EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Development and Evaluation

Assessment Report
For
Faslodex
(fulvestrant)

Procedure No.: EMEA/H/C/000540/II/0018

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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1. Scientific discussion

1.1. Introduction

Fulvestrant is indicated for the treatment of postmenopausal women with estrogen receptor positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-estrogen therapy or disease progression on therapy with an anti-estrogen. The Marketing Authorisation was granted on 10 March 2004.

Fulvestrant is an anti-estrogen without agonist properties. It blocks the trophic actions of estrogens without itself having any partial agonist (estrogen-like) activity on the endometrium of post-menopausal women. Fulvestrant binds to estrogen receptor (ER) in a competitive manner with a high affinity comparable with that of oestradiol.

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 a long acting (LA) injection, designed to deliver the required dose of 500 mg of fulvestrant over a 1 month period from two consecutive 5 ml injections (pre-filled syringes contains 250 mg fulvestrant in 5 ml solution) by slow intramuscular injection (1-2 minutes/injection), one in each buttock.

In this application, the MAH re-evaluated data from a previously submitted pivotal study CONFIRM (assessed by CHMP as part of FUM 005), as well as supportive studies NEWEST and FINDER1/FINDER2 (assessed as part of FUM 006 and Type II-17 respectively), to support an extension of indication to include patients who have failed on aromatase inhibitor therapy. Considering that the extension of indication was not approvable by the CHMP, the MAH agreed on an update of the section 5.1 in regards to the data submitted.

In addition, the MAH proposed to remove information on potential risk of osteoporosis in section 4.4 of the SmPC, and to include data from the NEWEST study relating to mechanism of action, effects on bone and postmenopausal endometrium in section 5.1 of the SmPC. Furthermore, the MAH proposed to remove information on 'venous thromboembolism' from sections 4.4 and 4.8 of the SmPC.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) N° 1901/2006 as amended, the application included an EMA decision (P/146/2009) on the granting of a class waiver.

1.2. Non-Clinical aspects

No new pre-clinical toxicity studies have been submitted in this application, however the highest dose levels used in the preclinical toxicological studies conducted for the original application (250 mg/month) corresponded to exposure ratios of 2-5 times the ones expected upon the proposed human maximal dose (500 mg/month). The safety margins achieved at the No Observed Adverse Effect Levels (NOAEL's) in these studies against the 500 mg dose used in the current variation are summarised in Table 1.

Table 1. Ratio of animal/human exposure to fulvestrant based on mean AUC values following multiple intramuscular doses

Parameter	Rat (male) (TPR 2042)	Rat (female) (TPR 2042)	Dog (TFD 913)	Human *
Dose	10 mg/rat/15 days	10 mg/rat/15 days	40 mg/kg/28 days	500 mg
AUC $_{0\text{-}t}$ (ng.h/ml)	46,656	92,688	36,000	13104
AUC ratio	3.6	7.1	2.75	

* the value for human AUC is the 3 month steady state level derived FINDER 2.

Major findings in the toxicological studies, especially findings such as vasculitis and arteritis in dogs, were re-assessed in relation to this exposure. The MAH discussed the reasons why these toxicological findings were not considered related to treatment, in part because these changes may be related to the specific strain of Beagle dogs used, however the CHMP was of the opinion that a treatment related effect could not be totally excluded and information regarding these findings has been added to Section 5.3 of the SPC. In addition 'vasculitis' is currently included as a potential risk within the fulvestrant EU RMP.

1.3. Clinical aspects

The CONFIRM study (D66997C00002 [9238IL/0064]), a Phase III, randomised, double-blind, multicentre study, evaluated the safety and efficacy of the ER antagonist fulvestrant in post-menopausal breast cancer patients with estrogen receptor positive disease, who have relapsed or progressed on prior endocrine therapy. The study was assessed by CHMP as part of FUM 005 and was the basis to support an extension of the indication to include patients who have failed on prior aromatase inhibitor therapy.

In addition data from three phase II studies were assessed during the review. Two of these, FINDER1 and FINDER2, included patient populations relevant to the sought indication, whereas NEWEST studied fulvestrant in another setting. Unlike the CONFIRM study which included patients with non-measurable as well as measurable disease, the FINDER studies only included patients with measurable disease. The FINDER studies also included a treatment arm denoted as the 250 mg loading dose regimen (250mg + LD).

A summary of the studies considered for this application is provided in Table 2.

Table 2. Studies of the fulvestrant 500 mg dose regimen

Study acronym and number	**Indication/Setting***	**Study design**	**Objectives (Primary)**	**Treatment groups**	**Number of randomised patients**
CONFIRM D6997C0002 Pivotal	Advanced breast cancer after failure on prior endocrine therapy	Randomised, double blind, parallel group, multicentre (multi-	Efficacy and Safety (TTP)	Fulvestrant 500 mg Fulvestrant 250 mg	362 374

		continental)			
FINDER1 D69970004	Advanced breast cancer after failure on prior endocrine therapy	Randomised, double blind, parallel group, multicentre (Japan)	Efficacy, PK and Safety (ORR)	Fulvestrant 500 mg Fulvestrant 250 mg Fulvestrant 250mg + LD	47 45 51
FINDER2 D69970006	Advanced breast cancer after failure on prior endocrine therapy	Randomised, double blind, parallel group, multicentre (Europe, Canada)	Efficacy, PK and Safety (ORR)	Fulvestrant 500 mg Fulvestrant 250 mg Fulvestrant 250mg + LD	46 47 51
NEWEST D6997C00003	Neoadjuvant treatment of primary breast cancer	Randomised, open label, multicentre	Efficacy, PK, PD and Safety (Ki67 LI)	Fulvestrant 500 mg Fulvestrant 250 mg	109 102

* All studies include postmenopausal women with confirmed estrogen receptor positive breast cancer.
CBR: clinical benefit rate, LD: loading dose, ORR: objective response rate, PD: pharmacodynamics, PK: pharmacokinetics, TTP: time to progression

- ***Clinical Pharmacology***

This variation included clinical pharmacology data from the three clinical phase II studies NEWEST, FINDER 1 and FINDER 2. Data from the neoadjuvant study NEWEST were the basis for proposed changes relating to the mechanism of action, effects on bone and postmenopausal endometrium in section 5.1. This data had been previously assessed by CHMP as part of FUM 006.

The NEWEST study was a randomised, open-label, Phase II multicentre study in postmenopausal women with newly diagnosed ER+ breast cancer. The study incorporated a screening phase, a treatment phase, a study completion visit at Week 16 (unless treatment discontinuation criteria were met earlier), surgery (mastectomy or breast conserving) for tumour removal, and a follow-up safety visit 8 weeks after surgery or on their 6^{th} visit (as applicable).

The targeted population included women with histologically or cytologically confirmed invasive ER+ breast cancer who were postmenopausal as defined by one of the following criterion: (1) ≥60 years old, (2) ≥45 years old with amenorrhea for at least 12 months and an intact uterus, (3) history of bilateral oophorectomy, or (4) estradiol and follicle-stimulating-hormone (FSH) levels in the postmenopausal range (as determined by the testing laboratory). Tumors had to be newly diagnosed and either operable or potentially operable depending on the degree of advancement; the largest tumour diameter had to measure at least 2 cm. (Acceptable TNM classifications were T2, 3, 4b, N0-3, M0). Patients also had to have a World Health Organization (WHO) performance status of 0, 1, or 2 and be willing to undergo biopsies and surgery as outlined in the protocol. Patients with more than 2 major

tumour nodules or metastatic disease and patients previously treated for breast cancer were not eligible for study participation. Additional criteria excluded patients with conditions that could potentially interfere with efficacy evaluations or pose unacceptable health risks.

Patients who met study entry criteria were assigned to 1 of 2 randomised treatments: either fulvestrant 500 mg intramuscularly (im) every 28 days, with a supplemental loading dose given on Day 14 (total of 5 doses) or fulvestrant 250 mg im every 28 days (total of 4 doses). Treatment at each dosage extended across a 16-week period. Patients assigned to the 500-mg dosage received 2 injections on Days 0, 14, 28, 56, and 84. Patients assigned to the 250-mg dosage received single injections on Days 0, 28, 56, and 84.

The primary objective was to compare the effects of fulvestrant 500 mg and fulvestrant 250 mg on the proliferation marker Ki67 after 4 weeks of treatment. Secondary objectives were to compare the tolerability of fulvestrant 500 mg with that of fulvestrant 250 mg; to compare the effects of fulvestrant 500 mg and fulvestrant 250 mg on serum bone markers, endometrial thickness, and uterine dimensions; to assess the correlation between changes in Ki67 labeling index (LI) and changes in estrogen-receptor (ER) expression and progesterone-receptor (PgR) expression; to compare the effects of fulvestrant 500 and 250 mg on tumour response assessed by ultrasound; to compare actual surgery performed at 16 weeks with the baseline-predicted feasible surgery for each treatment group; and to correlate response after 16 weeks of treatment with biological endpoints detected after 4 and 16 weeks of treatment.

Criteria for evaluation (main endpoints):

- Primary endpoint: Ki67 LI at Week 4 (change from baseline)

- Secondary endpoints: changes from baseline in ER index, PgR index, and Ki67 LI (at Weeks 4 and 16); tumour response rate as assessed by changes in tumour volume (per ultrasound); extent of breast surgery; change from baseline in Ki67 LI, ER index, PgR index, and HER-2, by responder status at Week 16; responder status at Week 16 by HER-1 and HER-2 expression at baseline.

Sample size was calculated relative to change in Ki67 LI from baseline to Week 4. Using a standard deviation of 0.616% (taken from an earlier study, which looked at pre- and post dose Ki67 LI after a single 250-mg dose of fulvestrant), 80 patients per treatment group were required to provide 80% power to detect a 24% decrease in Ki67 LI at Week 4 for fulvestrant 500 mg relative to fulvestrant 250 mg at a 2-sided 0.05 significance level.

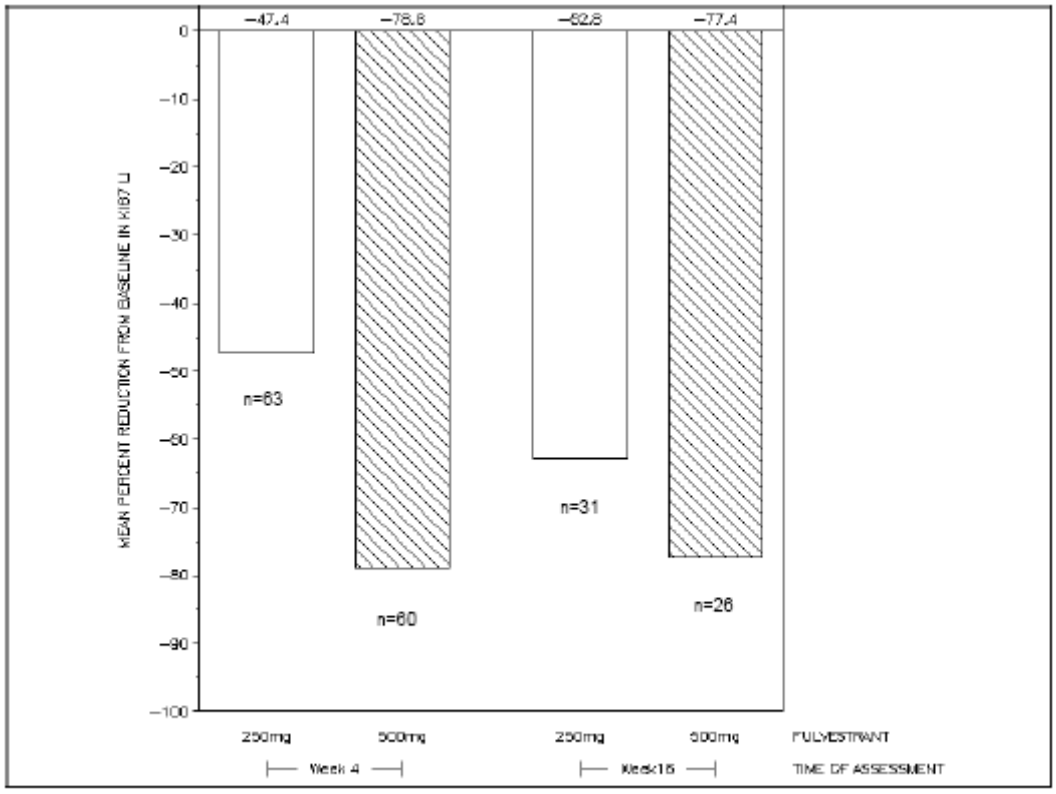
The population assigned to randomised treatment (ITT) comprised 211 women enrolled from 36 investigational sites. Patients were assigned to treatment as follows: 109 to treatment with fulvestrant 500 mg and 102 to treatment with fulvestrant 250 mg.

Mechanism of action (Ki67 and ER)

Results from the neoadjuvant NEWEST study were the basis for the MAH proposal to include data in section 5.1 of the SmPC regarding mechanism of action, i.e. effect on proliferation marker Ki67 and the estrogen receptor (ER).

<u>Ki67</u>

The fulvestrant 500-mg regimen reduced Ki67 LI to a significantly greater extent, compared with fulvestrant 250 mg (mean % change: –78.8% vs. –47.4%, respectively, $p<0.0001$) after 4 weeks of treatment. At Week 16, reduction in Ki67 LI was still greater at the higher dosage (–77.4% and –62.8% for the 500- and 250-mg dosages, respectively) but, in an exploratory analysis, the difference was not statistically significant (Figure 1).



