculations
Are there any of the key model outputs missing from the analysis?	No
Can the model results be reproduced (including any scenario analyses) as presented in the CS?	Yes- for all the scenario analyses- except for “no arms model” in CS Table 96
Set all the values to "0" and check if the results still pull through some figures	1. Cohort size = 0; no results are pulled through
	2. inputs for "safety", "utility" and "costs"= 0, model pulls through results of only LYs
Does the sum total of the number of patients in each of the health states at any given point (dead or alive) in time (time t+ n) equate to the total number of patients entering the model ?	Yes- except in the last cell of sheet "Pat_flow"
Set the same setting (including the drug) in both the intevention and comparator arm. Are the results for both the arms are similar?	Yes- checked for fulvestrant vs anastrozole
Was an exhaustive list of parameters included within the DSA and PSA?	yes
Are appropriate distributions used for the parameters included in the sensitivity analyses?	yes
Is the deterministic mean ICER approximately equal/close to the probabilistic mean ICER?	yes
Set difference in efficacy for all drugs to 0 ' equal health outcomes in all model arms	Yes
Set adverse event rate to 0%. No adverse events should occur	Yes
Set medical resource use to 0	Yes- get disease management costs as 0
Set unit cost for drugs and administration to 0. Total costs of drugs should be zero.	Yes- model behaves as expected; administration costs as 0
Use different discount rates (e.g. 0%, 3%, 7%)	Used in sensitivity analyses- model behaves as expected
For costs, total costs should decrease with increasing discount rates	
For health benefits, total number of events should decrease with increasing discount rates	
Set utility values to 0, utility adjusted health outcomes should be zero	Yes
Set utility values to 1, utility adjusted health outcomes should be equal to unadjusted life years	Yes- utility adjusted health outcomes = life years

Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer

ERRATUM

Replacement pages for factual inaccuracies in Evidence Review Group report

25 July 2017

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Both trials were judged by the Evidence Review Group (ERG) to be of good methodological quality. The ERG believes that the company has identified all the relevant RCTs of fulvestrant.

There are no head-to-head RCTs of fulvestrant versus tamoxifen or letrozole so the company conducted a frequentist fixed-effect network meta-analysis (NMA) to perform an indirect treatment comparison. The company's systematic review identified a further four RCTs for inclusion in the NMA initially, of which three compared anastrozole versus tamoxifen (the North American trial; the TARGET trial and a trial by Milla-Santos et al.) and one compared letrozole versus tamoxifen (the PO25 trial). The North American and TARGET studies were prospectively designed to allow for combined data analysis and the combined data are described as NorthAmTarget in the CS. The Milla-Santos trial was subsequently excluded from the NMA as its inclusion led to heterogeneity, used a dose of tamoxifen not recommended by the European Medicines Agency (EMA) and reported the outcomes of interest only for a subset of participants.

The CS summarises the methodological and patient characteristics for all six trials (two for fulvestrant, four for other comparators) that were identified for inclusion in the NMA. Individual patient data (IPD) were available for the two fulvestrant trials and also the combined NorthAmTARGET data set. This enabled the company to select patient data from the FIRST and NorthAmTARGET trials that matched the criteria of the FALCON trial in respect of ER+/PgR+ status and endocrine treatment naive status. Only aggregate data were available for the PO25 study which therefore could not be matched to FALCON. The possible advantages and disadvantages of this matching process were not discussed in the CS. The ERG understands that by matching to FALCON it was possible to exclude participants [redacted] (except for study PO25). Although the ERG has concerns about whether there may be unknown potential disadvantages to this matching approach, the ERG has concluded that these would likely be outweighed by the benefits of reduced heterogeneity in the NMA. The company used appropriate methods to investigate whether there was a constant relative treatment effect over time. The company concluded that methods for NMA that rely on the assumption of proportional hazards were inappropriate and therefore used an alternative method (Ouwens et al.). Fixed-effect NMA results are presented for the outcomes of PFS and overall survival (OS) and these inform the economic model. The company provided reasons for the use of a fixed-effect model and why it was not possible to run the NMA using a random-

lower range of the confidence interval) increased the ICER of fulvestrant vs anastrozole to £208,231 (an increase of £174,132 per QALY from the base case ICER) whereas the ICER increased to £40,761 per QALY (an increase of £6,662 from the base case ICER) when the incremental scale parameter was set at [redacted]. The incremental results obtained from scenario 3 to 6 were comparable to the company's base case results, with ICERs ranging between £32,084 and £35,496 per QALY for fulvestrant vs anastrozole.

For the ERG base case, we combined scenarios 3, 4, 5 and 6. The incremental results obtained are presented in Table 1. The ERG base case ICER for fulvestrant vs anastrozole is £33,455 per QALY which is slightly less than the company's base case ICER of £34,099 per QALY.

