Public Assessment Report

Femara 2.5mg Tablet

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FEMARA 2.5mg Tablet

LAY SUMMARY

On 1st December 2005, MHRA granted a variation to the Marketing Authorisation to extend the indication for Femara (letrozole) to include adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.

Many breast cancers express oestrogen and progestagen receptors, making their growth hormone dependent. In post-menopausal women, despite loss of ovarian oestrogen production, oestrogens continue to be produced from androgens in peripheral tissues by the enzyme aromatase. Femara contains letrozole, which selectively inhibits aromatase at these sites. This leads to a drop in circulating oestrogen levels by around 95%, which suppresses the growth of hormone-sensitive breast tumours. Letrozole may have some additional effect from inhibiting aromatase in the tumour itself

The clinical evidence presented in this report demonstrates that letrozole significantly prolonged disease-free survival compared to tamoxifen, the current standard treatment for hormone receptor positive invasive early breast cancer.

SCIENTIFIC DISCUSSION

Background

Femara (letrozole) was first assessed for use in advanced metastatic breast cancer with disease progression despite anti-oestrogen therapy in 1996. The data submitted were fully evaluated by the MHRA (then MCA) in relation to the appropriate standards required in the relevant European and National Rules and Regulations on Medicinal Products, and CSM advice was sought on 26 September 1996. It was considered that the data submitted in support of the application demonstrated that safety, quality and efficacy of the product was satisfactory for its intended use in advanced metastatic breast cancer with disease progression despite anti-oestrogen therapy. A Market Authorization was granted on 18th November 1996.

A variation to the Marketing Authorisation for Femara was granted to allow use in first-line endocrine treatment for locally advanced or metastatic, hormone receptor positive or unknown breast cancer on 10th October 2001 and also for pre-operative therapy of localized hormone receptor positive breast cancer to permit breast-conserving surgery (15th January 2001). The indications for Femara were also extended on 9th September 2004 to include extended adjuvant treatment of postmenopausal women with receptor positive primary breast cancer following standard adjuvant tamoxifen treatment.

Introduction

Many breast cancers express oestrogen and progestagen receptors, making their growth hormone dependent. In post-menopausal women, despite loss of ovarian oestrogen production, oestrogens continue to be produced from androgens in peripheral tissues by the enzyme aromatase. Femara contains letrozole, which selectively inhibits aromatase at these sites. This leads to a drop in circulating oestrogen levels by around 95%, which suppresses the growth of hormone-sensitive breast tumours. Letrozole may have some additional effect from inhibiting aromatase present within the tumour itself.

As letrozole does not inhibit ovarian oestrogen synthesis it is only indicated in post-menopausal women. It was initially licensed in advanced breast cancer, and also has an indication in the pre-operative (neo-adjuvant) setting. Most recently it gained an indication in the "extended adjuvant" setting in early breast cancer, which means following completion of prior (around 5 years) tamoxifen therapy.

Letrozole is licensed in the UK on a national basis.

THERAPEUTIC BACKGROUND

The indication for the variation to the Marketing Authorisation discussed in this report is the treatment of early breast cancer. The majority of new cases of breast cancer will present at this stage of the disease, which can be further divided into stage I disease, which is confined to the breast, or stage II, where one or more local lymph nodes are involved.

For most women with early breast cancer, surgery (breast-conserving where possible) with or without radiotherapy is indicated. These primary treatments are potentially curative. However, giving this "local" therapy alone carries a real threat of tumour recurrence. The

risk of recurrence is highest during the first 5 years, but the risk remains even 15–20 years after surgery.

Recurrence is thought to occur because of micrometastases undetectable at the time of the primary diagnosis. The rationale for giving supporting or "adjuvant" drug therapy after surgery/radiotherapy is therefore to reduce the risk of relapse by eradicating these micrometastases. The term "adjuvant" should not be confused with "neo-adjuvant" therapy, which refers to therapy *before* surgery, generally to decrease tumour size and facilitate breast-conserving surgery.

The need for adjuvant drug therapy should be considered in all cases, with the risk of recurrent disease assessed and balanced against the risks of drug therapy. Nodal status is the most important determinant of recurrence risk, but tumour size, histological grade and tumour receptor status are also important considerations. The menopausal status of the patient is also an important consideration in choosing the type of therapy.

Cytotoxic chemotherapy should be considered, especially for premenopausal and post-menopausal women with oestrogen receptor (ER) negative tumours. However, the majority of tumours express oestrogen and/or progesterone receptors (ER, PgR) and are therefore amenable to hormonal-based therapies, which include progestagens, gonadorelin analogues, the aromatase inhibitors (anastrozole, letrozole), aromatase inactivators (exemestane), and oestrogen receptor antagonists (tamoxifen, toremifine).

Up until recently, tamoxifen had been considered the gold standard in post-menopausal women with hormone-responsive early breast cancer. It has shown clear efficacy in increasing disease-free survival and mortality, and also reduces the incidence of contralateral breast cancers. The current consensus is that 5 years of tamoxifen treatment is the optimal duration of adjuvant therapy, in post-menopausal women with hormone-responsive early breast cancer. This has not however been decided beyond all doubt, particularly in node-positive patients, and several studies have been initiated which relate to this question.

In post-menopausal women, newer aromatase inhibitors are beginning to supersede tamoxifen in a number of settings. <u>This is discussed further in the regulatory background section below.</u> In particular, a widened adjuvant indication in early breast cancer has now been approved for anastrozole (Arimidex). Before this, anastrozole it had been approved in this indication in a "second line" setting, in patients unable to take tamoxifen. This was a significant change in the treatment of early breast cancer.

Older therapies like progestagens and the unselective aromatase inhibitor aminoglutethimide have largely been relegated to second or third-line therapy in advanced breast cancer. The gonadorelin analogue goserelin (Zoladex) is used in oestrogen receptor positive early breast cancer but this applies to pre/ peri-menopausal women only. The oestrogen receptor antagonist toremifine (Fareston) only has a licence in advanced breast cancer at present.

REGULATORY BACKGROUND

Letrozole

Letrozole (Femara) has a national marketing authorisation in the UK. Femara was first licensed in the UK in 1996, for the palliative treatment of "*advanced breast cancer in post-*

menopausal women when tamoxifen or other first-line anti-oestrogen therapy has failed". This was based on a pivotal trial comparing to the unselective aromatase inhibitor, aminoglutethimide.

In 2001, 2 additional licence variations were approved for Femara. These were:

"First-line treatment in postmenopausal women with advanced breast cancer."

"Pre-operative therapy in postmenopausal women with localised hormone receptor positive breast cancer, to allow subsequent breast-conserving surgery in women not originally considered candidates for breast-conserving surgery. Subsequent treatment after surgery should be in accordance with standard of care."

In 2004, based on the results of the MA-17 study a further indication in the "extended adjuvant" setting was approved as follows:

"Treatment of early invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy."

The SPC notes that in this setting, following standard (around 5 years) adjuvant tamoxifen therapy, treatment with Femara should continue for 3 years or until tumour relapse occurs, whichever comes first. There is also a warning that there is a currently a lack of long-term data in the extended adjuvant setting, thus the optimal duration of therapy has not yet been established. Warnings regarding clinical surveillance of bone mass loss, and that an overall mortality effect has not been demonstrated in this setting, were also added to the SPC during consideration of this variation.

Anastrozole

Anastrozole is the only other non-steroidal aromatase inhibitor currently licensed in the UK. It is indicated for for the adjuvant treatment of postmenopausal women with hormone receptor positive early invasive breast cancer, as well as in advanced breast cancer. Anastrozole has the same basic pharmacology and pharmacokinetic profile as letrozole, and they suppress circulating oestrogen levels to the same degree at comparable therapeutic doses.

Exemestane

Exemestane is more properly classed separately as an aromatase inactivator, rather than an aromatase inhibitor, although it is similar to letrozole and anastrozole. Exemestane was first licensed for postmenopausal women with advanced breast cancer in whom anti-oestrogen therapy has failed. Recently (August 2005), an indication in the adjuvant early breast cancer setting was approved, based on the Intergroup Exemestane study. The indication granted was *"adjuvant treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer, following 2 – 3 years of initial adjuvant tamoxifen therapy*

CLINICAL ASSESSMENT

Summary of submitted data

The pivotal efficacy data come from a single study in which 8010 patients were randomised to therapy, referred to as the BIG 1-98 study. These results have been presented at scientific meetings and were published in the New England Journal Of Medicine, December 2005 (Thurliman et al , 353(26):2747-57).

As part of BIG 1-98, 2 sub-studies were initiated to look at effects on bone and lipid. Both studies only recruited a small number of patients by the time enrolment in the main study was complete (BMD study: n=43, lipid study 58) and both had a limited follow-up

Review of BIG 1-98 study

Design

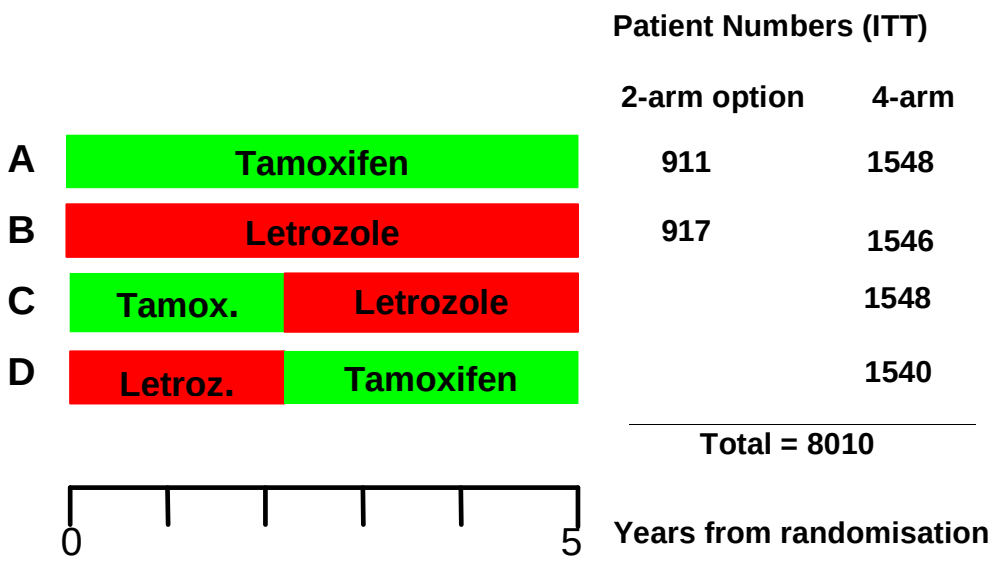
The BIG 1-98 trial was a double blind, double dummy, phase III randomised study designed to evaluate the use of letrozole as adjuvant therapy for postmenopausal patients with operable hormone receptor positive breast tumours.

The study started in March 1998 as a Novartis study comparing letrozole monotherapy for 5 years vs. tamoxifen monotherapy for 5 years (FEMTA study). 1828 patients were enrolled under this basis, referred to as the "2 arm randomisation option"

The study was later placed under the guidance of BIG (Breast International Group), which is a network of collaborating cooperative groups, specializing in the conduct of trials in the adjuvant treatment of early breast cancer. The International Breast Cancer Study Group (IBCSG), a member of BIG, became the coordinating group for the study.

The BIG 1-98 study, as it became known, had 2 additional treatment arms, which were two years of tamoxifen followed by three years of letrozole, and two years of letrozole followed by three years of tamoxifen. This "4-arm randomisation option" started accrual in April 1999, 6182 patients were enrolled on this basis.

The design, with the numbers of patients allocated to each arm (ITT population) as part of the 2 and 4-way randomisation options, is summarised in the figure below. In total the ITT population formed 8010 patients.



There were therefore 2 primary study questions:

Question 1) Does letrozole for 5 years improve outcome compared with tamoxifen for 5 years?
Question 2) Does a sequence of adjuvant endocrine therapies improve results, compared with a continuous course of a single endocrine agent?

The application and Market Authorisation is based on the 1st question only, and thus takes into account data from arms A and B in the above figure, as well as data truncated 30 days after the switch, from the two switching arms C and D. The analysis pertaining to this question is termed by the MAH the "Primary Core Analysis"

As noted in the statistical assessment, the decision to truncate data for arms C and D at 30 days is arbitrary. Obviously, an event the day after the switch is attributable to the previous treatment, not the new treatment, but when to place the cut-off is debatable. A reassuring point is that if the duration were too long, it would bias the treatment arms towards similarity rather than showing a difference.