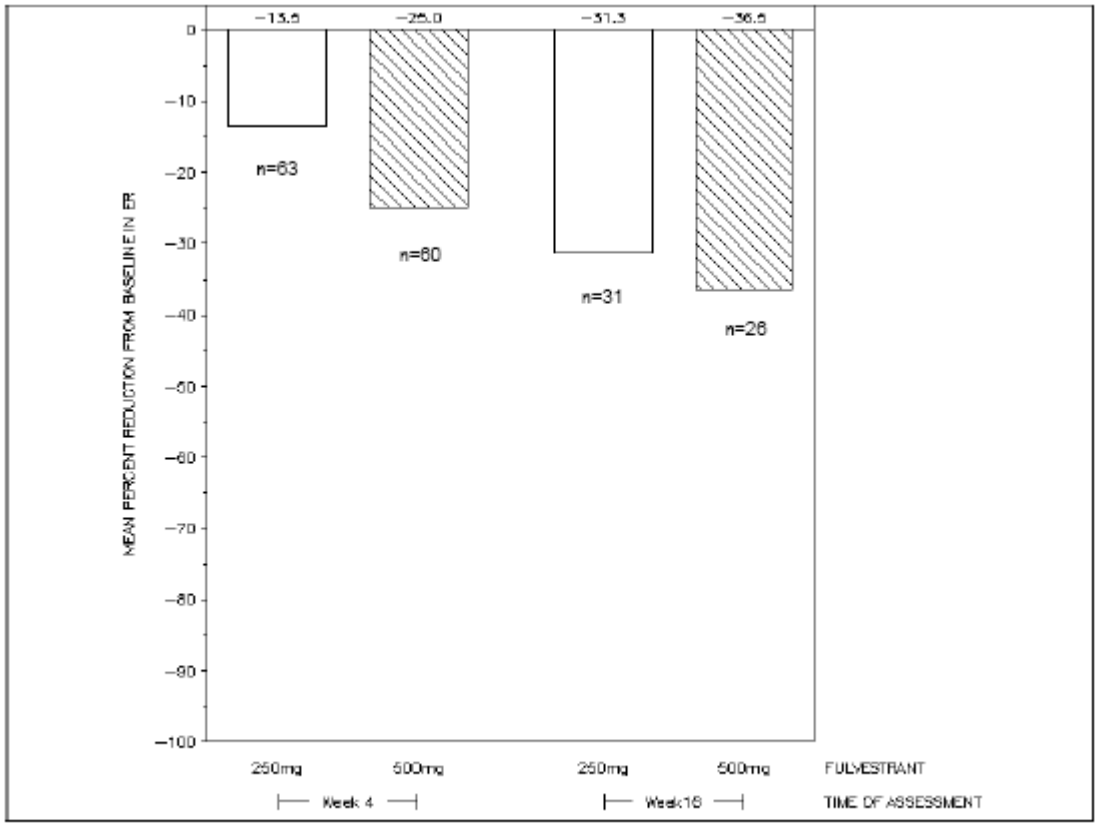
LI Labeling index.

Figure 1. Change (mean % reduction) in Ki67 LI at Weeks 4 and 16 in the NEWEST study

In conclusion it has been shown that fulvestrant 500 mg downregulates the proliferation marker Ki67, to a greater degree than fulvestrant 250 mg in breast tumours in postmenopausal neoadjuvant setting.

Estrogen receptor

Both dosages of fulvestrant reduced ER expression at Weeks 4 and 16, with greater effects seen at the 500 mg dosage. In an exploratory analysis, mean % reduction in ER expression (downregulation) at Week 4 was significantly greater for the 500 mg treatment group, compared with that for the 250 mg treatment group (–25.0% vs –13.5%, p=0.0002) (Figure 2). Correlations between change from baseline in Ki67 LI and ER index were not apparent.



ER Estrogen receptor.

Figure 2. Change (mean % reduction) in ER index at Weeks 4 and 16 in the NEWEST study

In conclusion it has been shown that fulvestrant 500 mg downregulates ER and the proliferation marker Ki67, to a greater degree than fulvestrant 250 mg in breast tumours in postmenopausal neoadjuvant setting.

Bone biomarkers

Data from the NEWEST study were the basis for the conclusions on the effect of fulvestrant on bone. A secondary objective of the NEWEST study was to compare the effects of the fulvestrant 500 mg and 250 mg regimens on three serum bone-turnover markers, i.e. bone-specific alkaline phosphatase (b-ALP), c-telopeptide type 1 collagen crosslinks (CTX-1), and procollagen type 1 amino terminal propeptide (PINP). See tables 3, 4 and 5 for results.

Table 3. b-Alkaline phosphatase (µg/L): change from baseline over time, by treatment group**:** safety population

b-Alkaline phosphatase	n	Fulvestrant 500 mg (N=107)	n	Fulvestrant 250 mg (N=101)
Baseline, mean (SD)	105	15.19 (5.72)	99	14.78 (5.13)
Mean change[a] (SD)				
At Week 4	96	–0.42 (2.60)	96	–0.14 (2.16)
At Week 8	88	–0.40 (2.78)	92	–0.44 (3.05)
At Week 12	90	–0.26 (2.40)	85	–0.01 (3.31)
At Week 16	73	–0.36 (3.22)	73	–0.15 (4.93)
LSmean change[b,c] (SE)		–0.388 (0.255)		–0.070 (0.263)
p-value[d]		0.792		

[a] From baseline.
[b] From baseline over time.
[c] From repeated-measures ANCOVA with effects for treatment, visit, and treatment*visit interactions.
[d] From repeated-measures ANCOVA on observed value at visit with effects for baseline, treatment, visit, and treatment*visit interactions.
ANCOVA Analysis of covariance. b-ALP Bone-specific alkaline phosphatase. SD Standard deviation.
SE Standard error.

Table 4. C-Telopeptide of type 1 crosslinks (ng/mL): change from baseline over time, by treatment group: safety population

CTX-1	n	Fulvestrant 500 mg (N=107)	N	Fulvestrant 250 mg (N=101)
Baseline, mean (SD)	103	0.70 (0.44)	99	0.67 (0.36)
Mean change[a] (SD)				
At Week 4	93	–0.01 (0.22)	92	+0.01 (0.20)
At Week 8	84	+0.01 (0.30)	91	+0.07 (0.23)
At Week 12	89	+0.01 (0.25)	85	+0.09 (0.25)
At Week 16	71	+0.02 (0.30)	70	+0.04 (0.25)
LSmean change[bc] (SE)		+0.005 (0.021)		+0.047 (0.022)
p-value[d]		0.893		

[a] From baseline.
[b] From baseline over time.
[c] From repeated-measures ANCOVA with effects for treatment, visit, and treatment*visit interactions.
[d] From repeated-measures ANCOVA on observed value at visit with effects for baseline, treatment, visit, and treatment*visit interactions.
ANCOVA Analysis of covariance. CTX-1 C-Telopeptide of type 1 crosslinks. SD Standard deviation.
SE Standard error.

Table 5. Procollagen type 1 amino terminal propeptide (µg/L): change from baseline over time, by treatment group: safety population

P1NP	n	Fulvestrant 500 mg (N=107)	n	Fulvestrant 250 mg (N=101)
Baseline, mean (SD)	104	52.23 (25.86)	98	51.57 (26.27)
Mean change[a] (SD)				
At Week 4	96	+0.16 (14.26)	92	+0.38 (9.82)
At Week 8	91	–0.59 (16.67)	92	–0.22 (12.68)
At Week 12	90	+0.27 (15.55)	85	+0.82 (12.83)
At Week 16	72	–0.35 (17.26)	72	+0.35 (17.82)
LSmeans change[bc] (SE)		–0.205 (1.279)		+0.247 (1.307)
p-value[d]		0.931		

[a] From baseline.
[b] From baseline over time.
[c] From repeated-measures ANCOVA with effects for treatment, visit, and treatment*visit interactions.
[d] From repeated-measures ANCOVA on observed value at visit with effects for baseline, treatment, visit, and treatment*visit interactions.
ANCOVA Analysis of covariance. P1NP Procollagen type 1 amino terminal propeptide.
SD Standard deviation. SE Standard error.

In conclusion, neoadjuvant treatment for up to 16 weeks in breast cancer patients with either Fulvestrant 500 mg or Fulvestrant 250 mg did not result in clinically significant changes in serum bone-turnover markers.

Effects on endometrium

Based on the NEWEST study the MAH proposed to add information on the effects of fulvestrant on the postmenopausal endometrium. The results are shown in table 6 below.

Table 6. Endometrial thickness: change from baseline at Week 16: safety population [a]

Endometrial thickness (mm)	n	Fulvestrant 500 mg (N=107)	n	Fulvestrant 250 mg (N=101)
Any baseline value				
Baseline, mean (SD)	83	4.76 (4.50)	74	4.89 (4.54)
Week 16, mean (SD)	46	3.46 (2.28)	44	3.93 (3.20)
Mean change (SD)	46	–1.34 (3.93)	44	–1.10 (2.99)
Median change	46	–0.15	44	0.00
Baseline value ≤5 mm[a]				
Baseline, mean (SD)	67	2.96 (1.24)	53	3.01 (1.21)
Week 16, mean (SD)	37	2.85 (1.53)	30	2.95 (1.26)
Mean change (SD)	37	–0.03 (1.45)	30	–0.18 (1.41)
Median change	37	0.00	30	0.00 0.00
LSmean change (SE)[b]		–0.027 (0.235)		–0.180 (0.261)
95% CI		–0.497 to 0.443		–0.702 to 0.342
p-value[b]		0.665		

[a] Only patients with baseline endometrial thickness ≤5 mm are included in the statistical analysis.
[b] From analysis of variance on change from baseline with effects for treatment.

In conclusion neoadjuvant treatment for up to 16 weeks in breast cancer patients treated with either Fulvestrant 500 mg or Fulvestrant 250 mg did not result in clinically significant changes in endometrial thickness, indicating a lack of agonist effect. There is no evidence of adverse endometrial effects in the breast cancer patients studied.

▪ *Clinical efficacy*

MAIN STUDY

The CONFIRM study (D66997C00002 [9238IL/0064]) is a Phase III, randomised, double-blind, multicentre study comparing two doses of the estrogen receptor (ER) antagonist fulvestrant in post-menopausal breast cancer patients with estrogen receptor positive disease, who have relapsed or progressed on prior endocrine therapy.

Methods

Study participants

The CONFIRM study included postmenopausal women with histologically/cytologically confirmed estrogen receptor positive advanced breast cancer, who had either relapsed while on adjuvant endocrine therapy (or within 12 months of its completion), or progressed on first endocrine therapy for advanced disease (including *de novo* advanced disease). Measurable disease according to RECIST criteria (Response Evaluation Criteria in Solid Tumours) or bone lesions was required, as well as baseline WHO performance status of 0-2, adequate liver function and platelet levels, and written informed consent.

Important exclusion criteria were presence of life-threatening metastatic visceral disease, more than one chemotherapy regimen for advanced disease, more than one regimen of endocrine therapy for advanced disease (not counting oophorectomy, ovarian ablation or LHRH analogue therapy), bleeding tendency/disorder or anticoagulant therapy (low molecular weight heparin allowed), and severe concomitant medical condition.

Restrictions regarding a number of concomitant treatments were also applied, including anticancer substances, radiotherapy (need for it counted as progression), bisphosphonate treatment for the prevention (but not management) of bone metastases, systemic sex hormone containing drugs, other drugs possibly affecting sex hormone status or disease response (such as systemic ketokonazole, corticosteroids and adrenocortical suppressants), and anti-platelet therapy.

Treatments

Patients received either fulvestrant 500 mg or 250 mg every 28 days. The 500 mg arm also included one extra dose on Day 14 of the first treatment cycle:

- Fulvestrant 500 mg was administered as two 5 ml intramuscular injections, one in each buttock, on Days 0, 14, 28 and every 28 (±3) days thereafter.
- Fulvestrant 250 mg was administered as two 5 ml intramuscular injections (1 fulvestrant injection plus 1 placebo injection), one in each buttock, on Days 0, 14 (2 placebo injections only), 28 and every 28 (±3) days thereafter.

Treatment continued until disease progression, unless any of the other criteria for discontinuation were met first. Upon progression, the patients were withdrawn from their randomised treatment. Discontinuation criteria were: voluntary discontinuation by the patient, safety reasons, severe non-

compliance to protocol, disease progression, patient lost to follow-up, other reason according to investigator's judgement.

Objectives

The primary objective was to compare the efficacy of fulvestrant 500 mg treatment with fulvestrant 250 mg treatment in terms of time to progression. Primary and secondary objectives are summarised in Table7.

Outcomes/endpoints

Time to Progression (TTP) was the primary endpoint. TTP was defined as the time from randomisation to the time of the earliest evidence of objective disease progression or death from any cause prior to documented progression. The definition of TTP used in this study is also commonly referred to as Progression Free Survival (PFS). TTP was assessed by objective tumour assessments every 12 weeks using RECIST criteria, except for those patients with bone only disease. For secondary objectives and the variables used to assess them see Table 7.

Table 7. Primary and secondary objectives of the CONFIRM study

Objective	**Variable**
Primary	
1. To compare the efficacy of fulvestrant 500 mg treatment with fulvestrant 250 mg treatment in terms of time to progression.	Time to Progression (TTP)
Secondary	
2. To compare the objective response rate of patients treated with fulvestrant 500 mg with the objective response rate of patients treated with fulvestrant 250 mg.	Objective Response Rate (ORR = CR + PR defined by RECIST criteria)
3. To compare clinical benefit rate of patients treated with fulvestrant 500 mg with the clinical benefit rate of patients treated with fulvestrant 250 mg.	Clinical Benefit Rate (CBR = CR + PR + SD ≥ 24 weeks defined by RECIST criteria)
4. To compare duration of response of patients treated with fulvestrant 500 mg with the duration of response of patients treated with fulvestrant 250 mg.	Duration of Response (DoR)
5. To compare the duration of clinical benefit of patients treated with fulvestrant 500 mg with the duration of clinical benefit of patients treated with fulvestrant 250 mg.	Duration of Clinical Benefit (DoCB)
6. To compare the overall survival of patients treated with fulvestrant 500 mg with the overall survival of patients treated with fulvestrant 250 mg.	Overall Survival (OS)
7. To assess the tolerability of fulvestrant 500	Frequency and Severity of Adverse Events

mg treatment compared with fulvestrant 250 mg treatment.	
8. To assess the Health Related Quality of Life (HRQoL) of patients treated with fulvestrant 500mg as compared to fulvestrant 250 mg in a subgroup of patients.	Trial Outcome Index (TOI) derived from the Functional Assessment of Cancer Therapy - Breast Cancer (FACT-B) questionnaire. Data were collected from a subgroup of patients.

For the response to last endocrine therapy before fulvestrant, patients were categorised as "responsive" if they had recurrence after 2 or more years on their last previous adjuvant endocrine therapy, or if they experienced complete response (CR), partial response (PR) or stable disease (SD) for at least 24 weeks on first line endocrine therapy for advanced cancer.

Patients were categorised as "not responsive" if they had recurrence after less than 2 years on their last previous adjuvant endocrine therapy, or if they experienced SD for less than 24 weeks or progressive disease (PD) on first line endocrine therapy for advanced breast cancer.