Table 1 ERG base case results

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
Letrozole	£11,336	2.68	--	--	--
Anastrozole	£11,356	2.68	--	--	--
Tamoxifen	£11,852	2.47	£496	-0.21	Dominated
Fulvestrant	£29,866	3.23	£18,510	0.54	£33,455

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After the inclusion and exclusion criteria of FALCON had been applied to FIRST and NorthAmTarget, Kaplan-Meier (KM) plots of PFS and OS were produced for the matched subgroups of participants. For PO25 the published KM plots for the whole study population were digitised and then patient-level data were reconstructed using a published algorithm.[22]

The OS and PFS data were examined to determine whether there was a constant relative treatment effect over time by visual inspection of the KM plots for PFS (CS Figure 23, p. 92) and OS (CS Figure 24, p. 93), and visual inspection of log cumulative hazard plots for PFS (CS Figure 25, p. 98) and OS (CS Figure 26, p. 99) for each trial. The OS KM plots for the arms of the PO25 trial and the NorthAmTarget trial cross, suggesting that a constant relative treatment effect is unlikely in these studies. In the log cumulative hazard plots, a constant relative treatment effect (i.e. proportional hazards) could be assumed if the two lines for each trial run parallel to each other, but this is not the case for all studies.

The company therefore concluded that methods for NMA that rely on the assumption of proportional hazards being true would be inappropriate. The method used for NMA is one developed by Ouwens et al.[23] In this method the differences in the shape and scale parameters of the parametric survival function used to model PFS or OS between the intervention and each comparator over time are synthesised, and used both for the indirect comparison and to extrapolate the PFS and OS curves beyond the end of trial follow-up (see Section **Error! Reference source not found.**). The parametric distributions used to model the KM data were the Weibull, Gompertz, log-logistic, lognormal and generalised gamma. Although not explicitly stated in CS Section 4.10.1 (pp. 90 - 99), the ERG subsequently received clarification from the company (clarification question A19) that the analysis was undertaken under a frequentist framework in the software package R.

The shape and scale parameters were calculated for the baseline (reference), which was anastrozole. These baseline parameters were then used as the anchor to obtain the estimates for the shape and scale of the other interventions in the network (i.e. fulvestrant, letrozole and tamoxifen).

If the shape parameter is regarded as fixed between treatment arms, this effectively assumes a proportional treatment effect. This ‘no shape arm’ model was tested in sensitivity analysis for all but the generalised gamma model (which, as a three parameter model, was more complex and therefore not included).

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A fixed-effect meta-analysis was undertaken. The rationale for not including a random effects model was the limited number of trials in each network. Whilst the ERG agrees that the number of trials is limited, as noted earlier there is some evidence of heterogeneity in trial participants between the trials, which the ERG thought could potentially be accounted for by using a random effects model. The ERG and NICE therefore asked the company to provide results from a random effects NMA (clarification question A10). In response to clarification question A10, the company provided a more detailed explanation of the reasons why a random effects NMA could not be undertaken. Due to the presence of the pooled NorthAmTarget dataset, the only connection in the network where there are two or more trials is the fulvestrant-anastrozole comparison informed by the FALCON and FIRST trials (as shown in **Error! Reference source not found.**). The company cites a recent (2016) paper by Friede et al.[24] which states that, in the Bayesian framework, if the number of studies is small then the choice of prior for the between-trial standard deviation is critical. The company goes on to state that an attempt was made to identify an informative prior (as detailed in the response to clarification question A10) but this proved a "*difficult question to answer*" and therefore they concluded, as before, that the more robust approach was to use a fixed effect meta-analysis.

The ERG accepts that there are few trials in the network and that a random-effects NMA is not possible. The ERG nevertheless is concerned that the potential uncertainty around the effect estimates may not be adequately represented.

The final consideration regarding the NMA is that for the PO25 trial IPD were not available and thus this trial population could not be matched to the FALCON inclusion and exclusion criteria. Furthermore, crossovers between treatments occurred in this trial which may have confounded the survival analysis and there is now a general agreement that the efficacy and safety of anastrozole and letrozole are equivalent [e.g. NICE CG81[2] states "All aromatase inhibitors appear to be equally effective in terms of primary outcome (overall survival)"]. For these reasons a scenario analysis in the economic model assumes the efficacy of letrozole is equivalent to anastrozole by using the anastrozole curves for letrozole (i.e. efficacy data from the PO25 trial is not used). The ERG had an additional concern regarding whether the data for TTP and OS came from the whole PO25 population or the HR+ subgroup (66%) and clarification was requested on this by the ERG and NICE. The company confirmed in their response to clarification question A6 that data from the full study population were used. Because of the differences between the PO25 study and the others in the network, and the general agreement that the efficacy of anastrozole and letrozole are equivalent, the ERG and NICE requested in clarification question A13 that an analysis omitting study PO25 from

Deaths related to adverse events

In the FALCON trial 3% of deaths were considered to be related to AEs (6 in the fulvestrant group and 7 in the anastrozole group) at the 11th April 2016 data cut off (the point of PFS analysis). None of these deaths were considered to be causally related to study treatment. A similar proportion of deaths from the main study period and the follow-up period combined in the FIRST study were due to AEs [3 (3%) SAEs in the fulvestrant group and 5 (4.9) SAEs in the anastrozole group] (Table 2).

Table 2 Summary of deaths related to AEs

Parameters, n (%)	FALCON		FIRST	
	Fulvestrant (n=228)	**Anastrozole (n=232)**	**Fulvestrant (n=101)**	**Anastrozole (n=103)**
Deaths related to AEs	6 (3%)	7 (3%)	3 (3.0%)	5 (4.9%)

AE, adverse event; n, number

1.1 Summary

The systematic review of clinical effectiveness evidence in the CS identified two RCTs of fulvestrant as a treatment for people with untreated hormone-receptor positive locally advanced or metastatic breast cancer (FIRST and FALCON). Both trials compared fulvestrant to anastrozole.