The analysis pertaining to the second question is termed by the MAH the "Second Primary Analysis". To assess the arms involving sequential therapy fully will require further follow-up, and the final analysis for this is planned for 2008.
At first glance, BIG 1-98 might be viewed essentially as 2 studies. There are 2 randomisation options which started at different times, giving very differing levels of follow up between the 2 options. In addition, after the 2nd option was incorporated, centres could choose between the 2 options. However, it is reasonable to base the primary analysis upon combined data from the two halves. The combined analysis was pre-specified, it was never intended to analyse the two halves separately, and two of the arms carried directly through into both stages.

Inclusion criteria included freedom from distant metastases and an adequate resection of the primary tumour. Patients with positive nodes were allowed. Adjuvant radiotherapy, neoadjuvant hormonal therapy and neoadjuvant or adjuvant chemotherapy was permitted. Receptor-positive was defined either as ER and/or PgR ≥10 fmol/mg cytosol protein; or ≥10% of the tumour cells positive by immunocytochemical evaluation.

Significant protocol amendments

In administrative Amendment 1 (03 February 2004) provision was made for patients receiving 5 years tamoxifen to allow switching to letrozole therapy. This followed the results of the MA-17 "extended adjuvant" letrozole trial. An additional analysis was proposed in which the disease-free survival data of patients in monotherapy arms were truncated at 5 years after study entry. This additional analysis was to provide a check to determine if treatment differences were attenuated beyond 5 years.

In amendment 5 (April 27 2005), following a recommendation from the Independent Drug Safety Monitoring Committee, provision was made for patients assigned to tamoxifen 5 years (i.e. those who had not completed 5 years therapy) to be informed of their treatment and offered a switch of treatment to letrozole.

As below, there appears to be adequate patient exposure and follow-up to support the proposed 5 years treatment duration. These amendments were inevitable but will make a longer term survival comparison between letrozole and tamoxifen monotherapy more difficult to show.

Primary objective

The primary endpoint was disease-free survival (DFS). This was defined as the interval between date of randomization and first confirmation of invasive loco-regional recurrence, distant metastasis, an invasive contralateral breast cancer, a second invasive (non-breast) primary cancer, or death from any cause without a prior cancer event. An *in situ* ductal (DCIS) or lobular (LCIS) cancer either in the ipsilateral or contralateral breast was not considered a recurrence, but was reported in the CRF as a noteworthy event.

Secondary objectives

Overall survival (OS), defined as the time from randomization to death from any cause.

Systemic relapse, defined as any recurrent or metastatic disease in sites other than the local mastectomy scar, the ipsilateral breast in case of breast conservation, or the contralateral breast.

Systemic disease-free survival (SDFS) was defined as the time from randomization to systemic relapse, metastasis, appearance of a second (non-breast) primary cancer, or death from any cause, whichever occurred first.

The following were also evaluated:

- Sites of first treatment failure (DFS earliest events).
- Distant disease-free survival.
- Invasive contralateral breast cancer.
- Incidence of second (non-breast) invasive malignancies.

- Cause of death without a prior cancer event.
- Safety.

The 2 randomisation options make for a complicated assessment, but there are no major issues with the design of the study. The comparator of 5 years tamoxifen dosed at 20 mg per day was appropriate. The dose of 2.5 mg letrozole is as per all other approved indications, has been shown to be more effective than a lower dose in advanced breast cancer, and was assessed in early breast cancer in the extended adjuvant setting, in the recent MA-17 trial.

The choice and definition of the main efficacy endpoints DFS and OS and the choice of DFS as the primary endpoint were mostly in keeping with other recent adjuvant early breast cancer studies and regulatory guidance. However, inclusion of a second invasive non-breast primary cancer was not included in the definition of DFS for the ATAC study. Efficacy results excluding non breast cancers are noted later in the results section of this report.

The pathological/radiological assessments required to objectively determine local, regional or distant recurrence were also appropriate. The inclusion and exclusion criteria above, as well as the other criteria listed in the study report, were reasonable.

It is noted that quality of life was not assessed in the study.

Patient population

The median age at baseline was 61. Over 97% of patients were white. Disease characteristics and prior primary treatment at baseline are compared in the tables below:

Table: Patient characteristics at baseline (ITT population)

	Letrozole N=4003 n (%)	**Tamoxifen N=4007 n (%)**	**Total N=8010 n (%)**
Tumor size (cm)			
N	3958	3972	7930
Median	1.8	1.8	1.8
Min	0.1	0.1	0.1
Max	26.0	15.0	26.0
<= 2cm	2496 (62.4)	2461 (61.4)	4957 (61.9)
> 2cm	1462 (36.5)	1511 (37.7)	2973 (37.1)
Missing	45 (1.1)	35 (0.9)	80 (1.0)
Pathological stage: tumor			
pT1	2500 (62.5)	2463 (61.5)	4963 (62.0)
pT2	1334 (33.3)	1377 (34.4)	2711 (33.8)
pT3	112 (2.8)	114 (2.8)	226 (2.8)
pT4	34 (0.8)	35 (0.9)	69 (0.9)
Other	1 (<0.1)	0	1 (<0.1)
Missing	22 (0.5)	18 (0.4)	40 (0.5)
Pathological stage: node			
pNx (axilla not examined)	2 (<0.1)	3 (<0.1)	5 (<0.1)
pNx (0 pos / 1-7 examined)	258 (6.4)	251 (6.3)	509 (6.4)

pN sentinel neg	383 (9.6)	371 (9.3)	754 (9.4)
pN0	1697 (42.4)	1723 (43.0)	3420 (42.7)
pN1	1372 (34.3)	1368 (34.1)	2740 (34.2)
pN2	96 (2.4)	103 (2.6)	199 (2.5)
pN1 / pN2 (NOS)	192 (4.8)	180 (4.5)	372 (4.6)
Missing	3 (<0.1)	8 (0.2)	11 (0.1)
No. of positive nodes for patients who had axillary dissection			
None	2296 (57.4)	2301 (57.4)	4597 (57.4)
1-3 positive nodes	1158 (28.9)	1137 (28.4)	2295 (28.7)
4-9 positive nodes	335 (8.4)	359 (9.0)	694 (8.7)
10+ positive nodes	166 (4.1)	150 (3.7)	316 (3.9)
Missing	5 (0.1)	12 (0.3)	17 (0.2)
ER/PgR status			
Positive/Positive	2542 (63.5)	2513 (62.7)	5055 (63.1)
Positive/Negative	808 (20.2)	823 (20.5)	1631 (20.4)
Positive/Unknown-Missing	579 (14.5)	575 (14.3)	1154 (14.4)
Negative/Positive	60 (1.5)	83 (2.1)	143 (1.8)
Other	14 (0.3)	13 (0.3)	27 (0.3)

Table: Prior primary treatment for breast cancer (ITT population)

	Letrozole N=4003 n (%)	**Tamoxifen N=4007 n (%)**	**Total N=8010 n (%)**
Primary surgery			
Less than mastectomy	2249 (56.2)	2299 (57.4)	4548 (56.8)
Mastectomy	1749 (43.7)	1703 (42.5)	3452 (43.1)
Other	3 (<0.1)	5 (0.1)	8 (<0.1)
Missing	2 (<0.1)	0	2 (<0.1)
Axillary clearance			
None	41 (1.0)	45 (1.1)	86 (1.1)
Axillary dissection	3560 (88.9)	3563 (88.9)	7123 (88.9)
Axillary sentinel lymph node biopsy only	400 (10.0)	396 (9.9)	796 (9.9)
Missing	2 (<0.1)	3 (<0.1)	5 (<0.1)
Radiation therapy			
Yes	2872 (71.7)	2872 (71.7)	5744 (71.7)
No	1129 (28.2)	1129 (28.2)	2258 (28.2)
Missing	2 (<0.1)	6 (0.1)	8 (<0.1)
Left breast radiation	1476 (36.9)	1472 (36.7)	2948 (36.8)
Chemotherapy			
Completed before study	949 (23.7)	955 (23.8)	1904 (23.8)
None	2998 (74.9)	2998 (74.8)	5996 (74.9)
Start concurrent	56 (1.4)	54 (1.4)	110 (1.4)

Anthracycline-containing CT	301 (7.5)	334 (8.3)	635 (7.9)
Completed before study	284	318	602
None[1]	1	0	1
Start concurrent	16	16	32

[1] Patient not intended to receive chemotherapy but did.

Overall, 62% of the patients had pT1 tumours. Almost the same number of patients (62%) had small tumours of up to 2 cm. Overall, 41% of the patients had node positive tumours at surgery. More than half of the patients had breast-conserving surgery prior to study entry, 72% had received local radiotherapy, and about 25% of the patients in each arm had received prior adjuvant chemotherapy. The patient population was representative of the proposed indication and other primary treatment was in accordance with the current standard of care.

Overall treatment groups were adequately balanced with respect to key baseline variables determining risk of recurrence including disease staging, nodal involvement and receptor status. No obvious between-treatment differences were observed with respect to the surgical procedures employed for resection, or the exposure to chemotherapy or radiation treatment. Some differences in baseline data between the 2 randomisation options are noted, but these are taken into account by the stratification of the primary analysis.

Patient disposition and extent of follow-up

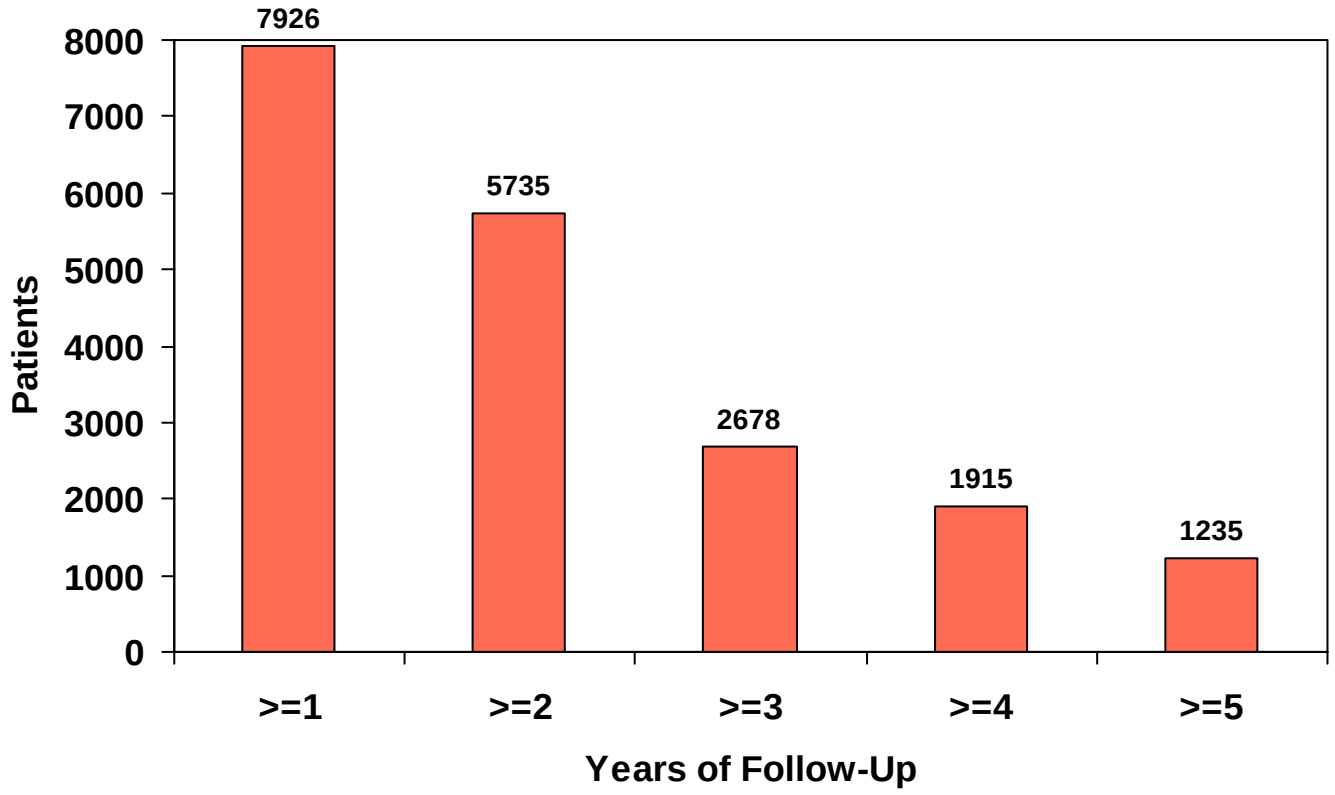
This is summarised in the table below:

	Letrozole N=4003 n (%)	**Tamoxifen N=4007 n (%)**	**Total N=8010 n (%)**
Patients not treated	28 (0.7)	19 (0.5)	47 (0.6)
Treatment ongoing	2555 (63.8)	2543 (63.5)	5098 (63.6)
Completed 5 years treatment	640 (16.0)	612 (15.3)	1252 (15.6)
Treatment discontinued on or before cutoff	780 (19.5)	833 (20.8)	1613 (20.1)
Reason for discontinuation			
Adverse event(s)	416 (10.4)	381 (9.5)	797 (10.0)
Progression of disease[1]	215 (5.4)	310 (7.7)	525 (6.6)
Subject withdrew consent	64 (1.6)	66 (1.6)	130 (1.6)
Death	39 (1.0)	30 (0.7)	69 (0.9)
Protocol violation	21 (0.5)	16 (0.4)	37 (0.5)
Lost to follow-up	14 (0.3)	11 (0.3)	25 (0.3)
Abnormal laboratory value(s)	3 (<0.1)	8 (0.2)	11 (0.1)
Administrative problems	4 (<0.1)	4 (<0.1)	8 (<0.1)
Abnormal test procedure result(s)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Missing	1 (<0.1)	2 (<0.1)	3 (<0.1)
Other	2 (<0.1)	4 (<0.1)	6 (<0.1)

[1]Includes second malignancies

The overall median duration of study medication in BIG 1-98 was 24 months, although in option 2 (in which patients were randomised to letrozole for 5 years or tamoxifen for 5 years) the majority of patients had completed 5 years adjuvant therapy. The median follow-up for letrozole presented is 26 months. Follow-up is detailed further in the figure below

Figure: Extent of follow-up



As discussed above, this submission is based on the "Primary Core Analysis" and looks at whether letrozole taken for 5 years is superior to tamoxifen taken for 5 years. The data thus involve data from patients enrolled into the 2-arm randomisation option, as well as data truncated 30 days after the switch, from the two switching arms.

A total of 779 progression events occurred for the Primary Core Analysis – 351 (8.8%) in the letrozole arm, 428 (10.7%) in the tamoxifen arm – giving a hazard ratio of 0.81 (95% CI 0.70, 0.93), p=0.003 (see table and figure below)

The 5-year disease-free survival rates were 84.0% for letrozole and 81.4% for tamoxifen.

Letrozole significantly reduced the risk of recurrence compared with tamoxifen in both randomization options and irrespective of whether adjuvant chemotherapy was given, these were the 2 stratification factors at randomization (figure)

Figure: Forest plot of DFS by stratification factors (ITT population)

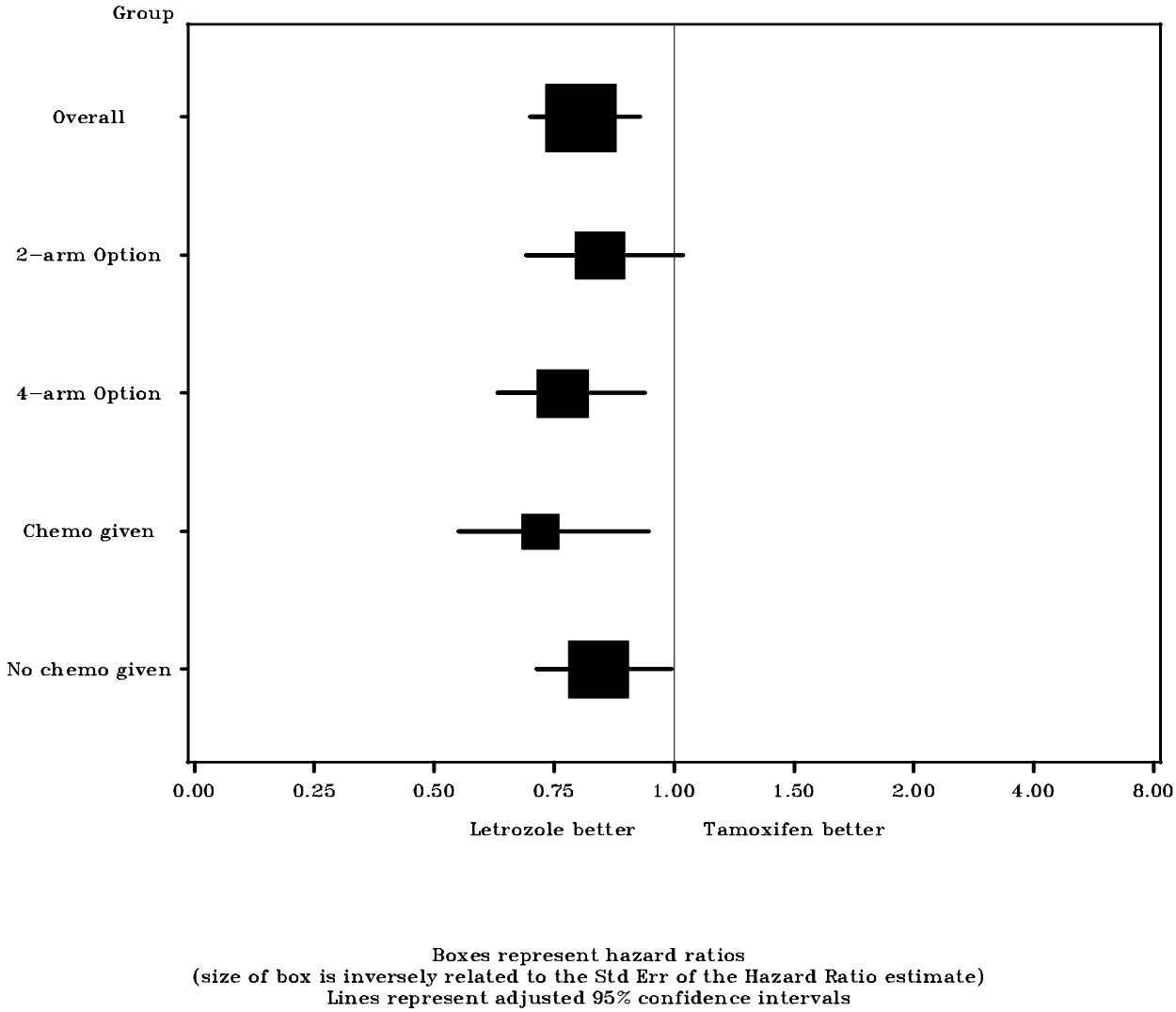
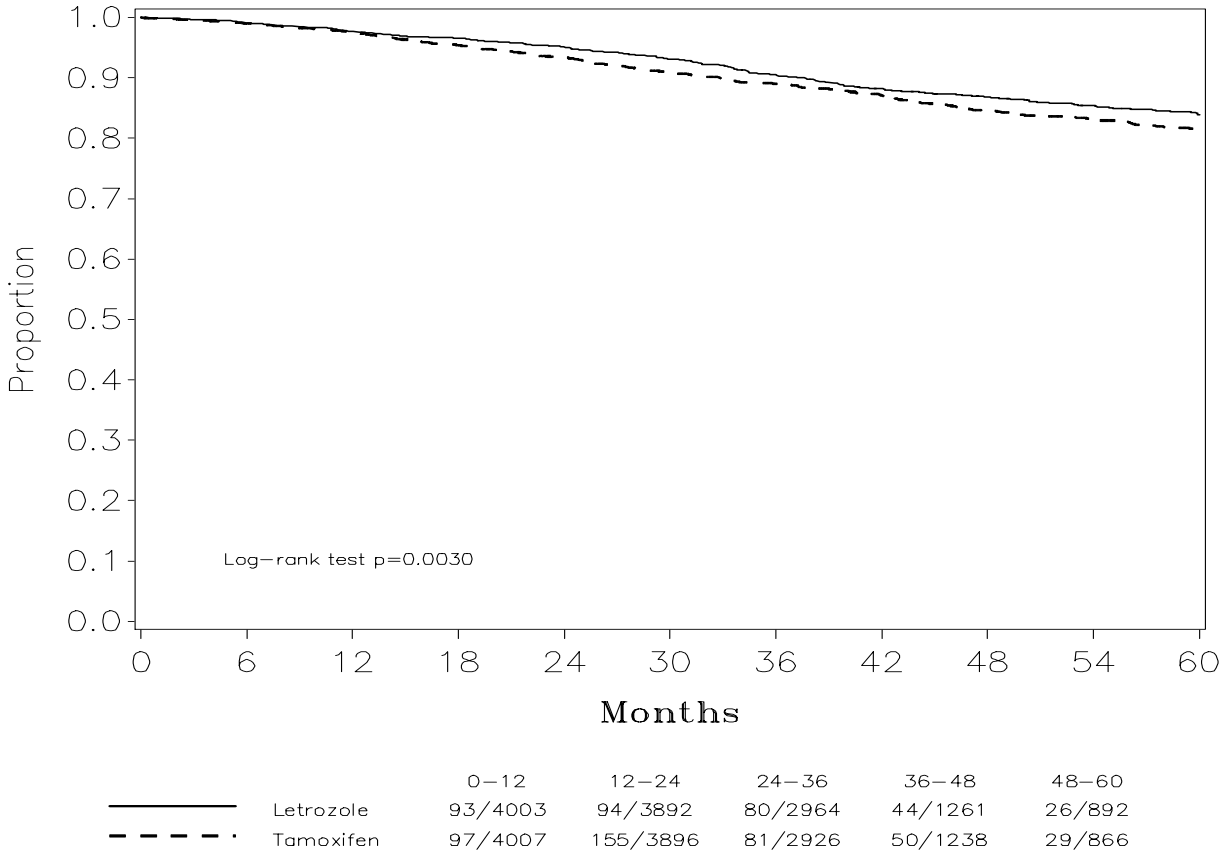


Table and figure: Primary analysis of disease-free survival (ITT population)

	Number of DFS events	**Hazard ratio**	**95% C.I.: lower bound**	**95% C.I.: upper bound**	**Stratified logrank *P*-value**
Letrozole N=4003	351	0.81	0.70	0.93	0.0030
Tamoxifen N=4007	428				



The nature of the recurrences are given in the following table. Approximately half of the events of first failure were in distant sites.

Table: Summary of first events in the analysis of disease-free survival (ITT population)

Site of first failure	**Letrozole N=4003 n (%)**	**Tamoxifen N=4007 n (%)**
Total failures (DFS events)	351 (8.8)	428 (10.7)
Local	21 (0.5)	37 (0.9)
Contralateral breast (invasive)	16 (0.4)	27 (0.7)
Regional[1]	13 (0.3)	12 (0.3)
Distant soft tissue	11 (0.3)	19 (0.5)
Bone	80 (2.0)	99 (2.5)
Viscera	86 (2.1)	114 (2.8)
Second malignancy	69 (1.7)	82 (2.0)
Death without prior cancer event	55 (1.4)	38 (0.9)

[1] Including axillary or internal mammary nodes

Letrozole reduced the risk of recurrence or relapse by 19% compared with tamoxifen (approx 2% absolute difference), which was both highly statistically significant and of clinical relevance. In a few patients, hormone receptor status was unknown or missing, the relative risk of reduction in recurrence for women with known hormone receptor positive tumours (the actual proposed indication) was 20% (95% CI 0.69, 0.92; p=0.002)

Sensitivity analyses of DFS results excluding various combinations of 2nd primary cancers, contralateral breast cancer & death without recurrence all gave a statistically significant reduction in the risk of recurrence in favour of letrozole.

Overall, only 10% reached the point of a recurrence event. However around 20% of the patients involved in the 2-arm randomisation option had a recurrence event. Note that overall median follow-up is 26 mths, but the data are from patients randomised into the 2-arm and 4-arm randomisation options. In the 2-arm option, (which started 18 months before the 4-arm option) there is more follow-up, almost all patients had completed 5 years adjuvant therapy and 1235 patients have over 5 years of follow-up.

The 5-year disease-free survival rates were 84.0% for letrozole and 81.4% for tamoxifen.

From historical data (EBCTG meta-analysis in Lancet 2005;365:16687-1717), the 5-year DFS rates in node-positive and node –negative patients treated with 5 years of tamoxifen were 75% and 89% respectively. Based just on this and given the proportions of node positive and node-negative patients in BIG 1-98, the 5 year DFS rate expected for tamoxifen-treated patients in BIG 1-98 comes out at 83%. This is slightly less than what was seen. It is odd at first glance that tamoxifen performance is inferior to this historical comparison, given that improvements in primary therapy would tend to improve results over time. In addition, the above figures from EBCTG include some ER negative/ ER unknown patients, thus understating the effects of tamoxifen. However, the comparison is not so crucial as it would be in a non-inferiority study, some difference between studies is to be expected as so many variables are involved, and the difference does not raise serious concerns.