Safety data were reviewed by a multidisciplinary Independent Data Monitoring Committee (IDMC), including physicians and statisticians.

Sample size

A total number of 736 patients were randomised from 128 participating centres in 17 countries (Belgium, Brazil, Chile, Colombia, Czech Republic, Hungary, India, Italy, Malta, Mexico, Poland, Russia, Slovakia, Spain, USA, Ukraine and Venezuela) between 8 February 2005 and 31 August 2007.

Data cut-off date was 28 February 2009.

Randomisation method

Patients who fulfilled the eligibility criteria were randomised into the study 1:1 to receive either fulvestrant 500 mg (including one extra dose on the first Day 14) or 250 mg every 4 weeks, according to a computer generated randomisation schedule. Patients were allocated treatment in balanced blocks.

Blinding

All study personnel were unaware of the randomised treatment until all decisions on the quality of data from all patients had been made and documented. The single-dose pre-filled syringes supplied for the injections of active study drug and placebo, respectively, looked identical. Both contained 5 ml of castor oil based solution with /without 250 mg of fulvestrant.

Statistical methods

The primary analysis for the primary endpoint TTP, was an unadjusted log-rank test. Two-sided tests were performed.

The secondary analysis was performed using a Cox proportional hazard model, adjusted for treatment and six other predefined baseline covariates:

- Age (≤ 65 years vs. >65)
- Response to last therapy received prior to fulvestrant (recurrence vs. progression)
- Receptor status at diagnosis (both ER+ and PgR+ vs. ER+ and PgR other)
- Visceral involvement (Yes vs. No)

- Last therapy received prior to fulvestrant (Aromatase Inhibitor vs. Anti-Estrogen Therapy)
- Measurable disease (Yes vs. No)

The secondary endpoints were analysed as follows:

- OS was analysed by an unadjusted log-rank two-sided test.

- ORR and CBR were analysed using a logistic regression model with treatment factor only.

- DoR and DoCB were analysed in those patients who received an OR or CB, respectively.

- Health related quality of life (HRQoL) was studied using a longitudinal model including treatment and other covariates.

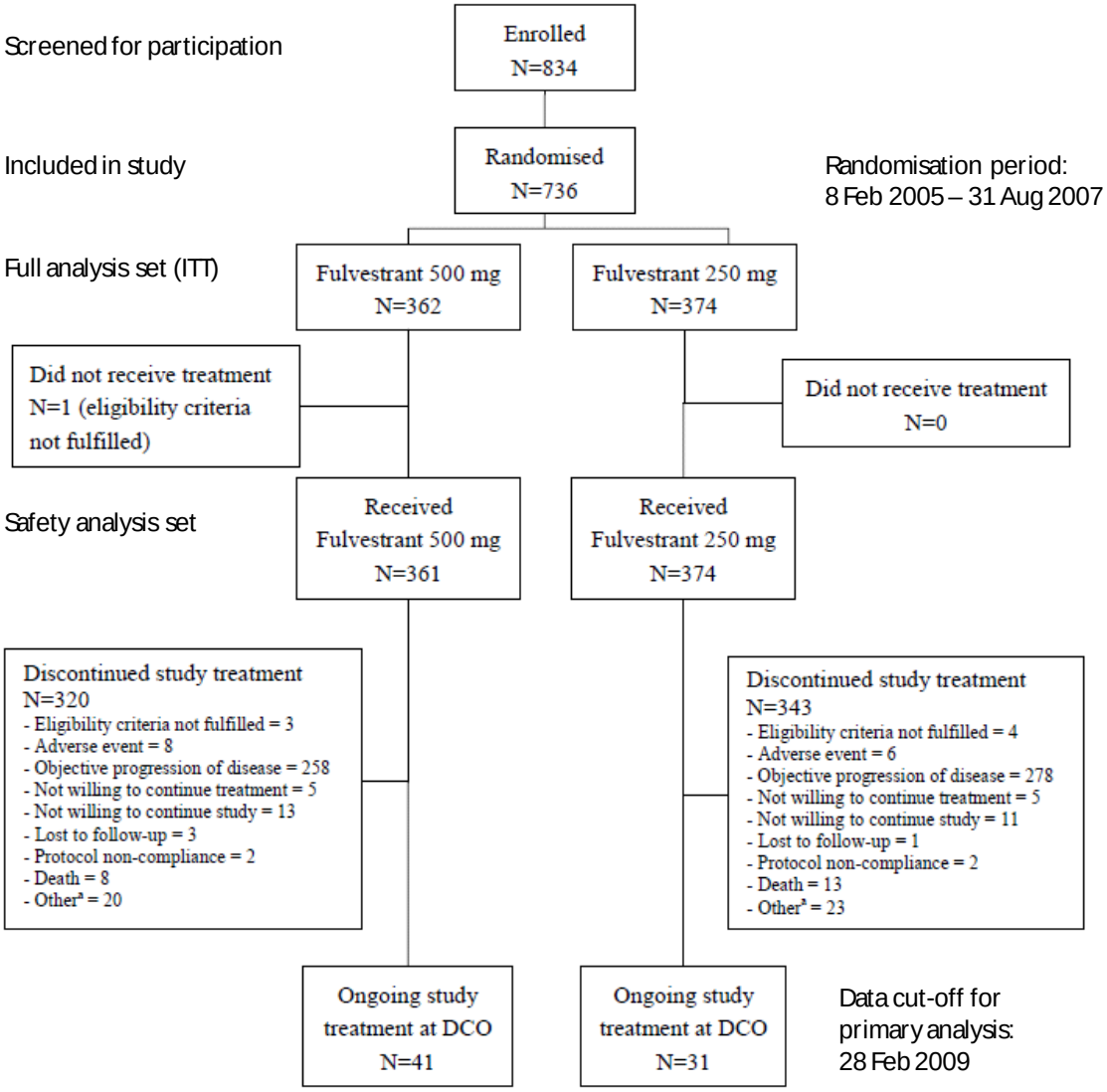
An additional analysis of Expected duration of response (EDoR) and Expected duration of clinical benefit (EDoCB) was performed by fitting a log-normal distribution to the durations. The EDoR/EDoCB is calculated based on all patients and not only those who responded. The EDoR/EDoCB gives the average probability of being in response/clinical benefit for all patients, thereby allowing formal and unbiased comparison of treatments for DoR/DoCB.

Efficacy and HRQoL endpoints were analysed according to the randomised treatment, using the Full Analysis Set (FAS), and the subset of FAS who took part in HRQoL registration. Objective response was analysed in the Evaluable for Response Set (ERS), another subset of FAS. Safety endpoints were analysed according to the treatment actually received, using the Safety Analysis Set. The primary endpoint was also analysed in the Per Protocol Set (PPS), including only those patients who received treatment and did not have any important protocol deviations or violations.

No interim analyses were performed in this study.

Results

Participant flow



Recruitment

Patients were "enrolled" after signing the Informed Consent form and subsequently screened for the study. Eligible patients were then randomised into the study. Recruitment dates and numbers of patients are shown in the participant flow chart above.

Before start of each new treatment cycle physical examination was performed and patients were assessed with regard to adverse events, concomitant therapy, and quality of life (the latter only in a subgroup of patients). Adverse events and concomitant therapy were followed until 8 weeks after last injection.

Laboratory assessments (haematology and biochemistry) were performed before treatment cycles 1, 2 and 4 (week 0, 4 and 12) and at 12 week intervals thereafter.

Tumour assessments, using the same methodology each time and according to RECIST criteria, were performed every 12 weeks. When an objective response of CR or PR was found, a repeated imaging was performed 4 weeks thereafter.

After progression, patients were followed with regard to survival every 12 weeks, and details of type of first subsequent systemic breast cancer treatment and response thereon.

Conduct of the study

Important protocol deviations occurred in 48 patients in the fulvestrant 500 mg treatment arm and 59 in the fulvestrant 250 mg arm, leaving 314 and 315 patients, respectively, evaluable for Per Protocol analysis.

These deviations included eligibility criteria not fulfilled (n = 26+29 in the 500 mg and 250 mg mg treatment groups, respectively), fulvestrant never administered (n = 1+0), 2 or more consecutive fulvestrant injections missed (n = 1+1), use of prohibited concomitant pharmaceuticals (sex hormones, n = 2+0), non-compliance with unblinding procedures (n = 2+3), screening RECIST assessments not performed within specified time window or not at all (n = 18 + 38).

Baseline data

Baseline tumour and disease characteristics are shown in Tables 8-11. The median patient age was approximately 61 years, median weight 69 kg, and 96% were of Caucasian ethnicity in both treatment groups (not shown).

Table 8. Baseline tumour and disease characteristics: Full Analysis Set

Baseline characteristic	Number (%) of patients	
	Fulvestrant 500 mg N=362	Fulvestrant 250 mg N=374
Hormone receptor status (at primary diagnosis)		
ER+ve	362 (100.0)	374 (100.0)
PgR+ve	241 (66.6)	266 (71.1)
PgR-ve	92 (25.4)	96 (25.7)
PgR unknown	29 (8.0)	12 (3.2)
Disease characteristics (at randomisation)		
Locally advanced breast cancer only	4 (1.1)	11 (2.9)
Metastatic disease	358 (98.9)	363 (97.1)
Any visceral disease	239 (66.0)	232 (62.0)
Bone only	87 (24.0)	77 (20.6)
Measurable disease		
No	122 (33.7)	113 (30.2)
Yes	240 (66.3)	261 (69.8)
Histology type		
Adenocarcinoma	30 (8.3)	41 (11.0)
Undifferentiated carcinoma	6 (1.7)	7 (1.9)
Infiltrating ductal carcinoma	221 (61.0)	239 (63.9)
Infiltrating lobular carcinoma	55 (15.2)	46 (12.3)
Other	50 (13.8)	41 (11.0)
Tumour grade		
Well differentiated	24 (6.6)	30 (8.0)
Moderately differentiated	129 (35.6)	125 (33.4)
Poorly differentiated	73 (20.2)	81 (21.7)
Undifferentiated	1 (0.3)	5 (1.3)
Unassessable	21 (5.8)	13 (3.5)
Not done	114 (31.5)	120 (32.1)

Table 9. Previous cancer therapy Full Analysis Set

Previous therapy	Number (%) of patients	
	Fulvestrant 500 mg N=362	Fulvestrant 250 mg N=374
Adjuvant therapy[a]		
Endocrine therapy	231 (63.8)	249 (66.6)
AI	52 (14.4)	55 (14.7)
AO	202 (55.8)	217 (58.0)
Chemotherapy	185 (51.1)	200 (53.5)
Radiotherapy	214 (59.1)	206 (55.1)
Advanced disease therapy[a]		
Endocrine therapy	173 (47.8)	182 (48.7)
AI	101 (27.9)	108 (28.9)
AO	72 (19.9)	75 (20.1)
Chemotherapy	81 (22.4)	69 (18.4)
Radiotherapy	69 (19.1)	102 (27.3)
Last endocrine therapy received		
AI	152 (42.0)	161 (43.0)
AO	210 (58.0)	213 (57.0)

[a] Categories are not mutually exclusive.
AO:Antioestrogen; AI:Aromatase inhibitor.

Table 10. Relapsed or progressed on previous endocrine cancer therapy: Full Analysis Set

Relapsed/progressed	Number (%) of patients	
	Fulvestrant 500 mg N=362	Fulvestrant 250 mg N=374
During adjuvant endocrine therapy	175 (48.3)	169 (45.2)
0 to 12 months after completion of adjuvant endocrine therapy	16 (4.4)	27 (7.2)
>12 months after completion of adjuvant endocrine therapy and after progression on endocrine therapy for advanced breast cancer	36 (9.9)	52 (13.9)
Progressed on an endocrine therapy given as first treatment for patients with *de novo* advanced breast cancer	130 (35.9)	125 (33.4)
Other[a]	5 (1.4)	1 (0.3)
Number of prior endocrine regimens		
0	1 (0.3)[b]	0
1	318 (87.8)	317 (84.8)
2	43 (11.9)	57 (15.2)
Mean time from diagnosis to randomisation, months (range)	60.5 (0.9–338.6)	59.9 (1.9-418.4)

[a] Patients did not meet inclusion or exclusion criteria
[b] This patient was entered into the study due to an error at the study site
Mean time from diagnosis to randomisation in months assumes 1 month = 30.4375 days (365.25 days / 12 months).

Table 11. Response to last endocrine therapy: Full Analysis Set

Response to last prior endocrine therapy	Number (%) of patients	
	Fulvestrant 500 mg N=362	Fulvestrant 250 mg N=374
Responsive[a]	229 (63.3)	249 (66.6)
Not responsive[b]	133 (36.7)	125 (33.4)

[a] Defined as patients who experienced recurrence after ≥2 years on adjuvant endocrine therapy and/or patients who received clinical benefit (CR, PR or SD ≥24 weeks) from first-line therapy for advanced disease.

[b] Defined as patients who experienced recurrence after <2 years on adjuvant endocrine therapy and patients who received no clinical benefit (SD <24 weeks, PD) from first-line therapy for advanced disease. Patients who could not be classified were also included in this category.

Numbers analysed

Five analysis sets were used (Table 12 and participant flow chart):

- The Full Analysis Set (FAS) included all randomised patients and compared the treatment groups on the basis of randomised treatment, regardless of treatment actually received (Intention to treat).
- The Safety Analysis Set included all randomised patients who received at least one dose of the study treatment and compared the treatment groups on the basis of treatment actually received.
- The Per Protocol Set (PPS) included all treated patients who did not have any important protocol deviations or violations. Exclusion from the PPS was determined by a blinded medical review of protocol deviations. (See below regarding type of deviations.)
- The Evaluable for Response Set (ERS) included all randomised patients (regardless of whether any study treatment was received) for whom objective response could be assessed. The reason for exclusion from Evaluable for Response Set was no target lesion at baseline.
- Additionally, HRQoL was analysed in a subset of the FAS consisting of women from English and Spanish speaking countries, Italy and Brazil since the FACT-B questionnaire used to assess this endpoint was readily available in relevant languages for these countries.