The two RCTs were judged to be of good methodological quality although there was the potential for the FIRST trial to be at a high risk of bias due to the absence of blinding. Overall, both studies appear to have been well conducted. The main clinical efficacy outcomes reported in the CS are PFS, OS, CBR (response rates) and HRQoL. AE outcomes are also reported. Follow-up of participants from the FALCON study is continuing, particularly with regard to OS for which there are currently only interim results.

The company's SLR had broad inclusion criteria, enabling the identification of studies that could contribute to the wider evidence base where necessary. As there is no direct evidence comparing fulvestrant to either letrozole or tamoxifen it was necessary for the company to conduct an NMA. In addition to the two trials of fulvestrant versus anastrozole, the NMA included data from a further three trials: combined data from the North American and TARGET studies (these two trials were prospectively designed to allow for combined data

The company states that visual inspection of KM plots for PFS showed that treatment arms remained separated over the trial period. KM plots for OS depict late separation (21 months) for the FIRST trial and crossing plots for the PO25 trial and the NorthAmTarget trial. We agree with the company that, based on visual inspection, some of the treatment arms particularly for the KM plots of OS (NorthAmTarget and PO25) cross or separate beyond the median survival time. This suggests that NMA methods, which rely on the assumption of proportional hazards, may not be suitable for analysing the studies.

The CS further estimates the log cumulative hazard plots for PFS and OS for the four trials, to further investigate the violation of proportional hazards. These hazard functions are presented in CS Figures 25 and 26. Like the KM plots, visual inspection seems to suggest that the assumption of proportional hazards is violated: it can be observed that for OS, the treatment arms of the PO25 and NorthAm Target trial crossed. The log cumulative hazard arms in the FALCON, FIRST and NorthAmTarget trials cross for PFS, while for OS, arms cross for the NorthAmTarget and PO25 trials. The CS further argues that using HRs as outcomes for the analysis places a restriction on the choice of distributions (such as log-normal and log-logistic distributions) that can be used to extrapolate PFS and OS. The company therefore sought alternative methods suitable for assessing NMA to extrapolate the treatment effect. The CS implements a method developed by Ouwens et al.[23] The Ouwens et al. method is premised on the fact that survival distributions, such as the Weibull or Gompertz, commonly used to extrapolate outcomes for cost-effectiveness analysis, can be described by two parameters (shape and scale). Further, applying a constant HR implies that treatment only affects the scale parameter. The Ouwens et al. method can be applied to both IPD and data derived from published KM curves such as the PO25 trial. A previous NICE appraisal for fulvestrant for previously treated patients with ABC reports the use of the Ouwens et al. method.[21] The ERG finds this method appropriate for implementing NMA, given the violation of the proportional hazards assumption.

The CS argues in favour of a fixed-effect NMA for PFS and OS rather than the random-effects model. The company's preference for a fixed-effect NMA has been critiqued in section **Error! Reference source not found.** of this report. The CS describes two types of fixed-effect analyses. The first scenario is the 'All-shapes' model which permits the modelling of parametric survival distributions with the estimation of their shape and scale parameters, since it does not rely on the assumption of

proportional hazards. It forms the basis of the base case survival curves used in the cost-effectiveness model and tabulated results from the CS are reported in section **Error! Reference source not found.** of the ERG report. The second scenario is the 'No shape arm' model, which assumes proportional treatment effects between treatment arms. The ERG believes the choice of the 'all shapes' model for the base case analysis is reasonable. The ERG queried the inclusion of the PO25 trial in the analysis (see section **Error! Reference source not found.** of this report) and the company has provided cost-effectiveness results excluding this trial in its clarification response (Question A13, Table 25). The ERG has conducted a scenario analysis that excludes the PO25 trial data and the results are shown in this report section **Error! Reference source not found.**.

PFS extrapolation

The company extrapolated KM curves for all the selected parametric distributions (Weibull, Gompertz, log-logistic, lognormal and generalised gamma). The ERG verified that the extrapolated curves reported in the CS corresponded to those used in the economic model. Extrapolated curves for all distributions were simultaneously plotted along with observed data from each of the meta-analysed studies. See Figure 1 to Figure 2 below (CS Figures 29-32). Figure 13 represents the survival curve for fulvestrant and anastrozole used in the economic report, while the extrapolated curves used in the economic model for the comparators are presented in Figure 27 of the CS.