Primary endpoint: Efficacy in key subgroups

As noted above, letrozole significantly reduced the risk of recurrence compared with tamoxifen irrespective of whether adjuvant chemotherapy was given.

In node positive patients, letrozole significantly reduced the risk of recurrence compared with tamoxifen by 29% (HR 0.71; 95% CI 0.59, 0.85; *P*=0.0002)

There was no statistically significant difference in DFS in node negative patients (HR 0.98; 95% CI 0.77, 1.25; *P*=0.89).

Overall survival

There was a non-significant 14% reduction in the risk of mortality overall in favor of letrozole (HR 0.86; 95% CI 0.70, 1.06; *P*=0.15).

Table: Primary analysis of overall survival (ITT population)

	Number of OS PC events	Hazard ratio	95% C.I.: lower bound	95% C.I.: upper bound	Stratified logrank p-value
Letrozole N=4003	166	0.86	0.70	1.06	0.1546
Tamoxifen N=4007	192				

A breakdown of the cause of deaths, and the small imbalance in non-cancer deaths, discussed in the safety section below. A low number of deaths with the current follow-up is expected in the good-prognosis population studied. Given the patient population, further data on overall survival will not be available for several years. There was no planned test of whether letrozole was non-inferior to tamoxifen for overall survival, although the upper bound of the confidence interval is 1.06 and this is not considered to be an issue.

Other secondary efficacy endpoints

Systemic disease-free survival: The risk of systemic recurrence was significantly lowered in the letrozole arm compared with the tamoxifen arm (hazard ratio 0.83; 95% CI 0.72, 0.97; P=0.02; PTT 9.2-7).

Distant disease-free survival: Overall, the risk of distant failure was significantly lowered (by 27%) in the letrozole arm compared with tamoxifen (hazard ratio 0.73; 95% CI 0.60, 0.88; P=0.001).

Contralateral breast cancer: The number of patients who developed invasive contralateral breast cancer in the primary core analysis was relatively small in both treatment arms – 19 patients in the letrozole arm and 31 in the tamoxifen arm. The almost 40% reduction in the risk of contralateral breast cancer was not statistically significant.

Deaths

Table: Breakdown of all deaths (ITT population)

	Letrozole N=4003 n (%)	Tamoxifen N=4007 n (%)	Total N=8010 n (%)
No. of patients who died	166 (4.1)	192 (4.8)	358 (4.5)
Cause of death			
Progression of underlying breast cancer [1]	100 (2.5)	135 (3.4)	235 (2.9)
MI	10 (0.2)	2 (<0.1)	12 (0.1)
Stroke	6 (0.1)	1 (<0.1)	7 (<0.1)
Thromboembolic event	3 (<0.1)	5 (0.1)	8 (<0.1)
Other: cardiac	16 (0.4)	10 (0.2)	26 (0.3)
Other: CVA	2 (<0.1)	2 (<0.1)	4 (<0.1)
Other	19 (0.5)	14 (0.3)	33 (0.4)
Cause unknown	8 (0.2)	21 (0.5)	29 (0.4)
Cause missing	2 (<0.1)	2 (<0.1)	4 (<0.1)

[1] Including death from second non-breast primary cancer

Table: Deaths reported during treatment or within 30 days of stopping treatment (or switching treatment) (Safety population)

	Letrozole N=3975 n (%)	**Tamoxifen N=3988 n (%)**	**Total N=7963 n (%)**
Number of patients who died	50 (1.3)	48 (1.2)	98 (1.2)
Cause of death			
Progression of underlying breast cancer [1]	14 (0.4)	20 (0.5)	34 (0.4)
Myocardial infarction	6 (0.2)	1 (<0.1)	7 (<0.1)
Stroke	2 (<0.1)	1 (<0.1)	3 (<0.1)
Thromboembolic event	2 (<0.1)	2 (<0.1)	4 (<0.1)
Other cardiac	13 (0.3)	8 (0.2)	21 (0.3)
Other CVA	2 (<0.1)	0	2 (<0.1)
Other	10 (0.3)	8 (0.2)	18 (0.2)
Cause unknown	1 (<0.1)	6 (0.2)	7 (<0.1)
Cause missing	0	2 (<0.1)	2 (<0.1)

[1] Includes death from a second non-breast cancer

Both the above tables show that there is a small excess of non-cancer deaths, with more cardiovascular deaths in particular with letrozole.
Comparison of the tables shows that the majority of deaths occurred off-treatment. Cardiac deaths and cerebrovascular deaths which occurred on letrozole treatment or within 30 days of last letrozole dose also showed an approximately equal distribution over time. The overall reduction in mortality with letrozole should of course be taken into account, as should be the reduction in distant disease recurrence rate with letrozole, which predicts a further separation between treatments in mortality.
The overall reduction in mortality with letrozole also means that the numbers of patients "at risk" of a non-breast cancer death during the study is somewhat higher in the letrozole treatment group.

Given the relatively small numbers of non-breast cancer deaths, the deaths with cause unknown/missing are a significant proportion of these (e.g. for all deaths analysis, 10 for letrozole group and 23 for tamoxifen group). Further information on these might be requested.

A difference in CV deaths is plausible given the difference in pharmacology of the 2 drugs, although the increase in risk compared to women in the tamoxifen arm may be interpreted as compatible with either an increased risk of letrozole, or a decreased risk of tamoxifen, or both.

Table: Comparison of some CV events in ATAC study

	Anastrozole 1 mg (N=3092)	Tamoxifen 20 mg (N=3094)
Ischaemic cardiovascular disease	127 (4.1)	104 (3.4)
• Angina pectoris	71 (2.3)	51 (1.6)
• Myocardial infarct	37 (1.2)	34 (1.1)
• Coronary artery disorder	25 (0.8)	23 (0.7)
• Myocardial ischaemia	22 (0.7)	14 (0.5)

The MAH has compared cardiac mortality to an epidemiological study in 7944 post-menopausal women aged 57-65 years, who were followed up for 7 years[1]. The women in this study were those participating in mammography screening. The absolute risks per 1000 person years between BIG 1-98 and this study are summarised in the table below:

Table Incidence of cardiac mortality in Study BIG 1-98 and in the general population of postmenopausal women

Type of event	**Number of events per 1000 person years**		
	Letrozole*	**Tamoxifen***	**General population****
Fatal MI	0.7	0.1	1.1-1.2
Other CAD death	1.2	0.9	0.8-1.0
Total	1.9	1.0	1.9-2.2

*Death on treatment or within 30 days of last dose / total exposure approximately 10000 person years for each treatment

**Source: Sourander et al, 1998; absolute risk for women not receiving estrogen replacement therapy (range reflecting variation between former users and women who never used ERT)

In this analysis the incidence of fatal MI seen in the letrozole group is less than expected from the comparator population, with the incidence significantly less so for tamoxifen. However it is not clear that this Finnish study best matches the demographic profile of the study, the patients appearing to be at higher cardiovascular risk from the limited baseline information provided.

In addition, whilst the narrow age range of the study by Sourander matches the median age of BIG 1-98 patients, a range of age-specific comparisons would have been useful.
The assessor is aware from previous assessments that no population-based studies providing age-specific incidence of MI/cardiac failure in women with breast cancer are available. However, for MI and cardiac failure, the MAH might be asked to provide further comparisons to databases matching the demographic profile of the study and containing age-specific estimates similar to the age ranges of BIG 1-98.

In a related submission, standardised incidence ratios[2] for each age subgroup were compared to UK GPRD data[3] and Swedish registry data[4] for cardiac failure and MI incidence respectively.

[1] Sourander et al, Cardiovascular and cancer morbidity and mortality and sudden cardiac death in postmenopausal women on oestrogen replacement therapy (ERT). Lancet; 352:1965-9
[2] Rothman KJ, Greenland S. Modern Epidemiology, 2cnd Ed. Lippincott-Raven

Serious adverse events

The commonest SAEs are given in the table below. Fractures and cardiovascular events are discussed in more detail later. SAEs regardless of causality were seen in 14.7% of patients in the letrozole group vs. 16.2% in the tamoxifen group. Overall, 453 (5.7%) of all patients experienced an SAE that was judged by the investigator to be of suspected relationship to study drug. Of these, 177 patients (4.5%) were treated with letrozole and 276 patients (6.9%) with tamoxifen.

Table: Number (%) of patients with serious adverse events - by frequency 0.5% or greater in either treatment arm (Safety population)

	All grades		
Preferred term	**Letrozole N=3975 n (%)**	**Tamoxifen N=3988 n (%)**	**Total N=7963 n (%)**
Fracture NOS	67 (1.7)	46 (1.2)	113 (1.4)
Thromboembolism	23 (0.6)	60 (1.5)	83 (1.0)
CVA/TIA	34 (0.9)	37 (0.9)	71 (0.9)
Cholelithiasis	21 (0.5)	19 (0.5)	40 (0.5)
Uterine polyp NOS	2 (<0.1)	33 (0.8)	35 (0.4)
Vaginal hemorrhage	5 (0.1)	27 (0.7)	32 (0.4)
Endometrial hyperplasia	0	27 (0.7)	27 (0.3)

Adverse events – general

Only pre-specified AEs were reported, along with AEs leading to discontinuation and SAEs. Whilst the list of pre-specified AEs (below) covers events of major interest and this is not the first major study to adopt this approach, this is not seen as ideal. If you only look for expected adverse events, then this is all you are likely to find. Grades of severity were also not recorded for baseline signs and symptoms

Overall, 91% of the patients reported at least one AE in the letrozole arm compared with 86% in the tamoxifen arm regardless of relationship to study drug. AEs suspected of being related to study treatment were reported by 75.2% of the patients in the letrozole arm, compared with 70.8% in the tamoxifen arm.

AEs leading to discontinuation were reported in 11.3% of the letrozole group and 10.4% in the tamoxifen group.

The commonest AEs are given in the table below:

[3] Johansson S, Wallander MA, Ruigomez A et al. Incidence of newly diagnosed heart failure in UK general practice. Eur Heart Failure 2001;3:225-231

[4] Statistics – Health and Diseases. Myocardial infarction in Sweden 1987-1996. The National Board of Health and Welfare. Official Statistics of Sweden. Printed in Sweden by Norstedts Trickeri AB. Stockholm, 25 June 1998. Internet available at: http://www.sos.se/FULLTEXT/9842-006/9842-006.pdf

Table: Number (%) of patients with adverse events – by frequency (5% or more in any group) - Safety population

Preferred term	Letrozole N=3975 n (%)	Tamoxifen N=3988 n (%)	Total N=7963 n (%)
Flushing[1]	1338 (33.7)	1515 (38.0)	2853 (35.8)
Arthralgia	682 (17.2)	425 (10.7)	1107 (13.9)
Night sweats	554 (13.9)	647 (16.2)	1201 (15.1)
Weight increased	425 (10.7)	515 (12.9)	940 (11.8)
Nausea	350 (8.8)	381 (9.6)	731 (9.2)
Fracture NOS	226 (5.7)	161 (4.0)	387 (4.9)
Fatigue	211 (5.3)	218 (5.5)	429 (5.4)
Vaginal hemorrhage	132 (3.3)	265 (6.6)	397 (5.0)

Patients on letrozole were more likely to have arthralgia/arthritis and myalgia. Adverse events related to endometrial effects, as well as thromboembolic events, were more common in the tamoxifen arm. The pattern of AEs for each drug was as expected from previous experience. Other than the AEs discussed, adverse events were generally comparable in frequency and nature between treatment arms.