Table 12. Analysis sets

	Fulvestrant 500 mg group, (n)		Fulvestrant 250 mg group, (n)	
Full Analysis Set (ITT)	362		374	
Evaluable for Response Set	240		261	
*No target lesion at baseline**		*122*		*113*
Safety Analysis Set	361		374	
Per Protocol Set	314		315	
HRQoL subset of FAS	72		73	

*This is not an analysis set

Outcomes and estimation

Primary endpoint- TTP

The results for the primary analysis of TTP are shown in Figure 3 and Table 13.

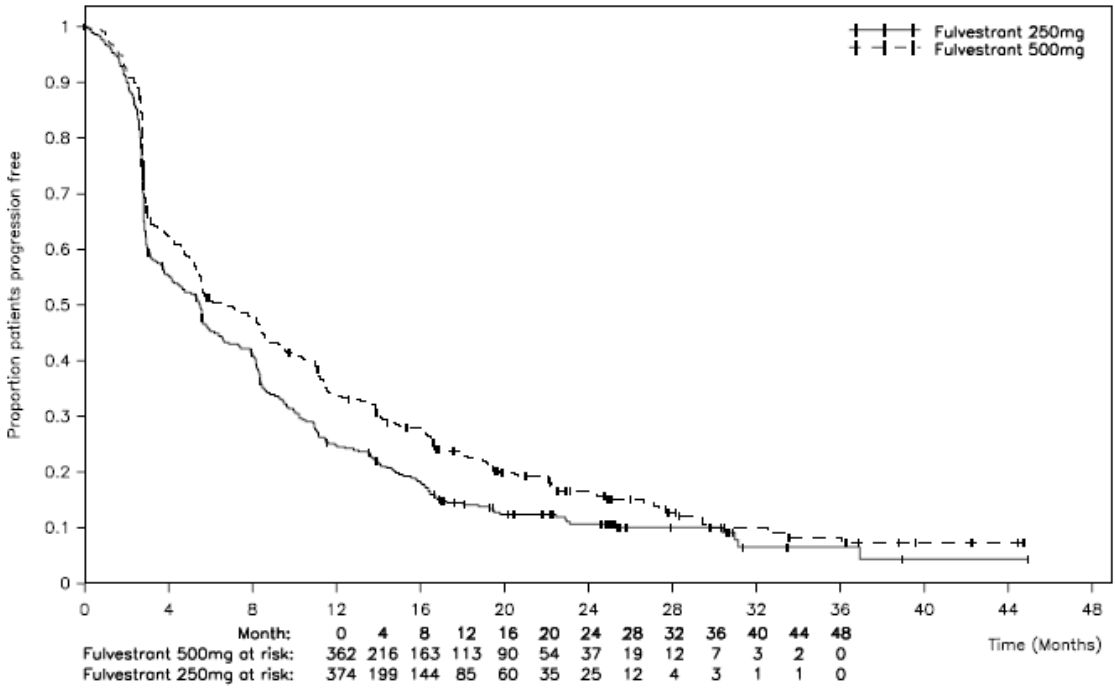


Figure 3. Kaplan-Meier plot of Time to Progression: Full Analysis Set (ITT)

Secondary analyses of the primary endpoint TTP, using the Cox proportional hazards regression analysis adjusted for treatment and the 6 pre-specified covariates are shown in Table 13. In addition sub-group analyses (pre-specified) unadjusted for baseline covariates are shown in Figure 4.

Table 13. TTP analyses in all patients and in pre-specified sub-groups.

Group analysed		Fulvestrant 500		Fulvestrant 250		500 mg vs. 250 mg		
		n	Median TTP	n	Median TTP	HR	95% CI	p
All patients	1' Unadjusted	362	6.5	374	5.5	0.80	0.68 – 0.94	0.006
All patients	2' Adjusted*	362	6.5	374	5.5	0.78	0.67 – 0.92	0.003
Receptor status	ER+, PgR+	241	7.0	266	5.5	0.85	0.70 – 1.02	0.086
	ER+, PgR-/unknown	121	6.5	108	5.4	0.69	0.52 – 0.92	0.013
Visceral involvement	No	123	11.1	142	6.5	0.74	0.56 – 0.98	0.035
	Yes	239	5.2	232	4.1	0.82	0.67 – 1.00	0.045

Last endocrine response	Responsive	229	7.0	249	6.6	0.85	0.70 – 1.04	0.116
	Non-responsive	133	5.8	125	2.9	0.70	0.53 – 0.92	0.010
Measurable disease	No	112	8.5	113	5.6	0.74	0.56 – 0.99	0.045
	Yes	240	5.6	261	5.3	0.84	0.69 – 1.01	0.068
Age	< 65 years	218	5.6	226	3.9	0.77	0.63 – 0.95	0.013
	≥ 65 years	144	10.4	148	8.1	0.85	0.65 – 1.10	0.207
Last prior endocrine therapy	**Aromatase inhibitor**	**152**	**5.4**	**161**	**4.1**	**0.85**	**0.67 – 1.08**	**0.195**
	Anti-estrogen	**210**	**8.6**	**213**	**5.8**	**0.76**	**0.62 – 0.94**	**0.013**

*= Cox proportional hazards regression model was used for the secondary analysis. Na= not applicable

Secondary endpoints

The main efficacy results for all secondary endpoints except HRQoL are summarised in Table 14.

Table 14. Summary of efficacy results for the main secondary outcome variables

Outcome variable	Analysis set	500 mg Faslodex	250 mg Faslodex	HR (95% CI)	OR (95% CI)	Ratio of EDoR* or EDoCB* (95% CI)	p-value
OS	FAS	25.1 months	22.8 months	0.84 (0.69-1.03)	_	_	0.091
ORR	ERS	13.8 %	14.6 %	_	0.94 (0.57 - 1.55)	_	0.795
CBR	FAS	45.6 %	39.6 %	_	1.28 (0.95-1.71)	_	0.100
DoR	ERS	19.4 months	16.4 months	_	_	0.89 (0.48-1.67)	0.724
DoCB	FAS	16.6 months	13.9 months	_	_	1.36 (1.07-1.73)	0.013
				HR < 1 favours 500 mg	OR > 1 favours 500 mg	Ratio > 1 favours 500 mg	< 0.05 is statistically significant

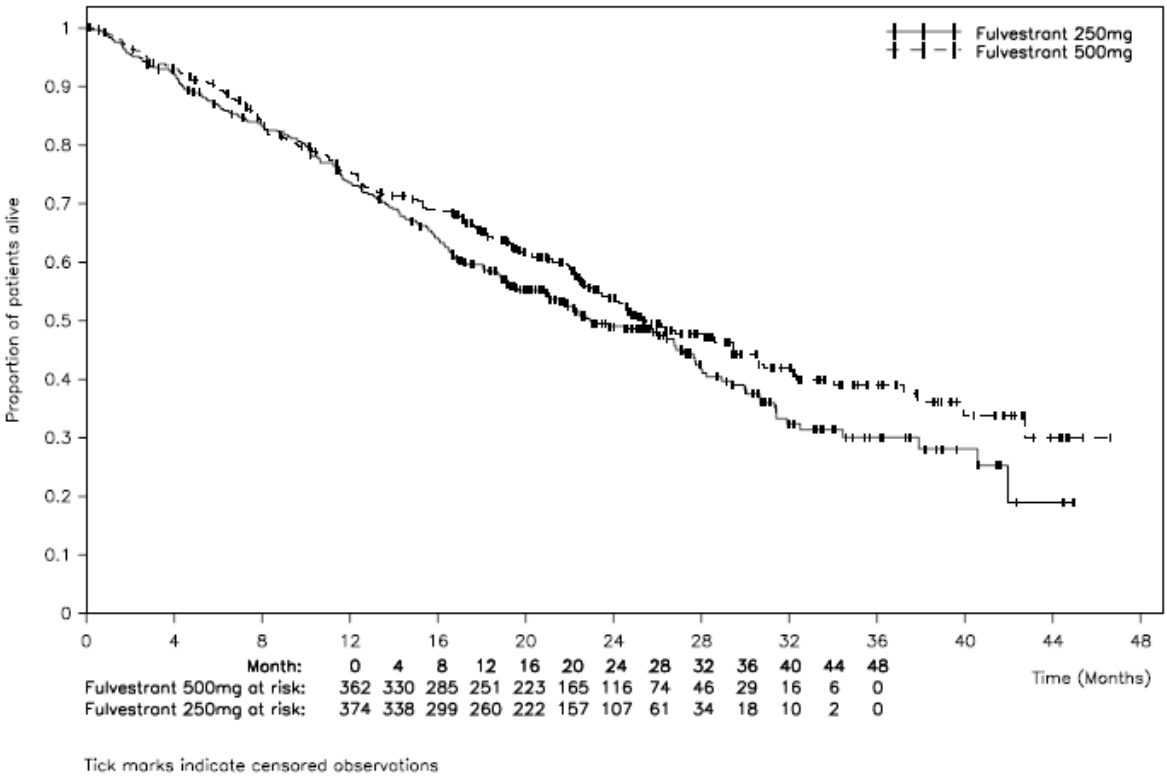
CBR = Clinical benefit rate, DoCB = Duration of clinical benefit, DoR = Duration of response, ERS =Evaluable for response set, FAS = Full analysis set, EDoCB = Expected duration of clinical benefit, EDoR = Expected duration of response, OR = Objective response (best response according to RECIST), ORR = Objective response rate, OS = Overall survival. * Please see Statistical methods page 8 for explanation.

Overall survival

At data cut-off (DCO) 175 patients (48 %) in the 500 mg treatment group and 203 (54 %) of the patients in the 250 mg arm had died. The overall survival analysis showed a median time to death of 25.1 and 22.8 months in the two treatment groups, respectively (see Table 14). A Kaplan-Meier plot is shown in Figure 4.

The hazard ratio for death in the unadjusted log-rank analysis was 0.84 (95% confidence interval: 0.69 – 1.03), p= 0.091. A retrospective analysis of OS, adjusted for the 6 predefined baseline covariates, showed similar results: HR 0.81 (95% confidence interval: 0.66 – 0.99), p= 0.037.

Figure 4. Overall survival: Full Analysis Set



Quality of Life

A total of 145 patients completed a baseline FACT-B questionnaire, which represented 82% of the 176 patients randomised in the countries that participated in HRQoL collection.

The on-treatment HRQoL in both treatment arms was good (mean TOI score of approximately 60 out of 92). Patients treated with fulvestrant 500 mg had a similar on-treatment HRQoL to patients treated with fulvestrant 250 mg and there were no statistically significant differences between the two treatment groups in terms of change in on treatment HRQoL as measured by both the TOI and FACT-B score, although there was a numerical advantage in TOI in favour of fulvestrant 500 mg.

Effect of fulvestrant after failure on anti-estrogen or aromatase inhibitor therapy

In comparison, the corresponding hazard ratio for TTP in the subgroup of patients who progressed/relapsed during ongoing aromatase inhibitor (AI) or anti-estrogen (AO) therapy was 0.80 with 2-sided 95% CI: 0.68; 0.94 (p= 0.006). The effect of fulvestrant after aromatase inhibitor versus after antiestrogen therapy was also analysed at the level of secondary endpoints (see Table 15).

Table 15. Comparison of exploratory analyses of secondary endpoints in CONFIRM by last endocrine therapy subgroup.

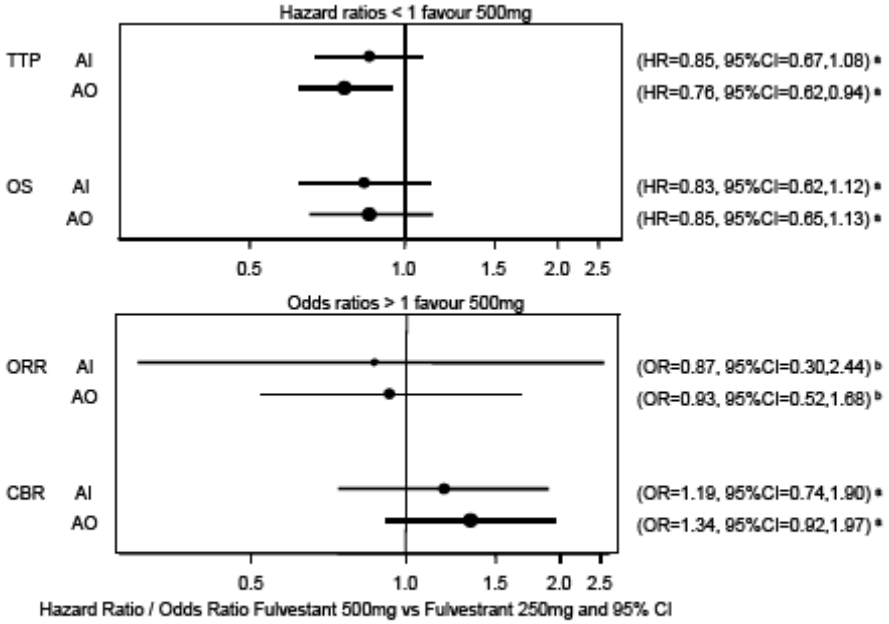
Endpoint (Analysis set)	Antioestrogen subgroup		Aromatase inhibitor subgroup		Overall	
	F500	F250	F500	F250	F500	F250
Objective response (Evaluable for Response Set)						
N	144	152	96	109	240	261
ORR (%)	18.1	19.1	7.3	8.3	13.8	14.6
Clinical benefit (Full Analysis Set)						
N	210	213	152	161	362	374
CBR (%)	52.4	45.1	36.2	32.3	45.6	39.6
Overall Survival (Full Analysis Set)						
N	210	213	152	161	362	374
Median (months)	27.9	25.9	24.1	20.8	25.1	22.8
Hazard ratio	0.85		0.83		0.84	

F500:Fulvestrant 500 mg; F250:Fulvestrant 250 mg.

The types of response differed between the AI and the AO groups, with 2.8 % complete responses (CR) in the 500 mg group and 0.7% in the 250 mg group following AO, compared with no CRs following AI. The rates of partial response (PR) were also higher following AO: 15.3% and 18.4% in the 500 mg and 250 mg groups, respectively, compared with 7.3% and 8.3% following AI. The rates of stable disease in the Evaluable for Response Set were similar following AO and AI; AO, 41.0% and 39.5%, AI, 40.6% and 39.4%, in the 500 mg and 250 mg groups, respectively.

The treatment effect of fulvestrant 500 mg vs. 250 mg was consistent in patients who had relapsed/progressed on prior aromatase inhibitor therapy vs. antiestrogen therapy (see figure 5).