Figure 1 FALCON PFS study fit with fixed effects 'all shapes' network meta-analysis model (CS Figure 29, p. 110)

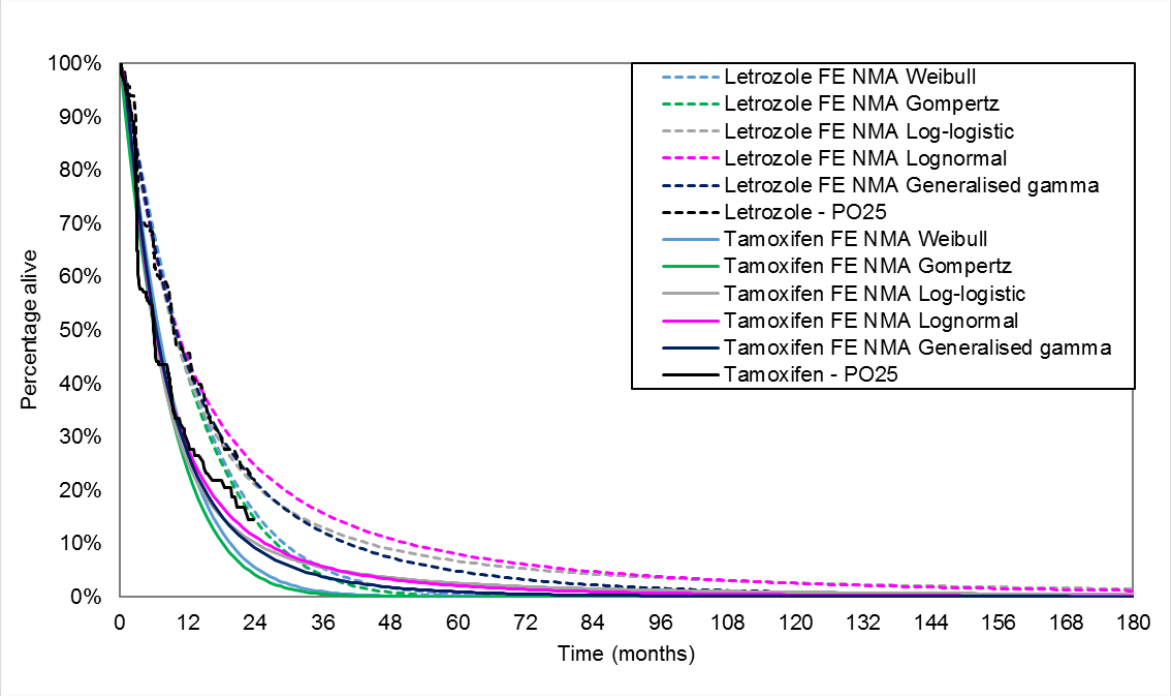

Figure 2 PO25 PFS study fit with fixed effects 'all shapes' network meta-analysis model adjusted for between-study differences (CS Figure 32, p. 111)

The ERG notes that the PFS curves in figures 12 to 15 are different for the same intervention. From subsequent clarifications with the company, the ERG understands that the curves were fitted to a combined dataset comprised of patient level data from the FALCON, FIRST and NorthAmTarget trials, and reconstructed data for the PO25 trial. The fitted curves were then used to produce outputs for their respective Akaike and Bayesian Information Criteria statistics.

The CS reports Akaike and Bayesian Information Criteria statistics for PFS (**Error! Reference source not found.**). The Bayesian information criterion (BIC) and the Akaike information criterion (AIC) are closely related statistics commonly used for model or distribution selection. The distribution with the lowest AIC or BIC value represents the best fit to the observed survival data. One limitation of the AIC and BIC is that they cannot be extended to make predictions of fitness beyond the observed data. The CS reports that visual inspection and expert opinion have been used to assess the different extrapolations of the survival data. Based on the company's clinical experts, 1-5% of patients treated with anastrozole are estimated to still be progression-free after 10 years (see **Error! Reference source not found.**). The company chose the generalised gamma distribution as the most appropriate fit, based on visual inspection and the opinion of the company's clinical experts,[29] although AIC and BIC (**Error! Reference source not found.**) placed the distribution at second best after the log-logistic

and are shown in Figure 3 to **Error! Reference source not found.** (CS Figures 34 -37). Similarly, we ascertained that extrapolated curves reported in the CS corresponded to those used in the economic model. While Figure 17 represents the parametric curve fit of OS for fulvestrant and anastrozole from the FALCON trial, the actual curves used for the comparators in the economic model are reported in figure 28 of the CS.

Figure 3 FALCON OS study fit with fixed effects 'all shapes' network meta-analysis model (CS Figure 34, p. 115)

1.1.1 Model validation

In line with the recommendations developed by a task force of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM)[54] for model quality assurance, the ERG checked the economic model for transparency and validity. These are discussed below.

Model transparency

The CS clearly described the model structure, parameter values and their sources, data identification methods, and assumptions used in the model. The model was technically transparent and the visual basic code used within the model was accessible. In general, the technical report and the model described the analyses clearly and provided adequate information to assess the model. The CS clearly presented the results of the NMA but did not present the R code used to derive those results.

Model validation

To validate the economic model, the company stated that the model was reviewed by their internal health economists. They undertook an assessment of the face-validity of the model, and conducted a third-party validation of the model calculations and the data sources. Extreme value and log tests were also conducted by the company to examine if the model behaved as expected and that the results obtained were logical.

The ERG checked the model for internal as well as external validity. The step-by-step approach used for this purpose is discussed below.