A number of adverse events of particular interest were "pre-specified" and given as a check-list on case record forms. These are tabulated below:

Table: Pre-specified adverse events

Adverse event	Letrozole N=3975 n (%)	Tamoxifen N=3988 n (%)	Total N=7963 n (%)
Hot flashes/flushes	1338 (33.7)	1515 (38.0)	2853 (35.8)
Arthralgia/Arthritis	841 (21.2)	537 (13.5)	1378 (17.3)
Night sweats	561 (14.1)	654 (16.4)	1215 (15.3)
Nausea	378 (9.5)	418 (10.5)	796 (10.0)
Fatigue (lethargy,malaise,asthenia)	333 (8.4)	345 (8.7)	678 (8.5)
Edema	286 (7.2)	288 (7.2)	574 (7.2)
Myalgia	256 (6.4)	243 (6.1)	499 (6.3)
Bone fractures	226 (5.7)	161 (4.0)	387 (4.9)
Vaginal bleeding	177 (4.5)	413 (10.4)	590 (7.4)
Headache	143 (3.6)	126 (3.2)	269 (3.4)
Vaginal irritation	139 (3.5)	122 (3.1)	261 (3.3)
Vomiting	109 (2.7)	107 (2.7)	216 (2.7)
Dizziness/light-headedness	97 (2.4)	112 (2.8)	209 (2.6)
Osteoporosis	80 (2.0)	44 (1.1)	124 (1.6)
Constipation	59 (1.5)	95 (2.4)	154 (1.9)
Cataract	48 (1.2)	39 (1.0)	87 (1.1)
Breast pain	40 (1.0)	47 (1.2)	87 (1.1)
Anorexia	33 (0.8)	31 (0.8)	64 (0.8)
Ovarian cyst	17 (0.4)	14 (0.4)	31 (0.4)
Endometrial proliferation disorders	10 (0.3)	73 (1.8)	83 (1.0)
Other endometrial disorders	3 (<0.1)	4 (0.1)	7 (<0.1)

Cardiovascular events

Deaths due to cardiovascular events have been discussed above. Overall cardiovascular events are detailed further in the tables below. For both tables, patients can have more than one event. For type of event a patient can be included in more than one category but is only counted once per category. Switch group patients are cut off at switch date + 30 days:

Table: Number (%) of patients with cardiovascular events during treatment or within 30 days of stopping treatment (all events, safety population)

	Letrozole N=3975 n (%)	Tamoxifen N=3988 n (%)	Total N=7963 n (%)
Number of patients with:			
Cardiovascular events			
No	3589 (90.3)	3570 (89.5)	7159 (89.9)
Yes	386 (9.7)	418 (10.5)	804 (10.1)
CRF pre-specified event			
Myocardial infarction	24 (0.6)	15 (0.4)	39 (0.5)
Cerebrovascular/TIA	49 (1.2)	42 (1.1)	91 (1.1)
Angina	27 (0.7)	24 (0.6)	51 (0.6)
Thromboembolic event	46 (1.2)	111 (2.8)	157 (2.0)
Other	275 (6.9)	258 (6.5)	533 (6.7)
Event by group[1]			
Arrhythmia	76 (1.9)	92 (2.3)	168 (2.1)
Cardiac failure	34 (0.9)	14 (0.4)	48 (0.6)
Cardiopathy	14 (0.4)	13 (0.3)	27 (0.3)
Cerebrovascular	56 (1.4)	43 (1.1)	99 (1.2)
ECG changes	1 (<0.1)	1 (<0.1)	2 (<0.1)
Hypertension	140 (3.5)	124 (3.1)	264 (3.3)
Ischemic CVD	60 (1.5)	46 (1.2)	106 (1.3)
Thromboembolic event	46 (1.2)	111 (2.8)	157 (2.0)
Other	14 (0.4)	13 (0.3)	27 (0.3)

[1] Includes specific and "other" CRF pre-specified events, grouping the cardiovascular terms according to their etiology.

Table: Number (%) of patients with CV events any time after randomization, safety population)

	Letrozole N=3975 n (%)	Tamoxifen N=3988 n (%)	Total N=7963 n (%)
Number of patients with:			
Cardiovascular events			
No	3562 (89.6)	3543 (88.8)	7105 (89.2)
Yes	413 (10.4)	445 (11.2)	858 (10.8)
CRF pre-specified event			
Myocardial infarction	31 (0.8)	17 (0.4)	48 (0.6)
Cerebrovascular/TIA	54 (1.4)	49 (1.2)	103 (1.3)
Angina	27 (0.7)	24 (0.6)	51 (0.6)
Thromboembolic event	56 (1.4)	120 (3.0)	176 (2.2)
Other	283 (7.1)	272 (6.8)	555 (7.0)
Event by group			
Arrhythmia	78 (2.0)	103 (2.6)	181 (2.3)
Cardiac failure	36 (0.9)	15 (0.4)	51 (0.6)
Cardiopathy	15 (0.4)	15 (0.4)	30 (0.4)
Cerebrovascular	60 (1.5)	50 (1.3)	110 (1.4)
ECG changes	1 (<0.1)	1 (<0.1)	2 (<0.1)
Hypertension	140 (3.5)	126 (3.2)	266 (3.3)
Ischemic CVD	68 (1.7)	49 (1.2)	117 (1.5)
Thromboembolic event	56 (1.4)	120 (3.0)	176 (2.2)
Other	15 (0.4)	13 (0.3)	28 (0.4)

Overall, the incidence of these events was comparable between letrozole and tamoxifen. For all cardiovascular events, there is a small excess in the tamoxifen group, however there was a small excess of MI and cardiac failure events in the letrozole arm. This was driven by events in patients aged 65 years or older.

On the other hand, thromboembolic events were around twice as frequent in patients on tamoxifen, irrespective of whether they were younger or older than 65 years.

Whether the thromboembolic events were of similar clinical significance to the events seen more frequently in the letrozole group is an important consideration It is important that the overall comparison of cardiovascular/cerebrovascular events is not "diluted" by numbers of superficial thrombotic events in the tamoxifen arm. DVT not requiring anticoagulation counted as a thromboembolic event as per the protocol. It is difficult to separate out what the events were, as many AEs were recorded as "thromboembolism". However, the number of AEs attributed to thromboembolism rated as SAEs were 23 in the letrozole group vs. 60 in the tamoxifen group. The numbers of serious adverse events for cardiovascular disorders overall were 2.1% vs. 1.3% respectively.

In patients randomized to the 2 arm option, the group with the longest follow-up, the overall rate of cardiovascular/cerebrovascular events (all events) was 17.2% in the letrozole arm and 15.5% in the tamoxifen arm, rates of MI 1.8% vs. 0.7%, rates of cardiac failure 2 vs. 0.7%.

As patients may potentially suffer from a sequence of multiple cardiovascular events, a hierarchical time-to-event analysis was performed by the MAH:

Table: All deaths and cardiovascular adverse events (safety population, any time after randomization)

Outcome	Letrozole N=3975 n (%)	Tamoxifen N=3988 n (%)	Hazard ratio (95% CI)
All deaths	164 (4.1)	192 (4.8)	0.85 (0.69, 1.05)
Death or MI	183 (4.6)	204 (5.1)	0.90 (0.73, 1.09)
Death, MI or angina	206 (5.2)	226 (5.7)	0.91 (0.75, 1.10)
Death, MI, angina or cardiac failure	224 (5.6)	235 (5.9)	0.96 (0.80, 1.15)
Death, MI, angina, cardiac failure or thromboembolic event	269 (6.8)	338 (8.5)	0.79 (0.67, 0.93)
Death or any cardiovascular event[1]	526 (13.2)	593 (14.9)	0.88 (0.78, 0.99)

When all deaths or any cardiovascular event are considered, patients in the letrozole arm still had a favourable hazard ratio of 0.88 compared to tamoxifen. This hierarchical analysis is an appropriate way to present the data.

Osteoporosis and fractures

In the main study, osteoporosis was approximately doubled in the letrozole arm (2% vs. 1.1%). This was presumably self reported without using a standardised definition.

Overall, the numbers of patients with bone fractures were significantly higher with letrozole (6.4%) than with tamoxifen (4.8%). As might be expected, these occurred more commonly in the elderly, and in patients with a history of osteoporosis or fracture.

The wrist was the most frequently affected location of bone fracture. The overall rate of hip fractures in the letrozole arm was 0.7% compared to 0.5% in the tamoxifen arm. Importantly, the risk of fracture appears to be relatively constant over time during treatment. The fracture data are detailed in the table below.

Table: Number of patients with bone fractures (at any time after randomization) (Safety population)

	Letrozole N=3975 n (%)	**Tamoxifen N=3988 n (%)**
Bone fractures		
No	3722 (93.6)	3796 (95.2)
Yes	253 (6.4)	192 (4.8)
Main cause		
Metastasis	18 (0.5)	26 (0.7)
Osteoporosis	18 (0.5)	18 (0.5)
Trauma	214 (5.4)	135 (3.4)
Other	2 (<0.1)	2 (<0.1)
Missing	7 (0.2)	14 (0.4)
Location of bone fracture		
Spinal compression*	32 (0.8)	34 (0.9)
Pelvis	14 (0.4)	12 (0.3)
Wrist	67 (1.7)	39 (1.0)
Ankle	24 (0.6)	12 (0.3)
Femur	26 (0.7)	19 (0.5)
Tibia	7 (0.2)	3 (<0.1)
Other	98 (2.5)	83 (2.1)
Missing	1 (<0.1)	3 (<0.1)

A patient can have more than one bone fracture. For the main cause and location of bone fracture a patient can be included in more than one category but is only counted once per category.
P-value based on Fisher's exact test
* Spinal compression includes cervical, thoracic and lumbar locations.

A sub-study to look at BMD was initiated after the main study had started, but only enrolled 43 patients, with 2 year data currently only available for only 2 patients. As such the available data from this is not very contributory.

Overall in the main study, about 1.3% of the patients overall were receiving bisphosphonates at baseline (4% of patients were reported to have osteoporosis at study enrolment). Post-baseline, slightly more patients in the letrozole arm (6.3%) than in the tamoxifen arm (5.0%) required bisphosphonates. Use of calcium and vitamin D were only formally recorded for the BMD sub-study.

Endometrial events

Rates of endometrial disorders were increased in the tamoxifen group. There were more frequent endometrial disorders described as simple hyperplasia (0.1% vs. 1.0%) or "other" (0% vs. 0.4%). The rates of vaginal bleeding were 4.5% in the letrozole group vs. 10.4% in the tamoxifen group. Vaginal bleeding recorded as a serious AE was seen in 0.7% of the

tamoxifen group but in no letrozole patients. Endometrial carcinoma was more frequent with tamoxifen (12 vs. 7 cases).

Lipids

Total cholesterol was recorded throughout the study. Hypercholesterolemia was one of the AEs pre-specified for review on the CRF, and was more frequent in patients treated with letrozole (43%) compared with tamoxifen (19%).

Overall, women allocated to tamoxifen experienced a prompt decrease in median serum cholesterol concentration (12%) at the 6-month visit. This decrease (median 10-15%) was maintained throughout the 5-year treatment period. In contrast, cholesterol remained stable over time in the letrozole arm. At 6 months of treatment, median total cholesterol in the letrozole arm was identical to the median baseline value. Small decreases (1-3%, maximally up to 7%) in median total cholesterol occurred throughout the study.

As the MAH notes, interpretation of this data is limited as the samples were generally taken non-fasting. Assessment of individual reports of hypercholesterolemia is difficult as this was not quantified further, i.e. it was recorded as being present or absent only.

Lipid-lowering agents were being used by around 8-10% of the patients overall at study enrolment, with slightly more patients in the letrozole arm continuing to receive lipid-lowering drugs (9.0% vs. 7.5%). At any time after randomization, lipid-lowering drugs were required more often by patients in the letrozole arm (18%) than in the tamoxifen arm (12%)

In addition, 400 of the patients enrolled into the core study were planned to be recruited to a substudy designed to assess the effect of letrozole and tamoxifen on serum lipid levels (HDL, LDL, HDL/LDL ratio, triglycerides and lipoprotein a), with samples taken under fasting conditions every 6 months for the first 3 years and annually thereafter. Additional exclusion criteria applied to this study, and the patients were required to have a baseline fasting cholesterol <6.2 mmol/l. An increase of at least one CTC grade over baseline was recorded for 4 patients on letrozole, compared to none on tamoxifen.

However, only 58 patients were enrolled into this lipid substudy by the time enrolment to the core study was completed, and the median follow-up was less than 2 years. As with the BMD sub-study, these data are not therefore very contributory.

5.1 Notes on supporting studies

The MAH has reviewed deaths and SAEs from ongoing studies MA-17, ZO-FAST, Z-Fast and E-ZO-FAST, for the period from January 1, 2004 to December 31 2004, and there is nothing of further concern from this.

Z-FAST aims to assess the addition of concomitant bisphosphonate therapy to letrozole treatment. It is an open-label, randomised, trial based in the US/Canada, target n=900, in postmenopausal women with stage I, II, IIIa, ER and/or PR+ breast cancer who have undergone complete tumour resection, with no clinical or radiological evidence of recurrent or metastatic disease. All patients are to be treated with letrozole for a maximum of five years, or until disease progression, the randomised intervention is one of the following:

- Zolendronic acid (Zometa) infusion every 6 months beginning on day one

- 6 monthly zolendronic infusions every 6 months, the start of which to be determined by a post-baseline bone mineral density below –2.0 SD.