Figure 5. Forest plot of analyses of CONFIRM data by last endocrine therapy subgroup



[a] CONFIRM Full Analysis Set.
[b] CONFIRM Evaluable for Response Set.
AI:Aromatase inhibitor; AO:Antioestrogen; HR:Hazard ratio; OR:Odds ratio; CI:Confidence interval.

The interaction between prior endocrine therapy and the fulvestrant treatment effect was tested for the efficacy endpoints of CONFIRM (TTP, OS, ORR, and CBR). For each endpoint, the interaction test was non-significant with p-values ≥0.3.

In response to CHMP questions and in order to further increase the stringency regarding aromatase inhibitor resistance, exploratory analyses of TTP and ORR were performed which excluded the patients who relapsed 0-12 months after the completion of adjuvant therapy. Thus only patients who progressed during ongoing endocrine therapy were included. Analyses of patients subdivided with regard to failure in the adjuvant or metastatic settings were also performed (Tables 16 and 17).

Table 16. Exploratory subgroup analyses of TTP in patients who progressed/relapsed during ongoing aromatase inhibitor therapy: CONFIRM Full Analysis Set

Unadjusted log rank analysis including treatment factor only	Hazard ratio[a]	2-sided 95% CI
Patients who relapsed/progressed during ongoing aromatase inhibitor therapy in the adjuvant/advanced disease setting[b]	0.83	0.65, 1.07
Patients who relapsed during ongoing adjuvant aromatase inhibitor therapy[b]	0.86	0.57, 1.31
Patients who progressed during ongoing aromatase inhibitor therapy for advanced disease	0.82	0.60, 1.11

[a] A hazard ratio >1 indicates fulvestrant 500 mg is associated with a shorter time to disease progression than fulvestrant 250 mg; a hazard ratio <1 indicates fulvestrant 500 mg is associated with a longer time to disease progression than fulvestrant 250 mg.

[b] Excluding patients who relapsed 0 to 12 months after completion of adjuvant aromatase inhibitor therapy, ie, patients who did not relapse during ongoing aromatase inhibitor therapy.

Table 17. Exploratory subgroup analyses of ORR in patients who progressed/relapsed during ongoing aromatase inhibitor therapy: CONFIRM Evaluable for Response Set

	ORR (patients with objective response/total)	
	Fulvestrant 500 mg	Fulvestrant 250 mg
Patients who relapsed/progressed during ongoing aromatase inhibitor therapy in the adjuvant/advanced disease setting[a]	7.4% (7/95)	8.7% (9/104)
Patients who relapsed during ongoing adjuvant aromatase inhibitor therapy[a]	6.7% (2/30)	10.3% (3/29)
Patients who progressed during ongoing aromatase inhibitor therapy for advanced disease	7.7% (5/65)	8.0% (6/75)

[a] Excluding patients who relapsed 0 to 12 months after completion of adjuvant aromatase inhibitor therapy, ie, patients who did not relapse during ongoing aromatase inhibitor therapy.

The MAH evaluated potential differences between the endocrine subgroups at baseline that may have contributed to the difference in the efficacy in these subgroups. The results are provided in Table 18:

Table 18. Summary of baseline imbalances in the endocrine subgroups (post-AO vs post-AI): CONFIRM full analysis set.

Demographic/baseline characteristic	Post AO patients N=423	Post AI patients[a] N=313
Age (years)		
Mean (SD)	58.4 (11.75)	64.2 (10.81)
Median (range)	58.0 (23 to 91)	65.0 (31 to 90)
Best response to first endocrine therapy for advanced disease		
No endocrine therapy for advanced disease	277 (65.5)	104 (33.2)
Received endocrine therapy for advanced disease	146 (34.5)	209 (66.8)
Complete response	12 (8.2)[b]	7 (3.3)[b]
Partial response	19 (13.0)[b]	53 (25.4)[b]
Stable disease	72 (49.3)[b]	114 (54.5)[b]
Other[c]	43 (29.5)[b]	35 (16.7)[b]
Responsive to last endocrine therapy		
Yes	252 (59.6)	226 (72.2)
No	171 (40.4)	87 (27.8)
Number of previous endocrine therapies		
0[d]	0	1 (0.3)
1	407 (96.2)	228 (72.8)
2	16 (3.8)	84 (26.8)
Time from initial breast cancer diagnosis to randomisation (days)		
Median (range)	1146.0 (28 to 10307)	1491.0 (62 to 12735)
Tumour grade		
Well differentiated	34 (8.0)	20 (6.4)
Moderately differentiated	153 (36.2)	101 (32.3)
Poorly differentiated	74 (17.5)	80 (25.6)
Undifferentiated	4 (0.9)	2 (0.6)
Other[e]	158 (37.4)	110 (35.1)

[a] There were 2 patients whose previous endocrine therapy was missing or was not an AI/AO. Consistent with definition of the endocrine subgroups (AI/AO) in the CONFIRM SAP, these patients are included in the "AI" category in this table.
[b] Percentage calculated using the number of patients who received endocrine therapy for advanced disease as the denominator.
[c] Includes non-evaluable, no response and missing.
[d] Violated inclusion/exclusion criteria.
[e] Included un-assessable and not done.

In addition the MAH provided additional data to evaluate the differences between the endocrine subgroups in the prior lines of endocrine therapies and the impact of these differences on the efficacy of fulvestrant in the endocrine subgroups in CONFIRM (see Tables 19 and 20).

Table 19. Relapsed or progressed on previous endocrine cancer therapy: CONFIRM Full Analysis Set

Relapsed/progressed	Number (%) of patients	
	Progressed/relapsed on an AO N=423	Progressed/relapsed on an AI[a] N=313
During adjuvant endocrine therapy	238 (56.3)	106 (33.9)
0 to 12 months after completion of adjuvant endocrine therapy	36 (8.5)	7 (2.2)
Total relapsed in the adjuvant setting	**274 (64.8)**	**113 (36.1)**
>12 months after completion of adjuvant endocrine therapy and after progression on endocrine therapy for advanced breast cancer	16 (3.8)	72 (23.0)
Progressed on an endocrine therapy given as first treatment for patients with *de novo* advanced breast cancer	130 (30.7)	125 (39.9)
Total progressed in the advanced setting	**146 (34.5)**	**197 (62.9)**
Other[b]	3 (0.7)	3 (1.0)

[a] There were 2 patients whose previous endocrine therapy was missing or was not an AI/AO. Consistent with definition of the endocrine subgroups (AI/AO) in the CONFIRM SAP, these patients are included in the "AI" category in this table and the other tables in this response.
[b] Patients did not meet inclusion or exclusion criteria
AI:Aromatase inhibitor; AO:Antioestrogen.
Data derived from Table 11.1.12.1 in the CONFIRM CSR.

Table 20. Analysis of TTP overall and by prior line of endocrine therapy: CONFIRM Full Analysis Set

Relapsed/progressed	Median (months)		Hazard ratio (95% CI)
	Fulvestrant 500 mg	Fulvestrant 250 mg	
Primary analysis (All patients, unadjusted log rank test)	(N=362) 6.5	(N=374) 5.5	0.80 (0.68 to 0.94); p=0.006
In the adjuvant setting[b]	(N=191) 5.6	(N=196) 4.2	0.80 (0.64 to 1.00)
Patients who relapsed on an AO	(N=136) 8.3	(N=138) 4.7	0.76 (0.59 to 0.99)
Patients who relapsed on an AI	(N=55) 3.5	(N=58) 3.6	0.92 (0.61 to 1.37)
In the advanced setting[c]	(N=166) 7.9	(N=177) 6.3	0.80 (0.64 to 1.02)
Patients who relapsed on an AO	(N=72) 11.4	(N=74) 8.3	0.77 (0.53 to 1.12)
Patients who relapsed on an AI	(N=94) 5.6	(N=103) 5.0	0.82 (0.61 to 1.11)

[a] The 6 patients who were categorised as 'Other' (see Table 1) were not included in this analysis.
[b] Includes patients who relapsed during adjuvant therapy and patients who relapsed 0 to 12 months after completion of adjuvant endocrine therapy.
[c] Includes patients who progressed >12 months after completion of adjuvant endocrine therapy and after progression on endocrine therapy for advanced breast cancer and patients who progressed on an endocrine therapy given as first treatment for de novo advanced breast cancer.
Hazard ratio <1 favours fulvestrant 500 mg.
N: Number of patients; CI:Confidence interval; AI:Aromatase inhibitor; AO:Antioestrogen.

The MAH was also requested to provide further data on the efficacy of fulvestrant in the following subgroups of subjects with AI as last endocrine therapy in CONFIRM: a) different prior lines of endocrine therapies (e.g. AI vs. AO followed by AI) and b) different AI regimen as last therapy (non-steroidal AI vs. exemestane). The analysis for TTP is summarised in Table 21.

Table 21. Analysis of TTP by different prior lines of therapy and by different AI regimen as last endocrine therapy: CONFIRM Full Analysis Set

Relapsed/progressed	Median (months)		Hazard ratio (95% CI)
	Fulvestrant 500 mg	Fulvestrant 250 mg	
Different prior lines of endocrine therapies[a]			
Endocrine therapy prior to fulvestrant = AI only	(N=95) 5.6	(N=89) 4.6	0.91 (0.66 to 1.26)
Endocrine therapy prior to fulvestrant = AO followed by AI	(N=56) 5.0	(N=68) 3.6	0.84 (0.58 to 1.22)
Different AI regimen as last therapy[b]			
Endocrine therapy prior to fulvestrant = non-steroidal AI	(N=140) 5.3	(N=147) 4.5	0.88 (0.69 to 1.13)
Endocrine therapy prior to fulvestrant = steroidal AI	(N=11) 5.6	(N=12) 3.0	0.63 (0.26 to 1.54)

[a] There were 5 patients in the post-AI subgroup in Table 1 (n=313) who did not fit into the 'AI only' and 'AO followed by AI' categories identified by the CHMP in Question 2 (eg, patients who received an AO in combination with a progestin as adjuvant therapy then an AI as first therapy for advanced disease).
[b] There were 3 patients in the post-AI subgroup in Table 1 (n=313) who did not fit into the 'steroidal AI' and 'non-steroidal AI' categories identified by the CHMP in Question 2 (eg, patients who relapsed on 'other' endocrine therapy but were included in the post-AI subgroup, as detailed in footnote a of Table 1).
Hazard ratio <1 favours fulvestrant 500 mg.
HR:Hazard ratio; CI:Confidence interval.

The relevance of the evidence of efficacy demonstrated in patients failing antiestrogen to patients failing aromatase inhibitors was also discussed. The prognosis (in terms of TTP, ORR and CBR) observed in CONFIRM was worse for patients who have failed on an AI compared to patients who have failed on an AO (see Table 22).

Table 22: Efficacy data based on the last prior endocrine therapy.

Efficacy endpoint	Last prior endocrine therapy	Total (fulvestrant 250 mg and fulvestrant 500 mg groups combined)
Time to progression, median (months)	Antioestrogen	8.1
	Aromatase inhibitor	5.1
Clinical benefit rate, %	Antioestrogen	48.7
	Aromatase inhibitor	34.2
Objective response rate, %	Antioestrogen	18.6
	Aromatase inhibitor	7.8

SUPPORTIVE STUDIES

Phase II FINDER studies

The data from the FINDER studies described below refer to the two treatment arms relevant for the comparison with CONFIRM.

The median age in FINDER1 was 61years in both the 500 mg and the 250 mg treatment arms, respectively; median weight was 52 and 55 kg, and ethnicity was 100% Japanese.

In FINDER2 the median age was 67 and 63 years in the 500 mg and the 250 mg treatment groups, respectively. The weight differed considerably from the Japanese study, with median weights at 71 and 68 kg in the two treatment groups, respectively. Ethnicity was 98% Caucasian.

In FINDER1 the patients in the 500 mg group were more heavily pre-treated with chemotherapy (70%) and radiotherapy (45%) than those in the 250 mg group (56% and 33%, respectively).

Similar proportions of the patients who had received prior aromatase inhibitor therapy were seen in FINDER2 and FINDER1, but different drugs were used. Letrozole was not used in FINDER1.

Last prior endocrine therapy was an aromatase inhibitor in approximately 80% of both treatment arms in FINDER1, and 76 vs. 66% in the 500 mg vs. 250 mg arms in FINDER2.

The expected proportion of patients with moderately differentiated > poorly differentiated > well differentiated tumours which was present in CONFIRM was also present in both treatment arms of FINDER1, but not in FINDER2 where the 250 mg group had a higher proportion than expected of patients with poorly differentiated tumours (34% vs. 31% moderately differentiated).

All patients were ER positive and 2/3 of the patients were PgR positive in both studies (as in CONFIRM).

Metastatic disease was present in 99% of patients in FINDER1 and 97% in FINDER2 (98% in CONFIRM). The presence of visceral disease was lower in FINDER1 (58%) compared with FINDER2 (76%) and CONFIRM (64%).

Baseline data are similar to the main study CONFIRM, with a few exceptions including (among others) ethnicity and weight in FINDER1, and a higher frequency of aromatase inhibitor as last prior endocrine therapy in both FINDER studies compared with CONFIRM.

The primary objective of the two FINDER studies was ORR, which was a secondary objective in the CONFIRM study.

The overall level of objective response and clinical benefit was similar in all three studies. None of the studies showed statistically significant differences between treatment arms. No difference in ORR or CBR was seen between the two treatment arms in FINDER1. FINDER2 showed a numerical difference in favour of the 500 mg regimen for both ORR and CBR, whereas in CONFIRM a relevant numerical difference was seen only for CBR, however not statistically significant.

Time to progression (TTP) was a secondary objective in the FINDER studies and primary objective in CONFIRM. Kaplan-Meier curves for TTP are shown in Figure 5. The TTP data is based on 84% of patients having progressed in the CONFIRM study, compared with 66% and 71% in FINDER1 and 2, respectively. The definition of TTP is equivalent to Progression-Free Survival (PFS) in all three studies.

Additional supportive studies apart from the main study (CONFIRM) and FINDER1, FINDER2 and NEWEST described above were submitted in support of the application (see Table 23).