- *Face validity*

The company conducted an extensive review of the existing NICE appraisals in advanced/metastatic breast cancer in May 2016 to inform their modelling approaches. They also conducted a structured review of utility studies in June 2016 to inform the quality of life parameters. The opinions of seven UK clinical experts were used to validate the extrapolation of PFS and OS within the company's analyses. The CS compared the long-term predicted model outcomes for PFS and OS with the corresponding clinical expert opinion as shown in **Error! Reference source not found.**. The modelled outcomes appeared comparable with the expert opinion.

1.1.2 ERG Scenario 2: Changes to the OS scale parameter for fulvestrant

The company model results were most sensitive to changes in treatment effectiveness by varying the OS scale parameter (see section **Error! Reference source not found.**). As shown in **Error! Reference source not found.**, varying the OS scale parameter between the lower and upper 95% confidence intervals resulted in the ICER for fulvestrant vs. anastrozole varying between £23,236 and £338,729 per QALY (Incremental scale parameter for fulvestrant varied between [redacted] and [redacted]).

The ERG considers that there remains uncertainty around the OS scale parameters due to the immature OS data from the FALCON trial. The long-term OS data from this trial was not available to be included in the NMA. The ERG considers that the survival benefit for fulvestrant compared to anastrozole is likely to be lower from the FALCON trial than observed in the FIRST trial. Therefore, when data from the FALCON trial becomes available, the treatment benefit for fulvestrant may be lower than estimated in the NMA. The ERG varied the OS scale parameter in scenario 2 between its mean value and the lower 95% confidence interval to illustrate the effect of changes to the treatment benefit. The results are shown for four scale parameters (incremental values from [redacted]) in Table 3.

Table 3 ERG scenario 2: Effect of changes of the fulvestrant OS scale parameter

Parameters		Base case ICER (OS: Weibull)	Scenario ICER
Scenario 2: Fulvestrant Incremental scale parameter [redacted]			
Fulvestrant vs	Letrozole	£29,991	£33,475
	Anastrozole	£34,099	£40,761
	Tamoxifen	£22,498	£24,432
Scenario 2: Fulvestrant Incremental scale parameter [redacted]			
Fulvestrant vs	Letrozole	£29,991	£38,326
	Anastrozole	£34,099	£52,405
	Tamoxifen	£22,498	£27,146
Scenario 2: Fulvestrant Incremental scale parameter [redacted]			
Fulvestrant vs	Letrozole	£29,991	£45,842
	Anastrozole	£34,099	£79,337
	Tamoxifen	£22,498	£31,404
Scenario 2: Fulvestrant Incremental scale parameter [redacted]			
Fulvestrant vs	Letrozole	£29,991	£59,000
	Anastrozole	£34,099	£208,231
	Tamoxifen	£22,498	£39,027

These illustrative results indicate that even with a relatively small change to the OS scale parameter to [redacted], produces an ICER of £40,761 per QALY for fulvestrant vs. anastrozole.

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Table 4 Comparison of the point estimates obtained from the deterministic and PSA analyses of the ERG base case

Intervention vs comparator	Deterministic ICER (£/QALY)	Probabilistic ICER (£/QALY)
Fulvestrant vs Anastrozole	£33,455	£32,956
Fulvestrant vs Letrozole	£33,495	£32,983
Fulvestrant vs Tamoxifen	£23,687	£23,999

It is worth noting that the above results should be treated with caution due to the following reasons:

i. Whilst the ERG incorporated the correct point-estimates from the NMA when PO25 trial was excluded for our base case, we did not have access to the associated variance-covariance matrices for the corrected model. The above PSA results were obtained by using the variance-covariance matrices from the NMA that included the PO25 trial and therefore do not reflect the ERG base case of excluding PO25 trial from the NMA.

ii. The ERG set anastrozole to have equal efficacy to that of letrozole, however we note that this produces PSA results for anastrozole and letrozole that have the same QALYs for each simulation, rather than simulating anastrozole and letrozole independently. We were unclear how to change the PSA calculations in the model to simulate anastrozole and letrozole independently as these calculations are not intuitive and have not been clearly explained.

1.2 Conclusions of cost effectiveness

The company used a model structure commonly used for economic models of cancer treatments with health states for progression-free survival, progression and death. The ERG considers the model structure to appropriate for the decision problem and the clinical pathway of advanced or metastatic breast cancer. The company used methods for the economic evaluation that are consistent with NICE methodological guidelines. The population, intervention and comparators used in the economic evaluation are consistent with the NICE scope.[1]

The company compares fulvestrant with anastrozole, letrozole and tamoxifen using an NMA that produces output in the form of parametric distributions of survival curves for PFS and OS. These curves are used directly in the economic model. The ERG considers that the distributions chosen by the company for PFS and OS are appropriate and provide a reasonable fit to the observed data. The ERG notes that using alternative parametric

distributions for PFS and OS do not have significant impact on the model results, with the exception of the Gompertz distribution for OS (which the ERG considers to provide a poor fit to the observed data).

The ERG notes that the OS data from the FALCON trial are immature. Therefore OS for fulvestrant vs, anastrozole is largely based upon the FIRST trial. The ERG notes that the gain in PFS for fulvestrant compared to anastrozole was significantly lower in the FALCON trial than in

the FIRST trial and therefore suggests that it is likely that the OS benefit will also be lower in the FALCON trial than in the FIRST trial. Given the sensitivity of the model results to changes in OS, the ERG therefore considers there is some uncertainty in the cost-effectiveness estimates and the ICERs are likely to be higher when the full results of the FALCON trial become available.