ZO-FAST is similar but is being carried out outside the US. As well as postmenopausal women, this will be open to newly postmenopausal women in whom menopause has been artificially induced by medical intervention, i.e. by oestrogen suppressive therapy or chemotherapy.
An abstract concerning the Z-Fast study is included in the submission. Based on a preliminary analysis of 6 months data, "upfront" zolendronic acid may prevent bone loss in postmenopausal women with early stage breast cancer receiving letrozole. This looks promising, although as the abstract notes, analysis of long-term endpoints is needed.

The current SPC already has a warning as follows:
…women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry e.g. DEXA scanning at the commencement of treatment and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored."

It is proposed that this is further strengthened (and indeed aligned more with recent changes to Aromasin and Arimidex licenses) as follows:
"As letrozole is a potent oestrogen lowering agent, reductions in bone mineral density can be anticipated. The impact of letrozole on long-term fracture risk remains undetermined. During adjuvant treatment with letrozole, women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry at the commencement of treatment. Although adequate data to show the effects of therapy in the treatment of the bone mineral density loss caused by letrozole are not available, treatment for osteoporosis should be initiated as appropriate. Patients treated with letrozole should be carefully monitored."

In particular, as it is not known for certain whether women totally deprived of oestrogen respond in the same manner to bisphosphonates as post-menopausal women generally (hence ZO-FAST and other studies being underway to assess this), it is considered useful to notes this. This wording would also prompt the MAH rapidly to submit a variation for review when appropriate data with bisphosphonates or other therapies are available

Literature review

No significant safety issues not already discussed arose from the review of the published literature submitted.

Periodic safety update report

In the last variation for Femara (extended adjuvant indication) an update from spontaneous reports and post-marketing surveillance data was submitted from July 31, 2001 (cut-off date of the last PSUR) until December 31, 2003.

With this submission the MAH presents a review of events from 1st January 2004 to 31st December 2004. No new safety findings of note were identified

STATISTICAL ASSESSMENT OF EFFICACY

Study BIG 1-98

This was a randomised, double-blind, double-dummy trial to comparing letrozole with tamoxifen.

The study was conducted under two randomisation "options".

In option 2 there were 2 randomised groups: tamoxifen for 5 years; letrozole for 5 years.

A total of 1835 patients were enrolled in option 1 between March 1998 and March 2000. Of these, 1810 were enrolled by early September 1999 when randomisation into the two-arm study was closed. The remaining 25 had signed informed consent before the closure of enrolment, and were randomised when their chemotherapy was completed.

In option 1 there were 4 randomised groups: tamoxifen for 5 years; letrozole for 5 years; tamoxifen for 2 years followed by letrozole for 3 years; letrozole for 3 years followed by tamoxifen for 2 years.
The first patient accrued to option 1 was enrolled in April 1999. However for logistic reasons the next patient was not enrolled until September 1999. The final patient was randomised in May 2003, when enrolment was closed. A total of 6193 patients were enrolled in option 1.
The question to be addressed by this analysis is "Does letrozole for 5 years improve outcome compared with tamoxifen for 5 years". A second primary question regarding whether a sequence of therapies improves results compared with a continuous course with a single therapy will be the subject of a subsequent analysis planned for 2008.

The primary efficacy endpoint was disease free survival, defined as the time between randomisation and the earliest confirmed event of disease recurrence or death. The primary analysis was done using the log-rank test stratified by randomisation option and chemotherapy use. Hazard ratios with their associated 95% confidence intervals were obtained using Cox's proportional hazards with randomisation option and chemotherapy use as covariates.

This is the conventional analysis for progression free survival data and is appropriate for the indication in question.

The primary analysis was planned for when 647 events had occurred. Events in the switching arm of option 1 were only counted up to the time of the switch in medication (+30 days). In the event the final analysis included 779 events. All data collected up to December 1st 2004 were included.

Comment: It is considered appropriate to use events from both randomisation options in the primary analysis. Using all events, if the proportional hazards assumption is appropriate, gives the best estimate of the treatment effect.

It is appropriate to censor patients randomised into the switching arms at the point where they make the switch. Allowing a 30 day period after the switch where events are still counted seems sensible, if arbitrary. A progression occurring the day after the switch seems clearly the responsibility of the original treatment, but the duration to allow before the responsibility

is more likely to lie with the second treatment is unclear. However it is reassuring to note that if the duration is too long, the bias is likely to be against letrozole showing superiority over tamoxifen as it will tend to push the efficacy of the treatments together.

Results

The final analysis was conducted at the 4.4% significance level to account for the 2 interim analyses (one conducted after 261 events, the other after 433). As shown in the table below there was a highly statistically significant advantage for letrozole over placebo in the primary analysis of disease free survival (p=0.0030 from stratified log-rank test). The overall survival data were immature, but still showed a trend in favour of letrozole.

Table: Efficacy summary

Disease free survival				
	Events	Hazard Ratio	95% CI	p-value*
Letrozole	351/4003 (8.8%)	0.81	(0.70,0.93)	0.0028
Tamoxifen	428/4007 (10.7%)			
Overall survival				
	Events	Hazard Ratio	95% CI	p-value*
Letrozole	166/4003 (4.1%)	0.86	(0.70,1.06)	0.1604
Tamoxifen	192/4007 (4.8%)			

* p-value from Cox proportional hazards model.

Long-term data

It is important to note that the question being tested is whether **5 years** treatment with letrozole is superior to 5 years treatment with tamoxifen. The primary analysis included many patients who were followed-up for only 1½ years (the last patients were randomised in May 2003 and data were collected up to December 2004).

An important question is whether there are enough patients with around 5 years follow-up to justify the efficacy of the posology being requested.

The applicant has provided three sets of analyses that can help address this concern.

Firstly, the table below shows the disease-free survival results including only patients randomised on or before 31 December 1999. As data were collected up to December 1st 2004, all of these patients had the potential for at least 4 years 11 months of follow-up.

Table: DFS results for patients randomised on/before 31 December 1999

Disease free survival				
	Events	Hazard Ratio	95% CI	p-value*
Letrozole	184/1006 (18.3%)	0.82	(0.67,0.99)	0.0422
Tamoxifen	219/1001 (21.9%)			

* p-value from Cox proportional hazards model.

We can see that the hazard-ratio is very similar to that seen from the overall data-set. In fact looking at all the annual cut-offs the odds-ratio stays fairly constant.

Table: Change of HR for DFS over time

Randomised on/before	**Minimum follow-up**	**Hazard-ratio**
31 December 1998	5 years 11 months	0.84 (0.62, 1.27)
31 December 1999	4 years 11 months	0.82 (0.67, 0.99)
31 December 2000	3 years 11 months	0.85 (0.71, 1.01)
31 December 2001	2 years 11 months	0.85 (0.72, 1.00)
31 December 2002	1 years 11 months	0.79 (0.69, 0.92)
31 December 2003	0 years 11 months	0.81 (0.70, 0.93)

The second analysis provided is one including only patients randomised to the original 2-arm option (letrozole 5 years vs. tamoxifen 5-years. Almost all of these patients had the potential for over 5 years follow-up. Although statistical significance is not seen here (possible because of the smaller patient numbers) the odds-ratio is again similar to that seen in the overall analysis.

Table: Efficacy in 2-arm patients

Disease free survival				
	Events	Hazard Ratio	95% CI	p-value*
Letrozole	177/917 (19.3%)	0.85	(0.69,1.04)	0.1097
Tamoxifen	202/911 (22.2%)			
Overall survival				
	Events	Hazard Ratio	95% CI	p-value*
Letrozole	98/917 (10.7%)	0.84	(0.64,1.10)	0.1963
Tamoxifen	116/911 (12.7%)			

* p-value from Cox proportional hazards model.

A further analysis gives independent incidence rates (quoted as rate per 100 patient years of follow-up) for each year of patient follow-up. [Note that year 1 refers to the first year of follow-up for each patient, regardless of whether this is 1999, 2000, 2001 etc. Similarly for subsequent years]. In each of the first 5 years of follow-up the incidence of disease free survival failures is lower for letrozole compared to tamoxifen, providing further reassurance that efficacy is not being solely driven by patients with short follow-up duration. For overall survival the rates are similar in the first 3 years but diverge sharply after that.

Table: Annual Incidence rates (events per 100 years follow-up)

	Total follow-up (years)		**Disease free survival**		**Overall survival**	
	Letrozole	Tamoxifen	Letrozole	Tamoxifen	Letrozole	Tamoxifen
Year 1	3959	3957	2.35	2.45	0.68	0.60
Year 2	3552	3523	2.65	4.40	1.24	1.59
Year 3	1646	1603	4.86	5.05	2.39	2.11
Year 4	1035	1010	4.25	4.95	2.80	3.35
Year 5	778	746	3.34	3.89	2.28	3.04
Year 6	154	152	9.07	10.53	1.77	6.99

In conclusion, the primary analysis provides highly statistically significant evidence of an advantage for letrozole over tamoxifen in terms of disease free survival. Supporting analyses have been provided which supply reassurance that the advantage is not solely driven by patients with short follow-up durations.

DISCUSSION

General comments

Clinical studies of tamoxifen in breast cancer began about 30 years ago, and it has previously been seen as a "gold standard" adjuvant therapy in hormone sensitive breast cancer.

However there is room for improvement over tamoxifen in terms of recurrence rate and side-effects (for example endometrial cancer and other endometrial abnormalities, serious thromboembolic complications), and in recent years there has been a proliferation of studies with letrozole and related drugs in this setting. Aromatase inhibitors are now challenging or beginning to supersede tamoxifen in several settings.

In advanced breast cancer and in neoadjuvant (pre-operative treatment), letrozole is demonstrably superior to tamoxifen in postmenopausal women with ER positive tumours. Letrozole has also shown to be confer additional efficacy benefits relative to no treatment, in women with early breast cancer completing 5 years of tamoxifen.

Following initial treatment for early breast cancer, i.e. in the indications now proposed for letrozole, anastrozole is agreed to be superior to tamoxifen in reducing risk of relapse. Whilst one should not extrapolate too much between the 2, and whilst there is currently a lack of direct comparative clinical data between them, the more extensive data available for anastrozole in the early breast cancer adjuvant setting are important as anastrozole has the same basic pharmacology and pharmacokinetic profile as letrozole, both are triazole non-steroidal selective aromatase inhibitors, and they suppress circulating oestrogen levels to a similar degree at comparable therapeutic doses.

Comments on the study design and conduct

The BIG 1-98 study was associated with several well-regarded study groups. It was large, well designed and well conducted in line with both general regulatory guidance and with specific regulatory guidance for cancer studies. The patient population was representative and the groups well balanced. There are no issues with the chosen dose of letrozole, the choice and dose of comparator, the choice, definition and hierarchy of endpoints, the way disease recurrence was assessed, and the methods of data analysis.

Efficacy results

The analysis in this submission corresponds to a median follow-up of 26 months for letrozole. However, as arms A and B were commenced before the other 2 arms, there are significant differences in length of follow-up so that for patients randomised to letrozole for 5 years/ tamoxifen for 5 years, the majority have completed 5 years adjuvant therapy. In the analysis submitted there were 1235 patients with 5 or more years of follow-up. The proposed duration of 5 years treatment is adequately justified by the current extent of exposure and follow-up in the pivotal study.

Letrozole significantly prolonged disease-free survival (primary endpoint) compared to tamoxifen (351 vs. 428 recurrence events, relative risk reduction 19% (95% CI 0.7-0.93, p=0.003). This is considered to be clinically relevant. The benefit was maintained in patients who had received chemotherapy. In node positive patients (41% of the population) the relative risk reduction for disease-free survival was 29%, whilst at this point there is only a weak trend in favour of letrozole for node-negative patients. Further differences were shown between treatments for distant disease free survival and contralateral breast cancer, although the latter analysis was not statistically significant. There was a non-significant 14% reduction in the risk of mortality overall in favour of letrozole, a low number of deaths being expected at this point in the follow-up for this population.

Although there are some difficulties in the comparison, the relative risk reduction in disease free survival compares well to the latest anastrozole results from ATAC.

Safety - general

In terms of "tolerability"- letrozole was generally comparable to tamoxifen in terms of the number of patients experiencing adverse events or having adverse events leading to study discontinuation

There were generally no unexpected adverse events with either drug, although this itself is not unexpected given that only a list of "pre-specified " AEs was evaluated. The pattern of AEs for each drug was rather different, as expected from previous experience. Patients on letrozole were more likely to have arthralgia/arthritis and myalgia. Adverse events related to endometrial effects, as well as thromboembolic events, were more common in the tamoxifen arm.