Table 23. Supportive studies in the present variation

Study acronym and number	**Phase**	**Study design**	**Indication/ Setting [a]**	**Objectives (Primary endpoint)**	**Treatment groups**	**Number [b] of randomised patients**
FIRST D6995C00006	II	Randomised, open label, parallel group, multicentre	First line treatment of metastatic breast cancer	Efficacy and Safety (CBR)	Fulvestrant 500 mg Anastrozole 1 mg	101 103
9238IL/0020 Pivotal for	III	Randomised, open-label,	Advanced breast cancer after	Efficacy and Safety	Fulvestrant 250 mg	219

registration		parallel group, multicentre	failure on prior endocrine therapy	(TTP)	Anastrozole 1 mg	230
9238IL/0021 Pivotal for registration	III	Randomised, double blind, multicentre	Advanced breast cancer after failure on prior endocrine therapy	Efficacy and Safety (TTP)	Fulvestrant 250 mg Anastrozole 1 mg	204 193
9238IL/0025	III	Randomised, double blind, multicentre	First line treatment of advanced breast cancer	Efficacy and Safety (TTP)	Fulvestrant 250 mg Tamoxifen 20 mg	310 271
EFECT "Study 48" 9238IL/0048	III	Randomised, double-blind, double-dummy , parallel group, multicentre	Advanced breast cancer following failure on prior non-steroidal aromatase inhibitor therapy	Efficacy and Safety (TTP)	Fulvestrant 250mg + LD Exemestane 25 mg	351 340

[a] All studies include postmenopausal women with estrogen receptor positive breast cancer.
[b] Numbers in the Safety analysis population.

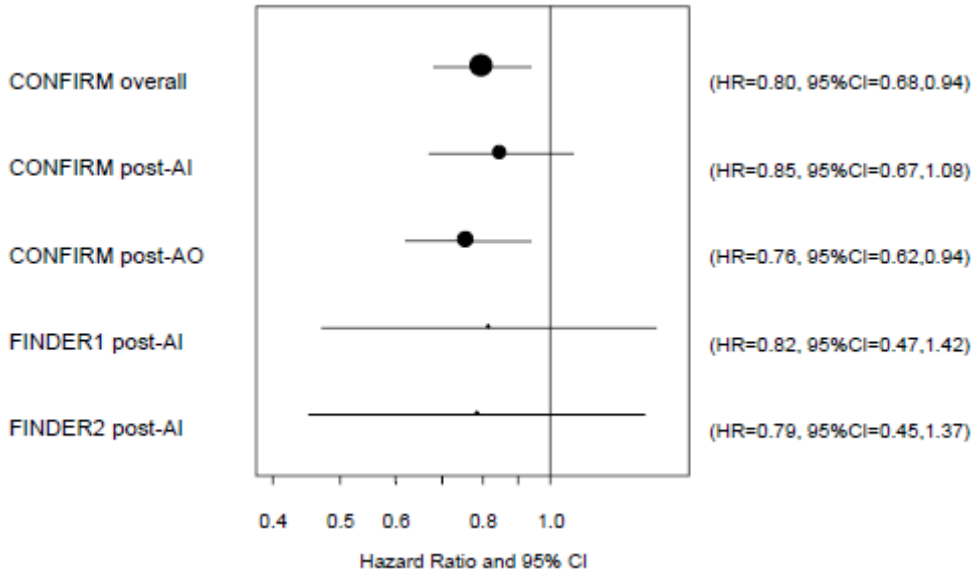
In response to CHMP questions the MAH was asked to justify why fulvestrant at a dose of 250 mg should be regarded as efficacious in patients failing aromatase inhibitor therapy (overall response rate 8%), as a trend towards higher efficacy for the 500 mg dose was not considered sufficient. The data provided is summarised in Tables 24 and 25.

Table 24: Clinical activity of fulvestrant 250 mg in patients who have failed on an AI

Clinical endpoint	Fulvestrant 250 mg treatment group			
	Ingle et al 2006	Perey et al 2007	Chia et al 2008[b]	CONFIRM post-AI subgroup
	N=77	N=86[a]	N=351	N=161
CBR, %	35.1	30	32.2	32.3
TTP, median (months)	3	-[c]	3.7	4.1

[a] Study reported data for 2 patient subgroups - Group A: patients who responded to prior AI therapy (N=67); Group B: patients who did not respond to prior AI therapy (N=19). For the purpose of this cross-study comparison a combined CBR is provided.
[b] Patients in the fulvestrant group received a fulvestrant 250 mg +LD (loading dose), ie, they received 500 mg instead of 250 mg on Day 0 and received an additional 250 mg dose on Day 14 (compared to the fulvestrant 250 mg dose regimen where patients receive 250 mg on Day 0 and every 28 days thereafter).
[c] Median TTP not provided for the overall study population (N=86). Median TTP for Group A was 3.6 months; median for Group B was 3.4 (see footnote a for Group definitions).
CBR: Clinical benefit rate=proportion of patients with complete response, partial response or stable disease ≥24 weeks.

Table 25: Forest plot of TTP for post-AI patients treated with fulvestrant 250 mg in CONFIRM, FINDER1 and FINDER2 (Full Analysis Set for each study)



Discussion on clinical efficacy

One of the major drawbacks of the pivotal study was the fact that lack of adequate control (placebo) made it difficult to evaluate the efficacy of fulvestrant in subjects with AI as last endocrine therapy in CONFIRM. A trend towards higher efficacy for the 500 mg dose was not considered sufficient and there was not enough evidence to justify why fulvestrant at a dose of 250 mg should be regarded as efficacious in patients failing aromatase inhibitor therapy.

Some imbalances were also observed at baseline between the endocrine subgroups (prior AI vs. prior AO as last endocrine therapy) regarding the number of prior (endocrine) treatments, the disease setting (adjuvant vs advanced) and age. These imbalances may partly explain the differences in activity of fulvestrant in the endocrine subgroups. In addition it made extrapolation between the two subgroups difficult. On the other hand, no mechanistic or other reasons were put forward in order to support the notion that the efficacy shown in the AO group would provide support in the interpretation of the results in the AI group.

Further to the assessment of the data submitted in the variation application and in the responses to the CHMP requests for supplementary information, the CHMP considered that efficacy data to support an extension of indication in this patient population was insufficient. However the CHMP considered acceptable to include relevant data on patients who have failed on prior anti estrogen and aromatase inhibitor therapy by subgroup in section 5.1 of the SmPC as the information can be helpful for the prescriber. In addition, the MAH has committed to provide more mature data on overall survival as a follow up measure.

▪ *Clinical safety*

Patient exposure

The safety analysis set included all patients who received the study drug. Only one of the study patients was excluded from the safety analysis set due to not receiving fulvestrant. The duration of the exposure is shown in Table 26.

Table 26. Duration of exposure: Safety Analysis Set

Duration (days)	Fulvestrant 500 mg N=361	Fulvestrant 250 mg N=374
Mean (sd)	313.0 (294.64)	248.6 (244.98)
Median (range), days	174.0 (10–1441)	145.5 (7–1387)
Median (range), months	5.7 (0.3-47.3)	4.8 (0.2-45.6)

Adverse events

The total numbers of adverse events (AEs), serious adverse events (SAEs), other significant adverse events (OAEs), adverse events leading to discontinuation of treatment (DAE) and adverse events that led to death are listed in Table 27. In addition the most commonly reported AEs (cut-off ≥ 5% in either treatment group) are summarised in Table 28.

Table 27. Number of adverse events

	Fulvestrant 500 mg N=361	Fulvestrant 250 mg N=374
AEs	1238	1205
Causally related AEs	267	247
SAEs	41	34
Causally related SAEs	1	1
DAEs	10	13
Causally related DAEs	3	3
OAEs	0	0
AEs of CTC grade 3 or higher	85	85
Causally related AEs of CTC grade 3 or higher	5	4
AEs with outcome of death	5	6
Causally related AEs with outcome of death	0	1

AE = adverse event, SAE = serious adverse event, OAE = other significant adverse event, DAE = adverse events leading to discontinuation of treatment, CTC = Common toxicity criteria, (This table has been modified from the original supplied by the MAH, where a numerical error was present.)

Table 28. Most commonly reported adverse events (cut-off ≥5% in either treatment group)

MedDRA PT	Number (%) of patients	
	Fulvestrant 500 mg N=361	**Fulvestrant 250 mg** N=374
Injection site pain	42 (11.6)	34 (9.1)
Nausea	35 (9.7)	51 (13.6)
Bone pain	34 (9.4)	28 (7.5)
Arthralgia	29 (8.0)	29 (7.8)
Headache	28 (7.8)	25 (6.7)
Back pain	27 (7.5)	40 (10.7)
Fatigue	27 (7.5)	24 (6.4)
Pain in extremity	25 (6.9)	26 (7.0)
Hot flush	24 (6.6)	22 (5.9)
Vomiting	22 (6.1)	21 (5.6)
Anorexia	22 (6.1)	14 (3.7)
Asthenia	21 (5.8)	23 (6.1)
Musculoskeletal pain	20 (5.5)	12 (3.2)
Cough	19 (5.3)	20 (5.3)
Constipation	18 (5.0)	13 (3.5)
Dyspnoea	16 (4.4)	19 (5.1)

MedDRA: Medical dictionary for regulatory activities. PT : Preferred term.

Discontinuation due to AEs

Seventeen patients had AEs that led to discontinuation of study (DAEs), 8 in the 500 mg group and 9 in the 250 mg group. Five of these patients had DAEs that were considered to be possibly causally related to study treatment. In the 500 mg group 2 patients together had a total of 3 causally related DAEs: dysphagia, hypersensitivity and interstitial lung disease. In the 250 mg group 3 patients had 1 causally related DAE each: acute respiratory failure, injection site erythema, and hypertension.

Serious adverse events and deaths

A total of 11 patients died following an AE during the treatment period, from 1st fulvestrant dose until 56 days after last dose. The AEs that ended in death were the following in the 500 mg group: Dyspnoea (2 patients), cardiopulmonary failure (1 patient), abdominal pain + vomiting + unknown cause of death (1 patient), and intestinal adenocarcinoma (1 patient). In the 250 mg treatment arm the AEs ending in death were: respiratory aspiration (1 patient), acute myocardial infarction (1 patient), meningitis (1 patient), suicide (1 patient), acute renal failure (1 patient), and hypertension (1 patient). Of these 11 cases of AEs, only the last one, hypertension, was considered causally related to the study medication by the investigator.

The most common SAEs, according to System organ class (SOC) are shown in Table 29:

Table 29. Most common SAEs by SOC

SOC	Fulvestrant 500 mg - N= 361	Fulvestrant 250 mg - N= 374
	Number of patients (%)	Number of patients (%)
Infections and infestations	6 (1.7)	2 (0.5)
Gastrointestinal disorders	5 (1.4)	3 (0.8)
Respiratory, thoracic and mediastinal disorders	5 (1.4)	6 (1.6)

SOC= System organ class

Causally related SAEs

Of all the SAEs only two, one in each treatment arm, were considered possibly causally related to the fulvestrant therapy by the investigator:

In the 500 mg group a 57 year old woman experienced interstitial lung disease (CTCAE grade 2) and left bronchopneumonia (CTCAE grade 2), which started 232 days from start of treatment and 7 days after discontinuation of study. Transbronchial biopsies showed advanced interstitial fibrosis, with presence of moderate dense inflammation infiltration, and without evidence of breast cancer metastasis. Microbiology tests were positive for Haemophilius influenzae. The events were considered serious due to hospitalisation. The patient was treated with moxifloxacin and was discharged from hospital 9 days later; however, at the time of DCO she had not yet recovered. The interstitial lung disease was considered as causally related to study therapy by investigator. The patient had a medical history of chronic obstructive pulmonary disorder and had received prior chemotherapy, which could have put the patient at risk of developing interstitial fibrosis.

In the 250 mg group a 63 year old woman experienced hypertension and generalised weakness, which occurred 48 days from start of treatment and 19 days after last dose (day 1 cycle 2). She died 23 days later due to "hypertension". The patient had a history of diabetes and concurrent treatment with a non-steroidal anti-inflammatory drug, ketorolac tromethamine, for which hypertension is a listed event, which could provide an alternative explanation for the event.

Deaths

All causes of death in the study are listed in Table 30.

Table 30. Causes of death in CONFIRM.

Joint disorders

Fulvestrant is a competitive ER antagonist and is associated with down-regulation of ER protein levels. ERs have been identified in many structures that are found in rheumatoid arthritic or osteoarthritic joints, including synovial cells. AstraZeneca's worldwide safety database was searched up to 31 July 2009 for reports of joint disorders in patients receiving fulvestrant. This identified 113 events in 105 patients. 42.55% were serious.

In the FIRST study, the frequency of joint disorders was higher in the fulvestrant 500 mg arm (13.9%, [14/101]) compared with the anastrozole 1 mg arm (9.7%, [10/103]). A prospective, formal statistical analysis was performed, which showed that the difference in the frequency of joint disorders between the two arms was not statistically significant (p=0.391). Joint pain/stiffness is listed as a common adverse reaction for anastrozole.

In the pooled analysis of studies comparing fulvestrant 500 mg with fulvestrant 250 mg (CONFIRM, FINDER1, FINDER2 and NEWEST), the frequency of joint disorders in each arm was:

500 mg arm: 12.1% (68/560 patients)

250 mg arm: 10.6% (60/567 patients)

In the Clinical Study Reports for CONFIRM, FINDER1 and FINDER, a broader group of MedDRA Preferred Terms was included in the predefined adverse event of 'joint disorders' including the Preferred Terms, back pain and neck pain. Using this broader group of Preferred Terms, the frequency of joint disorders in each arm of the pooled analysis was:

500 mg arm: 17.1% (96/560 patients)

250 mg arm: 17.5% (99/567 patients)

Following a request for supplementary information the MAH provided additional information on the frequencies of joint disorders irrespective of causality (see Table 31).

Table 31. Summary of reports in joint disorders in Fulvestrant studies.

Study	Number of patients with a joint disorder (%)	
	FASLODEX	Comparator
Second-line therapy with approved FASLODEX dose (pooled analysis of 2 Phase III studies):		
9238IL/0020 & 9238IL/0021 FASLODEX 250 mg (N=423) vs. anastrozole 1 mg (N=423)	23 (5.4)	45 (10.6)
Second-line therapy with loading FASLODEX dose (Phase III study):		
9238IL/0048 (EFECT) [a] FASLODEX 250 mg (N=351) vs. exemestane 25 mg (N=340)	93 (26.5)	99 (29.1)
First-line therapy with approved FASLODEX dose (Phase III study):		
9238IL/0025 FASLODEX 250 mg (N=310) vs. tamoxifen 20 mg (N=271)	13 (4.2)	16 (5.9)
First-line therapy with 'high' dose FASLODEX (Phase II study):		
D6995C00006 (FIRST) FASLODEX 500 mg (N=101) vs. anastrozole 1mg (N=103)	14 (13.9) [b]	10 (9.7)

[a] Of the 93 patients in the FASLODEX arm and 99 patients in the exemestane arm who had a 'joint disorder', 68 (73.1%) and 69 (69.7%) respectively, had relevant concurrent joint associated diseases/symptoms at study entry which may provide an alternative explanation for the high number of joint disorder events seen in this study.