2 End of life

The company do not consider fulvestrant to be an 'End of Life medicine' in this indication (CS p. 128).

3 Innovation

The CS highlights the innovative nature of fulvestrant based on its unique mechanism of action to block oestrogen by targeting and degrading the ER (CS section 2.5 p. 25). The CS states that this unique mechanism of action could potentially delay acquired resistance and increase OS. The ERG notes that evidence regarding resistance is not presented in the CS and whilst a significant improvement in OS was observed in the FIRST trial (where 72% of patients were endocrine therapy-naive [redacted]), median OS has not yet been reached in the FALCON trial.

In comparison to the AIs and tamoxifen which are oral therapies, the IM administration route for fulvestrant may improve compliance. The CS points out that a therapy with an IM route of administration may benefit patients who have difficulty swallowing and those whose compliance with oral therapy may be limited (e.g. the elderly or those with psychiatric illness). The ERG agrees that this would be the case. The ERG sought clinical advice regarding whether the IM administration would be unsuitable for any patients. The advice received was that for very thin women with little muscle in the gluteal area the injections would be very painful.

4 DISCUSSION

4.1 Summary of clinical effectiveness issues

The company identified one phase II RCT (the FIRST trial) and one phase III RCT (the FALCON trial) that are relevant to the decision problem. The two trials provide evidence on a total of 667 postmenopausal patients with hormone-receptor positive advanced breast cancer who were randomised to treatment with either fulvestrant or anastrozole. All participants in the FALCON

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer [ID951]

You are asked to check the ERG report from Southampton Health Technology Assessments Centre to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Tuesday 18 July 2017** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Description of method of network meta-analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11 of the ERG report states the following: "There are no head-to-head RCTs of fulvestrant versus tamoxifen or letrozole so the company conducted a Bayesian fixed-effect network meta-analysis (NMA) to perform an indirect comparison".	The company proposes the text be changed to the following: "There are no head-to-head RCTs of fulvestrant versus tamoxifen or letrozole so the company conducted a frequentist fixed-effect network meta-analysis (NMA) to perform an indirect comparison".	A Bayesian framework was not employed in the NMA. Indeed, the framework used was not stated in the submission, but was provided in response to clarification question A19.	The ERG agrees with the amendment but see response to issue 3.

Issue 2 Description of upper range of confidence interval

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17 of the ERG report states the following: "For instance, an incremental scale parameter of [redacted] (near the upper range of the confidence interval)…".	The company proposes the text be changed to the following: "For instance, an incremental scale parameter of [redacted] (near the lower range of the confidence interval)…".	The current statement implies that the point estimate (mean effect) is less than [redacted], which in turn implies that the projected survival associated with fulvestrant is inferior to that of anastrozole.	The ERG agrees with the amendment.

Issue 3 Statement regarding framework and software in which the network meta-analysis was undertaken

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 58 of the ERG report states the following: "Although not explicitly stated in CS Section 4.10.1 (pp. 90 – 99),	The company proposes the text be changed to the following: "Although not explicitly stated in CS Section 4.10.1 (pp. 90 – 99), the ERG subsequently	See Issue 1.	As the ERG report indicated the type of analysis was not explicitly stated in the CS. The ERG agrees that clarification question A19 indicates the use

the ERG assumes that the analysis took a Bayesian approach using a Markov Chain Monte Carlo method implemented using the WinBUGS software package (as describe by Ouwens et al.)".	clarified with the company that the analysis was undertaken under a frequentist framework in the software package R.		of a frequentist framework, however the response to clarification question A10 appears to suggest the use of a Bayesian framework. The ERG accepts that their initial assumption was incorrect and the text has been amended in a similar way to that suggested by the company.

Issue 4 Statement regarding plausibility of random-effect network meta-analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 59 of the ERG report states the following: "The ERG accepts that there are few trials in the network and that, with the methodology the company have used for the NMA, a random-effects NMA is not possible; the ERG nevertheless is concerned that the potential uncertainty around the effect estimates may not be adequately represented".	The company proposes the text be changed to the following: "The ERG accepts that there are few trials in the network and that a random-effects NMA is not possible; the ERG nevertheless is concerned that the potential uncertainty around the effect estimates may not be adequately represented".	A random-effects model of a one-dimensional treatment effect (hazard ratio) would also not have been possible in this instance. The problem stems from the fact that only one link in the network is populated by more than one study, so this is an issue associated with random-effects, due to a limitation in the evidence network, rather than because of the methodology developed by Ouwens et al.[1], and used in the analysis.	The ERG agrees that the paucity of the studies in the network is the chief limiting factor in the ability to run a random-effects model, and this is the case regardless of methodology. The text has been updated as proposed by the company.

[1] Ouwens, M. J., et al. (2010). "Network meta-analysis of parametric survival curves." Res Synth Methods 1(3-4): 258-271.