BMD loss and fractures

In the main study, osteoporosis was approximately doubled in the letrozole arm (2% vs. 1.1%). The number of patients with bone fractures was 6.4% with letrozole and 4.8% with tamoxifen. As might be expected, these occurred more commonly in the elderly, and in patients with a history of osteoporosis or fracture. The wrist was the most frequently affected location of bone fracture. The overall rate of hip fractures in the letrozole arm was 0.7%, compared to 0.5% in the tamoxifen arm. Importantly, the risk of fracture appears to be relatively constant over time during treatment. The increase of spine/hip/wrist fracture compared to tamoxifen is of the same order as that seen in the ATAC study with anastrozole.

Full data from studies such as Z-FAST are awaited, although some promising results from this and other studies have been reported in abstract which appear to show that bisphosphonates can have beneficial effects on bone mineral density (and probably lipids too) in the context of the very low circulating oestrogen levels induced by aromatase inhibitors. It is considered that BMD loss may be an aspect of aromatase inhibitor therapy which is predictable, and can be monitored and managed. There are already some SPC warnings about this, and it is proposed to strengthen these further.

Lipids/Cardiovascular events

There is a small excess of non-cancer deaths, with more cardiovascular deaths in particular seen with letrozole. The majority of deaths occurred off-treatment. Cardiac deaths and cerebrovascular deaths which occurred on letrozole treatment or within 30 days of last letrozole dose also showed an approximately equal distribution over time.

Treatment with letrozole, compared to tamoxifen, was associated with fewer thromboembolic events (56 vs. 120) but more myocardial infarctions (31 vs. 17) and events of cardiac failure (36 vs. 15). The majority of the latter were associated with a history of ischemic heart disease or other cardiovascular co-morbidities, implying that these patients may have multiple cardiac events. In addition, slightly more cerebrovascular events were reported for patients in the letrozole arm (54 vs. 49), translating into a numerical difference with fatal strokes in favor of tamoxifen (5 vs. 1). When all cardiovascular events were considered (myocardial infarction, cerebrovascular events and thromboembolic events) there was a trend towards more cardiovascular events in the tamoxifen arm (413 vs. 445). Combined analysis of all deaths with stepwise inclusion of specific cardiovascular events showed that the combined cancer/cardiovascular mortality risk associated with the letrozole arm was still lower than that for tamoxifen (HR=0.88).

Hypercholesterolemia was approximately twice as frequent in the letrozole arm, although the interpretation of the lipid data is limited due to the way this was collected and reported.

As with the effects on BMD, these differences are plausible given the difference in pharmacology of the 2 drugs. The increase in risk compared to women in the tamoxifen arm may be interpreted as compatible with either an increased risk of letrozole, or a decreased risk of tamoxifen, or both. To address this, the MAH has compared the results to some general epidemiological study data which does not show an increased risk for letrozole. However, for MI and cardiac failure in particular the MAH is asked to provide further comparisons to databases best matching the demographic profile of the study and containing age-specific estimates similar to the age ranges of BIG 1-98.

An increase in cardiovascular events was seen to some extent with the ATAC and IES studies with anastrozole and exemestane respectively, although it is difficult to directly compare these studies. However, in the latest analysis of ATAC, the slightly increased rate of angina seen earlier with anastrozole had not translated into a significant increase in the rate of myocardial infarction nor a significant difference between treatment groups in for either ischaemic cardiovascular deaths or cardiovascular deaths generally.

Given the relatively small numbers of non-breast cancer deaths in the study submitted, the deaths with cause unknown/missing are a significant proportion of these, and further information on these is requested to aid assessment. Despite this missing data, the overall reduction in mortality with letrozole, whilst not yet reaching statistical significance, should of course be taken into account, as should be the reduction in distant disease recurrence rate with letrozole, distant recurrence being an ominous event in breast cancer.

As with all treatment decisions, women with breast cancer and their physician should assess the relative benefits and risks of the treatment. Particularly in women with adverse prognostic features, Femara seems a better option that tamoxifen. Otherwise and where there is concern over bone loss, cardiovascular events or other specific issue with anastrozole, tamoxifen clearly remains an alternative option. Another alternative in this situation would be to treat with tamoxifen for 2-3 years and then switch to an anti-aromatase drug for the remainder of the 5 year adjuvant treatment period (as recently

approved for exemestane study). Similar sequential data is forthcoming for anastrozole and letrozole.

In considering the safety issues with both tamoxifen and letrozole, it should be taken into account how they can be monitored and risk managed in routine clinical practice, and how they might affect morbidity, mortality and quality of life. Other factors in the risk: benefit analysis are clearly the clinical relevance of the absolute level of reduction in disease recurrence shown with letrozole compared to tamoxifen, the impact of disease recurrence in these patients, and importantly, the relative importance patients might attach to prevention of disease recurrence compared to all other aspects.

Points Arising from Assessment and Company Responses

Points are given below in bold text, with the MAH response given in italics, with further assessor comments in boxed text.

General comment: The MAH notes that since the original variation application submitted in July 2005, Novartis has conducted the analysis of the BIG 1-98 120-day safety update (this is an update requested by FDA during licensing), providing additional safety data as well as limited updated efficacy data. To establish the 120-day safety update database the submission database (cut-off 28th September 2004; database lock 20th December, 2004) has been updated with three components:

- New data relating to the visits occurring between 28th September, 2004 and 15th March, 2005
- Data relating to visits before 28th September, 2004, not included in the submission database before its lock by IBCSG on 20th December, 2004
- Data in the submission database reviewed and updated by the IBCSG as recommended by the independent DSMC (5th January, 2005)

For this response and for the proposed revision of the SPC the data of the 120-day update analysis have been consistently used, whereas efficacy claims are based on the data of the final analysis (Primary Core Analysis).

On review of this update the overall adverse event profile of letrozole relative to tamoxifen did not change compared with the Primary Core Analysis, and no unexpected side effects have been observed. A table showing the extent of the safety data available in the variation application (Primary Core Analysis) versus the 120-day safety update is given below:

Table: Denominators (patients) per year of follow-up (Safety population)

		Primary Core Analysis			120-day safety update		
Population	**Year**	**Letrozole**	**Tamoxifen**	**Total**	**Letrozole**	**Tamoxifen**	**Total**
General	Baseline	3975	3988	7963	3975	3988	7963
Safety	1	3932	3950	7882	3937	3952	7889
	2	3041	3049	6090	3628	3598	7226
	3	1332	1330	2662	1569	1561	3130
	4	954	950	1904	1066	1063	2129
	5	603	590	1193	742	734	1476
	6	67	57	124	241	225	466

Efficacy points

1. Results should be presented in patients who have received adjuvant radiotherapy, and in patients who have undergone mastectomy

MAH response: IBCSG planned and conducted an analysis by radiotherapy, but such an analysis was not included by Novartis in the submission dossier. Both IBCSG and Novartis

included breast-conserving surgery vs mastectomy as an exploratory analysis. In Table 2-2, "no mastectomy" represents breast-conserving surgery. All patients had resected early breast cancer. Table 2-2 summarises the results of the primary endpoint, disease-free survival, with respect to radiotherapy and to mastectomy.

Table 0-1 Disease-free survival by radiotherapy and by mastectomy (Primary Core Analysis, ITT population)

Stratification	*Treatment*	*Number of DFS events*	*Hazard ratio*	*95% CI lower bound*	*95% CI upper bound*	*Cox model P-value*
Overall	*Letrozole n=4003*	*351*	*0.81*	*0.70*	*0.93*	*0.0028*
	Tamoxifen n=4007	*428*				
Radiotherapy yes	*Letrozole n=2872*	*227*	*0.82*	*0.69*	*0.98*	*0.0289*
	Tamoxifen n=2872	*273*				
Radiotherapy no	*Letrozole n=1131*	*124*	*0.78*	*0.61*	*0.98*	*0.0348*
	Tamoxifen n=1135	*155*				
Mastectomy yes	*Letrozole n=1765*	*227*	*0.77*	*0.65*	*0.92*	*0.0037*
	Tamoxifen n=1718	*273*				
Mastectomy no	*Letrozole n=2238*	*124*	*0.83*	*0.66*	*1.05*	*0.1231*
	Tamoxifen n=2289	*155*				

Overall, letrozole reduced the risk of recurrence by 19%, a difference which is significant. The superiority of letrozole over tamoxifen in reducing the risk of recurrence was maintained whether radiotherapy was given or not, and for patients who underwent mastectomy (Table 2-2). In patients who underwent breast-conserving surgery, there was a 17% reduction in the risk of recurrence with letrozole compared with tamoxifen, but this difference was not statistically significant.

Comment: No issues. Point addressed

2. The applicant should comment on whether an analysis by tumour HER-2 status is being considered, assuming the material is available for enough patients

MAH response: The HER-2 expression status (IHC and FISH) of the tumours from patients in BIG 1-98 is currently being assayed by the IBCSG in a central laboratory. Samples are currently available for over 4600 patients. Results are expected to be presented in December 2005 at the San Antonio Breast Cancer Symposium.

Comment: Point addressed

Safety points

3. Given the relatively small numbers of non-breast cancer deaths in the study submitted, the deaths with cause unknown/missing are a significant proportion of these, and any updated information on these is requested

MAH response: At the request of the Data and Safety Monitoring Committee, the IBCSG conducted a blinded medical review of CRFs and supporting documentation for cardiovascular adverse events, bone fractures and all deaths without a prior cancer event in the submission database. In the submission database, there were 93 deaths without a prior cancer event (55 in the letrozole arm and 38 in the tamoxifen arm). Review of all supporting documentation led to a revision of the cause of death in 22 cases, such that the revised cause of death for the 93 cases was as summarized in Table 2-3. Additional cases reported in the 120-day safety update are also included in Table 2-3. As a result of the blinded medical review, only one case with a previously unknown cause of death was resolved – the patient died in a road traffic accident. Deaths from unknown cause have been queried, but in all cases remaining as "unknown cause" (Table 2-3), no supporting documentation (e.g. autopsy report) is available. Narratives are provided in the 120-day safety update report for the deaths without a prior cancer event, when the death occurred during treatment or within 30 days of stopping treatment. The "other, miscellaneous" causes of death (without a prior cancer event) were diverse (such as infection/sepsis, pneumonia, suicide, road traffic accident, complications of diabetes). Details are provided in Table 2-4 for 34 deaths attributable to "other, miscellaneous" causes in the 120-day safety update analysis.

Table 0-3 Cause of death for deaths without a prior cancer event, according to the submission database, after IBCSG blinded medical review, and in the 120-day safety database (ITT population)

	Deaths without a prior cancer event					
	Submission database		*After blinded medical review*		*120-day safety update*	
Cause of death	*Letrozole N=4003*	*Tamoxifen N=4007*	*Letrozole N=4003*	*Tamoxifen N=4007*	*Letrozole N=4003*	*Tamoxifen N=4007*
Number of deaths	*55*	*38*	*55*	*38*	*65*	*46*
Progression (unconfirmed)	*1*					
Cardiac causes (MI, other cardiac causes)	*24*	*12*	*13*	*6*	*17*	*7*
CVA (Stroke, other cerebrovascular causes)	*7*	*1*	*7*	*1*	*7*	*3*
Thromboembolic event	*2*	*2*	*2*	*2*	*2*	*3*
Other miscellaneous causes	*15*	*11*	*23*	*19*	*18*	*16*
Cause unknown (including sudden death, cause unknown)	*5*	*10*	*10*	*10*	*21*	*17*
Cause missing	*1*	*2*				

Table 0-4 "Other, miscellaneous" causes of death without a prior cancer event (ITT population)

Other causes of death	***Letrozole***	***Tamoxifen***
Number of deaths due to other causes, in 120-day safety update	*18*	*16*
Suicide	*2*	*3*
Sepsis / Sepsis NOS / Septic shock / Candida sepsis	*4*	*2*
Accident / road traffic accident	*2*	*2*
Pneumonia NOS	*1*	*2*
Not coded (insufficient information)		*2*
Aortic aneurysm rupture		*1*
Chronic obstructive airways disease	*1*	
Crohn's disease		*1*
Diabetes mellitus	*1*	
Emphysema	*1*	
Femoral neck fracture (complications)	*1*	
Infected skin ulcer / Infection NOS / Postoperative infection	*2*	*1*
Pancreas infection	*1*	
Postoperative thoracic procedure complication	*1*	
Renal failure / Renal failure NOS		*2*
Thermal burn	*1*	

Comment: Appropriate efforts have been made to address this point. There are some outstanding "unknown" deaths but this is not a critical issue. Because of the blinded review mentioned, the number of patients with fatal cardiac events has decreased in each group, but as with the other events in table 2.3, above the ratio between treatment groups for each category has not significantly changed with the new analysis.