[b] Of the 14 patients in the FASLODEX arm and 10 patients in the anastrozole arm who had a joint disorder, 8 (57.1%) and 6 (60%) respectively, had relevant concurrent joint associated diseases/symptoms at study entry, which may provide an alternative explanation for the occurrence of the joint disorder. Of the 10 patients in the anastrozole arm who had a joint disorder, 6 (60%) had concurrent diseases/symptoms at study entry, which may provide an alternative explanation for the occurrence of the joint disorder. The incidence of reports of joint disorders was higher in the FASLODEX 500 mg-treated patients compared with the anastrozole-treated patients, however, the difference was not statistically significant (p-value = 0.391).

In addition based on literature the MAH discussed aromatase inhibitor induced arthralgia and summarised the different possible pathomechanisms of joint disorders in postmenopausal women with breast cancer, focusing on the possible role of estrogen in join symptoms. The lack of joint disorders associated with the treatment of fulvestrant was convincingly demonstrated.

Osteoporosis

Pooled analysis were performed on the CONFIRM, FINDER1, FINDER2, and NEWEST studies, which all compare fulvestrant at 500mg and 250 mg dose regimens. The frequency of events of osteoporosis and fractures are shown in Table 32. No events of reduced bone mineral density or osteopenia were reported. Based on these data the MAH initially requested to remove potential risk of osteoporosis from the SmPC section 4.4. and PL section 2.

Table 32. Pooled data, reported events of osteoporosis and fracture

Event type	**% (number of patients)**	
	Fulvestrant 500 mg (n = 560)	**Fulvestrant 250 mg** (n = 567)
Osteoporosis	0.7% (4)	0% (0)
Fracture	2.0% (11)	1.6% (9)

There is no significant difference in the reporting of osteoporosis or fracture in the dose comparing studies, however it should be noted that the NEWEST study (including over 200 patients) was an open study with potential risk of bias in the reporting of adverse events. In NEWEST 2 cases of osteoporosis were seen in the 500 mg arm and none in the 250 mg arm. Even when taking this into account no clinically significant difference is seen in the osteoporosis related adverse events of the dose comparing studies.

The potential mechanism for fulvestrant to cause osteoporosis is based on the down-regulation of the estrogen receptor (ER) by competitive binding to the ER. Both ER-alpha and ER-beta are present in bone and estrogens acting on these receptors are known to decrease osteoclast and increase osteoblast cell numbers thus increasing bone formation and decreasing bone resorption.

The request to remove the potential risk of osteoporosis from the SmPC was not accepted due to the fact that although bone turn-over markers in the NEWEST study were unaffected by 16 weeks of treatment with fulvestrant (see section on bone biomarkers, Tables 2, 3 and 4), the ability of the bone turn-over marker study to detect long-term effects on bone was questioned and the potential risk of osteoporosis could not be discarded. Nevertheless section 5.1 has been updated to reflect the data provided for the NEWEST study.

Venous thromboembolism

Based primarily on data from the CONFIRM study and nine supportive clinical trials (see Table 22) the MAH requested to remove venous thromboembolism from the precautions for use and the list of adverse drug reactions in the SmPC sections 4.4. and 4.8 and PL section 2.

The experience of venous thromboembolism and fulvestrant and the frequency of such events are summarised in Tables 33 and 34.

Table 33. Incidence of venous thromboembolic events in Fulvestrant 500 mg vs. 250 mg studies

Study	% (number of patients)		RR estimate and 95% CI [b]
	FASLODEX 500 mg	FASLODEX 250 mg	
CONFIRM	0.8% (3/361)	1.6% (6/374)	0.45 (0.11, 1.55)
FINDER1	0 (0/46)	0 (0/45)	0.91 (0.02, 35.55)
FINDER2	2.2% (1/46)	4.3% (2/47)	0.57 (0.07, 3.75)
NEWEST	0.9% (1/107)	2.0% (2/101)	0.59 (0.07, 3.88)
Pooled data [a]	0.9% (5/560)	1.8% (10/567)	0.43 (0.15, 1.26)

[a] Pooled data from CONFIRM, FINDER1, FINDER2 and NEWEST

[b] The combined analysis used the Mantel-Haenszel approach to estimate the overall relative risk (RR) and 95% CI, stratified by study. A Mantel-Haenszel-RR <1.0 indicates a lower event risk in the fulvestrant 500 mg group. A Mantel-Haenszel-RR >1.0 indicates a lower event risk in the fulvestrant 250 mg group.

Table 34. Incidence of venous thromboembolic events in other Fulvestrant studies

Study	% (number of patients)	
	FASLODEX	**Comparator**
FIRST FASLODEX 500 mg vs. anastrozole 1 mg[a]	1% (1/101)	1% (1/103)
9238IL/0020 FASLODEX 250 mg vs. anastrozole 1 mg	2.7% (6/219)	1.3% (3/230)
9238IL/0021 FASLODEX 250 mg vs. anastrozole 1 mg	2.5% (5/204)	5.7% (11/193)
9238IL/0025 FASLODEX 250 mg vs. tamoxifen 20 mg[b]	3.2% (10/310)	1.5% (4/271)
EFECT FASLODEX 250 mg + loading dose vs. exemestane 25 mg[c]	1.1% (4/351)	0.9% (3/340)

[a] Venous thromboembolic events are not listed in Section 4.8 of the Core Data Sheet for ARIMIDEX™
[b] Venous thromboembolic events are listed in Section 4.8 of the Core Data Sheet for NOLVADEX™
[c] Venous thromboembolic events are not listed in Section 4.8 of the exemestane UK SmPC (UK Aromasin™ SmPC)

The MAH also referred to published literature in which the frequency of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients with and without cancer using sampled data from the National Hospital Discharge Survey 1979-1999 was evaluated. In patients with breast cancer the frequency of a diagnosis of venous thromboembolism (defined as DVT or PE) was 1.7/100 hospitalisations, compared with 1.0/100 hospitalisations in patients without a cancer diagnosis.

A search has also been performed in AstraZeneca's worldwide safety database for venous thromboembolism-related MedDRA preferred terms, which identified 103 reports describing 111 venous thromboembolic events. In 91 of the reports risk factors for the development of venous thromboembolic events were present, and in three other reports concomitant medications that may also have resulted in the events were present, i.e. megestrol, capecitabine, and tamoxifen, respectively. These data from spontaneous reporting does however not rule out the possibility of fulvestrant harbouring a thrombogenic effect.

Quantitative signal detection for VTE and fulvestrant has also been performed using the AstraZeneca's worldwide safety database and the FDA AERS database by calculating the Empirical Bayesian Geometric Mean (EBGM) along with a 90% confidence interval (EB05 to EB95) and the AstraZeneca recommended signal threshold of EB05 ≥ 1.8. The relevant MedDRA preferred term which met the AstraZeneca's criteria for a potential safety signal was pulmonary embolism, with EB05s of 1.9 in the AstraZeneca database and 2.7 in the FDA database.

In addition, theoretical potential mechanisms by which fulvestrant might cause or contribute to the risk of venous thromboembolism have been identified:

Tissue factor pathway inhibitor-1(TFPI) is the physiological inhibitor of the tissue factor pathway of coagulation. One in vitro study showed that protein levels of TFPI in human endothelial cell cultures were reduced by the addition of the following compounds (at a concentration of 10nM): 17β-estradiol (34% reduction), 17α-ethinylestradiol (21%), raloxifene (28%), tamoxifen (16%), and fulvestrant (9%

reduction of TFPI). The cells used did not express the regular nuclear 66kDa ERα, but instead a 45 kDa ERα, which was not regulated by estrogens or ER modulators.
Based on available data the MAH has not been able to prove or make plausible the absence of a causal relationship in a situation where potential mechanisms for the ADR exists. Therefore the request remove venous thromboembolism from the product information was not accepted.

Increased risk of bleeding at the injection site

AstraZeneca's worldwide safety database was searched up to 31 July 2009 for reports of bleeding events at the injection site in patients receiving fulvestrant. This search identified 9 events (all non-serious) in 9 patients. The outcomes of the events were: recovered without sequelae (2 events), not yet recovered (1 event) and unknown (6 events).

In the pooled analysis of studies comparing fulvestrant 500 mg with fulvestrant 250 mg (CONFIRM, FINDER1, FINDER2 and NEWEST), there were 7 bleeding events at the injection site in the 500 mg arm; the outcomes of these events were recovered (6 events) and not yet recovered (1 event). In the 250 mg arm, there were 2 events of bleeding at the injection site; the outcomes of these 2 events were recovered. All 9 events were considered to be non-serious by the investigators.

In the pooled analysis of studies comparing fulvestrant 500 mg with fulvestrant 250 mg (CONFIRM, FINDER1, FINDER2 and NEWEST), the frequency of bleeding events at the injection site in each arm was:

500 mg arm: 1.3% (7/560 patients)

250 mg arm: 0.4% (2/567 patients)

Risk factors for a bleeding event following intramuscular administration include the presence of bleeding diatheses, thrombocytopenia, or concomitant treatment with anticoagulants.

Due to the intramuscular route of administration, fulvestrant should be used with caution if treating patients with bleeding diatheses, thrombocytopenia or those taking anticoagulant treatment (see Section 4.4 of the SmPC). Specific exclusion criteria and restrictions are in place for the studies included in the fulvestrant clinical development programme. In addition, all events reported in at risk patients are monitored to ensure that the warnings are adequate to reduce or manage patient risk.

The CHMP considered that bleeding at the injection site is an important identified risk. In addition to the existing warnings in the Section 4.4 of the SmPC regarding patients with bleeding diatheses, thrombocytopenia or those taking anticoagulant treatment; the CHMP considered necessary to include bleeding at the injection site in the table of adverse reactions in Section 4.8 of the SmPC.

Laboratory findings

There were no clinically relevant changes with time in median and mean haematology or clinical chemistry values in either of the treatment groups and no apparent differences between the treatment groups.

The proportion of patients reporting an abnormal haematology parameter at their treatment discontinuation visit was 31.8% in the fulvestrant 500 mg group compared to 30.2% in the fulvestrant 250 mg group.

The proportion of patients reporting an abnormal clinical chemistry parameter at baseline was 57.6% in the fulvestrant 500 mg group and 58.8% in the fulvestrant 250 mg group, compared with 67.4% and 57.7%, respectively, at treatment discontinuation.

Safety in special populations

Patients ≥ 75 years of age

Pooled data from CONFIRM, FINDER1, FINDER2, and NEWEST together comprising 560 patients in the 500 mg group and 567 in the 250 mg group. The subgroups of patients ≥ 75 years of age comprised 81 and 96 patients, respectively.

In an analysis of patients who had at least 1 AE by system organ class, higher frequencies of the following AEs were seen in the 500 mg vs. the 250 mg group in the patients aged ≥ 75 years: General disorders and injection site conditions (46% vs. 33%), skin and subcutaneous tissue disorders (15% vs. 4%), metabolism and nutrition disorders (17% vs. 11,5%), injury, poisoning and procedural complications (17% vs. 9%), ear and labyrinth disorders (5% vs.2 %). There was no difference between treatment groups with regard to cardiac disorders (5% in both).

In an analysis of AEs according to MedDRA preferred terms present in ≥ 5% of the patients, higher frequencies of the following AEs were seen in the 500 mg vs. the 250 mg group in the patients aged ≥ 75 years: Fatigue (17% vs. 8%), injection site pain (12% vs. 4%), diarrhoea (9% vs. 3%). On the other hand, the following AEs were more common in the 250 mg group: vomiting, asthenia, back pain and arthralgia. Fatigue and injection site pain were also markedly higher in the 500 mg vs. 250 mg group in the 65-74 year age group.

Safety by race

A pooled safety analysis of the studies named above divided patients into one of three racial groups: Caucasian (n=974), Oriental (n=99), and Black (n=11). Vascular disorders and cardiac disorders (SOC) appeared in a higher frequency in black patients compared with the other races, however the absolute numbers are low (n= 1-2). The frequencies of vascular disorders in the combined racial groups were 14% in the 500 mg group vs. 16% in the 250 mg group, and the corresponding figures for cardiac disorders were 3% in both groups. Oriental patients reported overall more AEs than the other race groups, including (SOC): general disorders and administration site conditions, gastrointestinal disorders, infections and infestations, nervous system disorders, skin and subcutaneous tissue disorders, and blood and lymphatic system disorders. Nasopharyngitis (MedDRA PT ≥ 5%) was reported in oriental patients in 33 and 34% in the 500 mg and 250 mg groups, respectively, and not at all (i.e. <5%) in the other race groups.

There was a consistency between the Caucasian and Oriental groups in the most common AEs (SOC) being: general disorders and administration site conditions, musculoskeletal and connective tissue disorders, gastrointestinal disorders, and infections and infestations.

Discussion on clinical safety

The distribution of AEs was well balanced between treatment groups. The average number of AEs was 3 per patient in both groups, approximately 20 % were judged causally related (22 and 20 % in the 500 mg and 250 mg arms, respectively), approximately 10 % of the patients experienced SAEs (11 and 9%, respectively) and only one patient in each group had a causally related SAE. The number of patients with AEs of CTC (Common toxicity criteria) grade 3 or higher, and with outcome of death were very similar. One patient died in a causally related AE in the 250 mg group. In addition, no clinically meaningful differences in discontinuations were seen between treatment groups.

In conclusion the data presented gave no evidence of dose-dependent AEs. Specifically, there were no increases in the two most common areas of AE, GI disturbances and joint disorders, or in thromboembolic events with the higher dose regimen.

Based primarily on data from the CONFIRM study the MAH requested to remove venous thromboembolism from the precautions for use and the list of adverse drug reactions in the SmPC sections 4.4. and 4.8 and PL section 2, however the request could not be accepted based on available data as the MAH has not been able to prove or make plausible the absence of a causal relationship in a situation where potential mechanisms for the ADR exists.