Issue 5 Number of trials stated to inform the network meta-analysis for PFS and OS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 81 of the ERG report states the following: "In addition to the two trials of fulvestrant versus anastrozole, the NMA included data from a further four trials: combined data from the North American and TARGET studies (these two trials were prospectively designed to allow for combined data analysis) which compared anastrozole to tamoxifen, and the PO25 trial which compared letrozole to tamoxifen".	The company proposes the text be changed to the following: "In addition to the two trials of fulvestrant versus anastrozole, the NMA included data from a further three trials: combined data from the North American and TARGET studies (these two trials were prospectively designed to allow for combined data analysis) which compared anastrozole to tamoxifen, and the PO25 trial which compared letrozole to tamoxifen".	Outside of the FALCON and FIRST trials, a further four were identified (North American, TARGET, PO25 and Milla-Santos); however, only three of these four trials (North American, TARGET and PO25) contributed data to the network meta-analysis.	This typographical error has been corrected.

Issue 6 Statement regarding crossing curves in trials contributing data to the network meta-analysis for OS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 93 of the ERG report states the following: "The log cumulative hazard arms in the FALCON, FIRST, and NorthAmTarget trials cross for PFS, while for OS, arms cross for the NorthAmTarget trials".	The company proposes the text be changed to the following: "The log cumulative hazard arms in the FALCON, FIRST, and NorthAmTarget trials cross for PFS, while for OS, arms cross for the NorthAmTarget and PO25 trials".	Visual inspection of Figure 26 in the CS (pp. 99) indicates that the cumulative hazard arms in the PO25 trial cross between approximately log(time) [redacted]	The ERG agrees with the amendment

Issue 7 Statement regarding the fitting of curves to individual trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 96 of the ERG report states the following: "The ERG notes that the PFS curves in figures 12 to15 are different for the same intervention. The ERG understands that the company has fitted the four curves to the observed data from the trials separately to give outputs for their Akaike and Bayesian Information Criteria statistics, but this is not stated explicitly in the CS".	The company proposes the text be changed to the following: "The ERG notes that the PFS curves in figures 12 to 15 are different for the same intervention. The ERG subsequently clarified with the company that the curves were fitted to a combined dataset comprised of PLD from the FALCON, FIRST and NorthAmTarget trials, and reconstructed data for the PO25 trial. The models included indicators for study and treatment arm, allowing the curves to be adjusted for different baselines, and therefore providing different curves for the same intervention. The AIC and BIC statistics present the fit of each model in the combined dataset (across all trials). For the purposes of the economic evaluation, the study indicator was treated as a nuisance parameter; that is, a necessary parameter for the estimation of effect size and in reducing the amount of unexplained variation around the estimate, but not used directly in the survival functions which informed the economic modelling (p96 of CS).	Parametric distributions were not fitted to individual data sets. Parametric models with indicators for study and treatment arm were fitted to a combined dataset of all included studies. An explicit statement to this effect could have been included in the original submission document.	The ERG has amended the ERG report in line with the company's additional clarifications.

Issue 8 Verification of extrapolated plots presented in the report are used in the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 94 of the ERG report states	The company proposes the text be changed to	Figures 13 and 17 in the ERG	The ERG has amended the

the following: "The ERG verified that the extrapolated curves reported in the CS correspond to those used in the economic model. Extrapolated curves for all distributions were simultaneously plotted along with observed data from each of the meta-analysed studies. See Figure 13 to Figure 16 below (CS Figures 29-32)".	the following: "The ERG verified that the extrapolated curves reported in the CS correspond to those used in the economic model. Extrapolated curves for all distributions were simultaneously plotted along with observed data from each of the meta-analysed studies. See Figure 13 to Figure 16 below (CS Figures 29-32). Please note that Figures 14 – 16 below show the results of the parametric curve fits to each trial when the study indicator is included in the models (other than FALCON, which is the baseline trial). Therefore, figure 13 presents the survival curves for fulvestrant and anastrozole used in the economic evaluation, but the survival curves for the comparators are presented in figures 27 and 28 in the CS (pages 102-104 and 106-108), and are not reproduced in this report".	report present the parametric curve fits for PFS and OS for fulvestrant and anastrozole from FALCON. As FALCON was the baseline trial, these curves are used directly in the economic modelling. Figures 14-16 and 18-20 present the parametric curve fits for PFS and OS for each of the additional trials included in the PFS and OS networks. These plots show the parametric curves when the study indicator is included in the model (included for the purposes of visual assessment of model 'fit'), but don't represent the actual curves used for the comparators in the economic model. Figures 27 and 28 in the CS (pages 102-104 and 106-108) present the extrapolated curves used in the economic model.	ERG report in line with the company's additional clarifications.
Page 98 of the ERG report states the following: "Similarly, we ascertained that extrapolated curves reported in the CS correspond to those used in the economic model".	The company proposes the text be changed to the following: "Similarly, we ascertained that extrapolated curves reported in the CS correspond to those used in the economic model. Please note, that as in the case with PFS, figure 17 presents the extrapolated curves for fulvestrant and anastrozole from FALCON, and therefore represents those curves used in the economic model. Figures 18-20 present the survival curves for the comparators when the study indicator was included in the models and therefore do not represent the curves used in	Please see above.	The ERG has amended the ERG report in line with the company's additional clarifications.

	the economic model. Figure 28 in the CS (pages 106-108) present the survival curves for OS used in the economic model for each of the comparators; these plots are not reproduced in this report".		

Issue 9 The software in which the network meta-analysis was undertaken

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 115 of the ERG report states the following: "The CS clearly presented the results of the NMA but did not present the WinBUGS code used to derive those results".	The company proposes the text be changed to the following: "The CS clearly presented the results of the NMA but did not present the R code used to derive those results".	A frequentist analysis was undertaken using the R software platform (p90 and p97 of the CS).	The ERG agrees with the amendment.

Issue 10 Lower and upper 95% confidence interval for OS log scale parameter

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 135 of the ERG report states the following: "As shown in Table 42, varying the OS scale parameter between the lower and upper 95% confidence intervals resulted in the ICER for fulvestrant vs. anastrozole varying between £23,236 and £338,729 per QALY	The company proposes the text be changed to the following: "As shown in Table 42, varying the OS scale parameter between the lower and upper 95% confidence intervals resulted in ICER for fulvestrant vs. anastrozole varying between £23,236 and £338,729 per QALY (Incremental scale parameter for fulvestrant varied between - [redacted] and [redacted])".	The value 0.20177 is the point estimate (mean) from the network meta-analysis for the log scale Weibull parameter for fulvestrant, and results in the base case ICER: £34,099.	ERG agrees with the amendment

(Incremental scale parameter for fulvestrant varied between - [redacted] and [redacted])".			

Issue 11 The range across which the OS log scale parameter is varied in ERG scenario 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 135 of the ERG report states the following: "The ERG varies the OS scale parameter in scenario 2 between its mean value and the upper 95% confidence interval to illustrate the effect of changes to the treatment benefit. The results are shown for four scale parameters (incremental values from [redacted]) in Table 52".	The company proposes the text be changed to the following: "The ERG varied the OS scale parameter in scenario 2 between its mean value and the lower 95% confidence interval to illustrate the effect of changes to the treatment benefit. The results are shown for four scale parameters (incremental values from [redacted]) in Table 52".	The ERG present the lower bound of the 95% confidence interval and the mean value as the lower and upper bound of the 95% confidence interval [redacted] and [redacted]). The 95% confidence interval presented in table 30 of the CS (pp. 105) is - [redacted] and [redacted] (reproduced here to 5 decimal places).	ERG agrees with the company's suggestion and has amended the text in the ERG report to reflect this.

Issue 12 Comparison of deterministic and probabilistic point estimates obtained from the ERG base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 140 of the ERG report states the following: "A comparison of results obtained from the deterministic base case and the point estimates from the average PSA are presented in	The company does not propose any text amends to this statement, but would like to highlight to the ERG and the committee that whilst the point estimates from the network meta-analysis when the PO25 study was excluded are incorporated into the corrected model, the associated variance-covariance	The ERG's probabilistic point estimates are not representative of the ERG base case. As stated previously, since the PO25 study was one of the last links in the networks, the results of the PSA when the variance-covariance	ERG agrees with the company's suggestion and has amended the text in the ERG report to reflect this.

Table 60".	matrices were not. Therefore, the ERG's probabilistic point estimates provided in the report use the variance-covariance matrices from the network meta-analyses when the PO25 study was included. Please note that since the PO25 study was the last link in the network, the results of the PSA when the variance-covariance matrices from the network meta-analysis when the PO25 trial is excluded are anticipated to be very similar to the results the ERG have generated.	matrices from the network meta-analysis when the PO25 trial is excluded are anticipated to be very similar to the results the ERG have generated.	

Issue 13 Designation of FALCON as a phase II RCT

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 142 of the ERG report states that: "The company identified one phase II RCT (the FIRST trial) and one phase II RCT (the FALCON trial) that are relevant to the decision problem".	The company proposes the text be changed to the following: "The company identified one phase II RCT (the FIRST trial) and one phase III RCT (the FALCON trial) that are relevant to the decision problem".	FALCON is a phase III RCT.	This typographical error has been corrected.

Issue 14 Designation of FALCON as a phase II RCT

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 19 of the ERG	We are sympathetic to the	Trials 0020 and 0021 compared fulvestrant 250mg with anastrozole	The ERG notes the

report states that: "…the OS benefit in FALCON may mirror that of PFS and not be as great as observed in the FIRST study."	ERGs concern in this regard, however we have reason to believe that this uncertainty should be put into context considering the established evidence for fulvestrant in breast cancer. As a result, the more extreme sensitivity analyses exploring the possibility of little or no difference in OS in this setting, should be interpreted with caution.	1mg in patients with advanced breast cancer who had progressed after previous endocrine treatment and showed no difference in OS (approximately 75% maturity, Fig 1 in Howell 2005). The CONFIRM study compared 250mg with 500mg fulvestrant in similar patients and demonstrated the superiority of the higher dose in this setting. At 50% maturity, OS survival curves were similar, but had started to separate; HR=084 (95% CI, 0.69 – 1.03). A more mature data cut at 75% maturity confirmed this separation of the survival curves which was maintained out to 80 months; HR = 0.81 (0.69 – 0.96, Figure 2 in Di Leo 2013). [redacted] 	company's comments

		We present these observations with the aim of demonstrating that fulvestrant has an established history of showing a superior OS benefit at high levels of data maturity and that we are confident that FALCON will follow this profile.	

(please cut and paste further tables as necessary)