The request to remove a potential risk of osteoporosis from the SmPC was not accepted due to the fact that although bone turn-over markers in the NEWEST study were unaffected by 16 weeks of treatment with fulvestrant, the ability of the bone turn-over marker study to detect long-term effects on bone was questioned and it was not considered sufficient evidence.

The CHMP considered that bleeding at the injection site is an important identified risk. In addition to the existing warnings in the Section 4.4 of the SmPC regarding patients with bleeding diatheses, thrombocytopenia or those taking anticoagulant treatment; the CHMP considered necessary to include 'injection site haemorrhage and haematoma' (frequency "uncommon") in the table of adverse reactions in Section 4.8 of the SmPC.

▪ *Pharmacovigilance*

Risk Management Plan

The MAA submitted a risk management plan.

Table Summary of the Risk Management Plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine)
General Activities that apply to all safety concerns	Routine pharmacovigilance	Routine Risk Minimising Activities
Injection site reactions	Routine pharmacovigilance	Use of the SmPC to emphasise that injection site reactions are associated with the use of fulvestrant. Detailed instructions on how to administer fulvestrant correctly are provided in Section 6.6 of the SmPC.
Increased risk of bleeding at the injection site	Routine pharmacovigilance	Use of the SmPC to emphasise that, due to the intramuscular route of administration, fulvestrant should be used with caution if treating patients with bleeding diatheses, thrombocytopenia or those taking anticoagulant treatment. Exclusion of patients who may be at increased risk of bleeding from fulvestrant studies.
Venous thromboembolic events	Routine pharmacovigilance	Use of the SmPC to emphasise that venous thromboembolic events have been observed in women with advanced breast cancer and have been observed in clinical trials with fulvestrant.

Table Summary of the Risk Management Plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine)
Hypersensitivity reactions	Routine pharmacovigilance	Use of the SmPC to emphasise that hypersensitivity reactions are associated with the use of fulvestrant and that fulvestrant is contraindicated in patients with a hypersensitivity to the active substance, or to any of the other excipients. Exclusion of patients with a history of hypersensitivity to active or inactive excipients of fulvestrant and/or castor oil from fulvestrant studies.
Reduced bone mineral density (osteopenia) and osteoporosis	Routine pharmacovigilance	For this potential risk, no risk minimising activities are proposed.
Ischaemic cardiovascular events	Routine pharmacovigilance	For this potential risk, no risk minimising activities are proposed.
Endometrial dysplasia	Routine pharmacovigilance	For this potential risk, no risk minimising activities are proposed.
Joint Disorders	Routine pharmacovigilance	For this potential risk, no risk minimising activities are proposed.
Interstitial lung disease	Routine pharmacovigilance	For this potential risk, no risk minimising activities are proposed.
Vasculitis	Routine pharmacovigilance	For this potential risk, no risk minimising activities are proposed.
Pulmonary microembolism of oily solutions	Routine pharmacovigilance	For this potential risk, no risk minimising activities are proposed.
Paediatric use	Routine pharmacovigilance Additional pharmacovigilance activity: Analysis of results of study D6992C00044 (9238IL/0044).	Use of the SmPC to emphasise the limited experience in the paediatric population and that fulvestrant is not recommended for use in children or adolescents.
Pregnancy and lactation	Routine pharmacovigilance	Use of the SmPC to emphasise that the use of fulvestrant is contraindicated in pregnant or lactating women. The protocols for fulvestrant studies include confirmation of the postmenopausal status of participants, or in the absence of confirmed postmenopausal status a requirement for the use of appropriate contraception.
Severe hepatic impairment	Routine pharmacovigilance	Use of the SmPC to emphasise that the use of fulvestrant is contraindicated in patients with severe hepatic impairment.
Severe renal impairment	Routine pharmacovigilance	Use of the SmPC to emphasise that fulvestrant should be used with caution in patients with severe renal impairment (creatinine clearance less than 30 ml/min).

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

▪ *Changes to the Product Information*

Update of section 4.8 of the SmPC

The CHMP considered that bleeding at the injection site is an important identified risk and the MAH was requested to include 'injection site haemorrhage and haematoma' (frequency category "uncommon") in the table of adverse reactions in Section 4.8 of the SmPC.

Update of section 5.1 of the SmPC

The request to include information on patients who have failed on prior anti-estrogen and aromatase inhibitor therapy from the CONFIRM in section 5.1 of the SmPC was agreed as the information can be helpful for the prescriber.

The following new table has been included:

Table 2 Summary of results of the primary efficacy endpoint (PFS) and key secondary efficacy endpoints in the CONFIRM study

Variable	**Type of estimate; treatment comparison**	**Faslodex 500 mg (N=362)**	**Faslodex 250 mg (N=374)**	**Comparison between groups (Faslodex 500 mg/Faslodex 250 mg)**		
				Hazard ratio	**95% CI**	**p-value**
PFS	**K-M median in months; hazard ratio**					
All Patients		**6.5**	**5.5**	**0.80**	**0.68, 0.94**	**0.006**
-AE subgroup (n=423)		**8.6**	**5.8**	**0.76**	**0.62, 0.94**	**0.013**
-AI subgroup (n=313)[a]		**5.4**	**4.1**	**0.85**	**0.67, 1.08**	**0.195**
OS	K-M median in months; hazard ratio					
All Patients		25.1	22.8	0.84	0.69, 1.03	0.091
-AE subgroup (n=423)		27.9	25.9	0.85	0.65, 1.13	0.264
-AI subgroup (n=313)[a]		24.1	20.8	0.83	0.62, 1.12	0.216
Variable	Type of estimate; treatment comparison	Faslodex 500 mg (N=362)	Faslodex 250 mg (N=374)	Comparison between groups (Faslodex 500 mg / Faslodex 250 mg)		
				Absolute difference in %	95% CI	
ORR[b]	% of patients with OR; absolute difference in %					
All Patients		13.8	14.6	-0.8	-5.8, 6.3	
-AE subgroup (n=296)		18.1	19.1	-1.0	-8.2, 9.3	
-AI subgroup (n=205)[a]		7.3	8.3	-1.0	-5.5, 9.8	

Variable	Type of estimate; treatment comparison	Faslodex 500 mg (N=362)	Faslodex 250 mg (N=374)	Comparison between groups (Faslodex 500 mg/Faslodex 250 mg)		
				Hazard ratio	95% CI	p-value
CBR[c]	% of patients with CB; absolute difference in %					
All Patients		45.6	39.6	6.0	-1.1, 13.3	
-AE subgroup (n=423)		52.4	45.1	7.3	-2.2, 16.6	
-AI subgroup (n=313)[a]		36.2	32.3	3.9	-6.1, 15.2	

[a] Faslodex is indicated in patients whose disease had recurred or progressed on an anti-estrogen therapy. The results in the AI subgroup are inconclusive.
[b] ORR was assessed in patients who were evaluable for response at baseline (ie, those with measurable disease at baseline: 240 patients in the Faslodex 500 mg group and 261 patients in the Faslodex 250 mg group).
[c] Patients with a best objective response of complete response, partial response or stable disease ≥24 weeks.
PFS:Progression-free survival; ORR:Objective response rate; OR:Objective response; CBR:Clinical benefit rate; CB:Clinical `benefit; OS:Overall survival; K-M:Kaplan-Meier; CI:Confidence interval; AI:Aromatase inhibitor; AE:Anti-estrogen.

In addition the term "time to progression (TTP)" has been replaced by "progression free survival (PFS)" as TTP defined in the protocol refers by definition to PFS.

Furthermore, the addition of data relating to mechanism of action (i.e. effects on proliferation marker Ki67 and the estrogen receptor) and effects on bone and endometrium in Section 5.1 of the SmPC was considered acceptable.

Update of section 5.3 of the SmPC
Major findings in the toxicological studies, especially findings such as vasculitis and arteritis in dogs and effects on pituitary in rats, were re-assessed in relation to the exposure. As a result, arteritis has been included in section 5.3 of the SmPC.

The package leaflet has been updated accordingly in line with the SmPC.

Changes were also made to the SmPC, Labelling and Package Leaflet to bring them in line with the current QRD template.

In addition, the list of local representatives in the Package Leaflet has been revised to amend contact details for the representative of Czech Republic.

Annex II has been updated in order to reflect the latest version of the RMP agreed.

2. Benefit-Risk Balance

The benefit for fulvestrant 500 mg in patients resistant to aromatase inhibitors has not been demonstrated. No statistically significant effect has been observed with fulvestrant 500 mg vs. 250 mg in TTP in the subgroup of subjects who had used an aromatase inhibitor as last endocrine therapy in the pivotal Phase III CONFIRM study (TTP 250 mg 4.1 mo vs. TTP 500 mg 5.4 mo; HR=0.85 (CI 95% 0.67-1.08, p=0.195). In line with the TTP results, there is a trend for a better survival in patients treated with fulvestrant 500 mg compared with the 250 mg group, however it was not statistically significant.

Although secondary endpoints have shown some activity for fulvestrant in terms of overall response rate (ORR) for the 500 mg (7.3%) and the 250 mg (8.3%) doses and clinical benefit (CBR) for the 500

mg (36.2%) and the 250 mg (32.3%) dose, they were not considered firm evidence of a clinically meaningful benefit in the subgroup of subjects who had used an aromatase inhibitor as last endocrine therapy in the CONFIRM study. In addition supportive phase II studies comparing fulvestrant 500 mg vs 250 mg (FINDER1 and FINDER2) have not shown statistically signifficant difference in ORR or CBR between the two treatment arms.

One of the major drawbacks of the pivotal study CONFIRM was the fact that lack of adequate control (placebo) made it difficult to evaluate the efficacy of fulvestrant in subjects with AI as last endocrine therapy. A trend towards higher efficacy for the 500 mg dose was not considered sufficient and there was not enough evidence to justify why fulvestrant at a dose of 250 mg should be regarded as efficacious in patients failing aromatase inhibitor therapy.

Some imbalances were also observed at baseline between the endocrine subgroups (prior AI vs. prior AO as last endocrine therapy) regarding the number of prior (endocrine) treatments, the disease setting (adjuvant vs advanced) and age. These imbalances may partly explain the differences in activity of fulvestrant in the endocrine subgroups. In addition it made extrapolation between the two subgroups difficult. On the other hand, no mechanistic or other reasons were put forward in order to support the notion that the efficacy shown in the AO group would provide support in the interpretation of the results in the AI group.

In terms of toxicity the distribution of AEs was well balanced between treatment groups. The average number of AEs was 3 per patient in both groups, approximately 20 % were judged causally related (22 and 20 % in the 500 mg and 250 mg arms, respectively), approximately 10 % of the patients experienced SAEs (11 and 9%, respectively) and only one patient in each group had a causally related SAE. The number of patients with AEs of CTC grade 3 or higher, and with outcome of death were very similar. There were no increases in the two most common areas of AE, GI disturbances and joint disorders, nor in thromboembolic events with the higher dose regimen. In conclusion there is not additional toxicity associated with the 500 mg dose of fulvestrant compared to the lower 250 mg dose.

As per CHMP request, an oncology Scientific Advisory Group (SAG) meeting was convened on 16 June 2010 to discuss the benefits of fulvestrant from a clinical perspective and whether fulvestrant at a dose of 250 mg should be regarded as efficacious in patients failing aromatase inhibitor therapy. The SAG provided advice on the following questions raised by the Committee:

1. While some activity in terms of overall response rate (8%) has been shown for fulvestrant 250 mg, efficacy (=clinically meaningful activity) cannot be deduced. Therefore it is not sufficient only to demonstrate a trend towards higher efficacy for the 500 mg dose (HR 0.85, 95% CI 0.67; 1.08). The sponsor is thus asked to justify why fulvestrant at a dose of 250 mg should be regarded as efficacious in patients failing aromatase inhibitor therapy.

The SAG agreed by consensus that insufficient evidence of efficacy has been presented to establish that fulvestrant at a dose of 250 mg can be regarded as efficacious in patients with disease progression after aromatase inhibitors. The CONFIRM trial was not designed to address this question and only indirect comparisons can be made. The efficacy results for fulvestrant at a dose of 250 mg do not show any dramatic activity in terms of response rate, PFS or any of the clinical outcomes presented and therefore no firm conclusions can be drawn from indirect comparisons. Thus, it is unknown if fulvestrant at a dose of 250 mg can be regarded as efficacious in patients failing aromatase inhibitor therapy.

The SAG agreed that formal evidence of efficacy should be provided according to rigorous scientific standards to establish the efficacy of fulvestrant in patients with disease progression after aromatase inhibitors. The best way to address this question is through randomised controlled trials.

Nevertheless, some SAG members argued that in view of the manageable toxicity profile, fulvestrant could be regarded as a possible option in this setting but this is not based on firm evidence, rather, on clinical expert judgement of exploratory analyses suggesting some antitumour activity. The level of evidence to support this currently does not fulfil conventional scientific standards, prompting the need for confirmatory studies.

2. Please discuss the relevance of the evidence of efficacy demonstrated in patients failing anti-estrogens to patients failing aromatase inhibitors.

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

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

3. Considering the points discussed above, the MAH is requested to review existing data on the efficacy and safety of available alternative treatment options (including chemotherapy) after failure with AIs and to discuss those findings in relation to the observed effects with fulvestrant in subjects after failure with AI in CONFIRM study.

The efficacy results for fulvestrant at a dose of 250 mg do not show any dramatic activity in terms of response rate, PFS or any of the clinical outcomes presented and therefore no firm conclusions can be drawn from direct or indirect comparisons with other treatment options. Based on the exploratory analyses presented, some antitumour activity has been observed but it is unknown to what extent this would result in a meaningful clinical benefit or how this would compare to relevant treatment options including "gentle" chemotherapy.

The CHMP considered the data submitted and the argumentation put forward by the applicant and the SAG experts. Based on the above findings, the CHMP considered that the benefit-risk balance for fulvestrant 500 mg in patients resistant to aromatase inhibitors was not favourable and that the therapeutic efficacy has not been properly and sufficiently demonstrated in order to support the extension of the current approved indication in section 4.1 of the SmPC . However the CHMP considered acceptable the inclusion of relevant data on patients who have failed on prior anti-estrogen and aromatase inhibitor therapy by subgroup in section 5.1 of the SmPC as the information can be helpful for the prescriber.