4. With regards to MI and cardiac failure, the MAH should provide further comparisons to databases best matching the demographic profile of the study and containing age-specific estimates similar to the age ranges of BIG 1-98, as detailed in the report

Comment: In the CSM paper it was noted that in a related submission, standardised incidence ratios[5] for each age subgroup were compared to UK GPRD data[6] and Swedish registry data[7] for cardiac failure and MI incidence respectively.

MAH response:

To position the findings in BIG 1-98 relating to myocardial infarction (MI) and cardiac failure (CF), Novartis has conducted several additional analyses. These included:

[5] Rothman KJ, Greenland S. Modern Epidemiology, 2cnd Ed. Lippincott-Raven
[6] Johansson S, Wallander MA, Ruigomez A et al. Incidence of newly diagnosed heart failure in UK general practice. Eur Heart Failure 2001;3:225-231
[7] Statistics – Health and Diseases. Myocardial infarction in Sweden 1987-1996. The National Board of Health and Welfare. Official Statistics of Sweden. Printed in Sweden by Norstedts Trickeri AB. Stockholm, 25 June 1998. Internet available at: http://www.sos.se/FULLTEXT/9842-006/9842-006.pdf

- *Estimates of standardized incidence ratios (SIRs) to compare the incidence rates of cardiac failure and MI in Study BIG 1-98 with the corresponding incidence in the UK and Sweden.*
- *In addition the age standardized rate of MI, calculated using the world standard population was compared with the rates from the WHO MONICA Project [Tunstall-Pedoe, et al (1999)].*

For details of the methodology we refer to the report in Appendix 2.

Table 2-5 gives estimates of the SIRs for cardiac failure as occurred in both treatment arms of study BIG 1-98 based on the UK General Practice Research Database (GPRD).

Table 2-5 Observed and expected numbers of cardiac failure based on the UK GPRD

Treatment arm	Number of observed cases	Number of expected cases	SIR (95% CI)
Letrozole	34	44	0.78 (0.54, 1.09)
Tamoxifen	15	43	0.35 (0.20, 0.58)

While the number of cardiac failure cases observed in the letrozole arm of Study BIG 1-98 is lower than that expected in the general population in the UK, the observed difference is not statistically significant. The number of cardiac failure cases observed in the tamoxifen arm is, however, significantly lower than expected.

Estimates of the SIRs for MI occurring in Study BIG 1-98 based on the UK GPRD and the Swedish MI Register are summarised in Table 2-6.

Table 2-6 Observed and expected numbers of MI based on the UK GPRD and Swedish MI Register

Comparison population	*Treatment arm*	*Number of observed cases*	*Number of expected cases*	*SIR (95% CI)*
GPRD	*Letrozole*	*26*	*32*	*0.81 (0.53, 1.19)*
	Tamoxifen	*17*	*31*	*0.54 (0.32, 0.87)*
Swedish MI Register	*Letrozole*	*27*	*55*	*0.49 (0.32, 0.71)*
	Tamoxifen	*17*	*54*	*0.32 (0.18, 0.51)*

While the numbers of observed MI cases in BIG 1-98 in the letrozole arm are lower than expected compared to both population datasets, only the difference compared to the Swedish population dataset is statistically significant. The numbers of MI cases observed in the tamoxifen arm of BIG 1-98 are significantly lower than the reference numbers from both the UK and Sweden.

The age standardised incidence rates of MI in Study BIG 1-98 are 73.90 per 100,000 person-years for the letrozole arm, and 31.45 per 100,000 person-years for the tamoxifen arm. For comparison, according to the WHO MONICA Project, the incidence rates of MI in women aged 35 to 64 years in 37 populations in 21 countries ranged from 35 to 265 per 100,000, with the mean rate of 101 per 100,000 [Tunstall-Pedoe, et al (1999)].

When viewing these data it is important to be aware of several limitations. First of all, the incidence of cardiovascular events in the general population increases with age and varies broadly according to several factors. These include the geographical area, baseline characteristics of the population included, and diagnostic criteria and methodology of case ascertainment (case definition) [Tunstall-Pedoe, et al (1999)].

In addition study BIG 1-98 is a multinational study. To address the issue of the geographical variation in cardiovascular risk factors, the age standardised rate of MI calculated using the world standard population adopted by the WHO MONICA Project was compared with the MI rates from the WHO MONICA Project. While this approach has been adjusted for age and geographical differences, it did not allow to address potential differences in case definitions.

It is also important to consider recently published preclinical and clinical data supporting the hypothesis that tamoxifen exhibits powerful cardioprotective effects [Grainger et al, (2005)]. The magnitude of the reduction in deaths due to myocardial infarction provided by tamoxifen is similar to that observed with the use of statins [The Scandinavian Simvastatin Survival Study, (1994)], [MRC/BHF Heart Protection Study, (2002)]. It is against this background that the observed difference between letrozole and tamoxifen with regards to MI and cardiac failure has to be viewed.

In conclusion, according to the data presented here, the incidence of MI and cardiac failure in patients treated with letrozole in study BIG 1-98 does not seem to be increased compared to the incidence reported in age- and sex-comparable general population databases from the UK and Sweden and the WHO MONICA project. This puts further weight on the results of the hierarchical time-to-first-event analysis presented in the BIG 1-98 CSR and the 120-day safety update reports, respectively, demonstrating that the risk of dying from cancer and the risk of experiencing a cardiac event (MI, angina, or cardiac failure) were not significantly different between the 2 treatments in trial BIG 1-98 (Submission analysis: HR 0.96; 95% CI 0.80, 1.15; 120-day safety update: HR 0.95; 95% CI 0.80, 1.13). The difference became significant in favor of letrozole only when thromboembolic complications were factored into the model (Submission analysis: HR 0.79; 95% CI 0.67, 0.93; 120-day safety update: HR 0.80; 95% CI 0.69, 0.93). Thus the net benefit gained by adjuvant letrozole treatment is to be considered a real and absolute gain, rather than a relative gain. Compared with tamoxifen in the setting of BIG 1-98, letrozole offers not only a slight, not statistically significant, benefit in overall survival, which remains (if diluted) when taking cognizance of the risk of experiencing cardiovascular events such as myocardial infarction, angina requiring surgical intervention, or cardiac failure, but offers a statistically significant, clinically relevant advantage over tamoxifen when the very substantial risk (more than double that with letrozole) of experiencing a thromboembolic event with tamoxifen is factored in.

Comments: The MAH has performed the requested comparisons with the requested methodology. Whilst the limitations of these indirect comparisons are realized, these additional analyses are helpful. The incidence of MI and cardiac failure for letrozole is similar to the range reported in the reference population. In contrast, the rate reported for tamoxifen was lower than expected from the reference population, a finding which is supported by several other studies and which has been noted in related submissions. Clearly the overall efficacy benefits of letrozole over tamoxifen in the proposed indication should be borne in mind, as should be the clinically important benefits shown for breast cancer recurrence and the anticipated long-term survival benefit from this. Conclusion: Point addressed

Points on SPC Section 4.1 (Therapeutic indications)

5. The correct indication wording, for consistency with the other early breast cancer indication is "...*invasive* *early breast cancer*" as patients with ductal carcinoma *in situ* etc were not included in the study

Comment: MAH has agreed to this. Point resolved

Points on SPC section 4.4 (Special warnings and precautions)

6. The current warning relating to bone mineral density loss should be further strengthened as follows:

"As letrozole is a potent oestrogen lowering agent, reductions in bone mineral density can be anticipated. The impact of letrozole on long-term fracture risk remains undetermined. During adjuvant treatment with letrozole, women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry at the commencement of treatment. Although adequate data to show the effects of therapy in the treatment of the bone mineral density loss caused by letrozole are not available, treatment for osteoporosis should be initiated as appropriate. Patients treated with letrozole should be carefully monitored."

MAH response: Novartis agrees with the proposed wording and suggests minor changes (see underlined text).

"As Femara is a potent oestrogen lowering agent, reductions in bone mineral density can be anticipated. The impact of Femara on long-term fracture risk remains undetermined. During adjuvant treatment with Femara, women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry e.g. DEXA scanning at the commencement of treatment. Although adequate data to show the effects of therapy in the treatment of the bone mineral density loss caused by Femara are not available, treatment for osteoporosis should be initiated as appropriate and patients treated with Femara should be carefully monitored."

Comment: Proposed wording is satisfactory. Point addressed.

Points on SPC section 4.8 (Adverse events)

7. The applicant should add a table to section 4.8 giving numbers and frequencies (irrespective of causality) of all pre-specified adverse events from the BIG 1-98 study, comparing the letrozole and tamoxifen groups

MAH response:

We agree to this point.

Table 3-1 lists the pre-specified adverse events (some including multiple MedDRA preferred terms), based on the BIG 1-98 CRF and on the analysis plan.

Table 0-2 Number (%) of patients with pre-specified adverse events grades 1-5 (safety population, during treatment or within 30 days of stopping treatment)

Pre-specified event	***Letrozole N=3975 n (%)***	***Tamoxifen N=3988 n (%)***
Hot flashes/hot flushes	*1367 (34.4)*	*1534 (38.5)*
Arthralgia/arthritis	*804 (20.2)*	*519 (13.0)*
Night sweats	*578 (14.5)*	*664 (16.6)*
Nausea	*394 (9.9)*	*424 (10.6)*
Fatigue (lethargy, malaise, asthenia)	*348 (8.8)*	*352 (8.8)*
Vaginal bleeding	*190 (4.8)*	*433 (10.9)*
Myalgia	*265 (6.7)*	*236 (5.9)*
Edema	*236 (5.9)*	*231 (5.8)*
Bone fractures	*252 (6.3)*	*187 (4.7)*
Headache	*148 (3.7)*	*139 (3.5)*
Vaginal irritation	*145 (3.6)*	*124 (3.1)*
Dizziness/light-headedness	*101 (2.5)*	*118 (3.0)*
Vomiting	*110 (2.8)*	*107 (2.7)*
Total serum cholesterol > 1.5 ULN* [1, 2]	*174 (5.4)*	*36 (1.1)*
Thromboembolic event	*48 (1.2)*	*119 (3.0)*
Constipation	*62 (1.6)*	*103 (2.6)*
Cerebrovascular accident/transient ischemic attack	*48 (1.2)*	*49 (1.2)*
Breast pain	*45 (1.1)*	*50 (1.3)*
Cataract	*49 (1.2)*	*43 (1.1)*
Endometrial hyperplasia or cancer [3]	*10 (0.3)*	*62 (2.0)*
Anorexia	*33 (0.8)*	*33 (0.8)*
Angina pectoris (new, or worsening or requiring surgical intervention)	*30 (0.8)*	*30 (0.8)*
Cardiac failure	*32 (0.8)*	*13 (0.3)*
Myocardial infarction	*20 (0.5)*	*15 (0.4)*
Ovarian cyst	*18 (0.5)*	*16 (0.4)*

[1] *Based on number of patients with normal serum cholesterol levels at baseline, and developing at least one value greater than 1.5 times the upper limit of normal in the laboratory measuring total serum cholesterol. Approximately 90% of the measured values were non-fasting measurements.*

[2] *Denominator is number of patients with baseline measurements of total serum cholesterol – letrozole, n=3207; tamoxifen, n=3228*

[3] *Denominator is number of patients not having undergone hysterectomy at baseline – letrozole, n=3090; tamoxifen, n=3157*

In the SmPC, Table 2 with all pre-specified events comparing Letrozole with tamoxifen has been added and also includes the incidence of endometrial cancer which has been removed from Section 5.1 of the SmPC in line with your comments below. In addition to ensure consistency with terminology we have replaced "Hypercholesterolaemia" in Table 1 with "raised plasma cholesterol". It is important to note that patients in the BIG1-98 study did not have systematic fasting plasma cholesterol testing, and that any raised cholesterol values are the result of random (non-fasting) testing, and therefore subject to meal or activity-related fluctuation. One reading of elevated plasma cholesterol meant that

an event of hypercholesterolaemia was recorded. It is good medical practice to assign a patient as having hypercholesterolaemia based on several fasting cholesterol readings with/without other cardiovascular risk factors. In the BIG1-98 study there was insufficient evidence to say that the patients had confirmed hypercholesterolaemia and we therefore propose changing the hypercholesterolaemia term to "raised plasma cholesterol" in Table 1 which ensures consistency with the new Table 2 of all pre-specified events.

Finally the cardiac events footnote (7) in Table 1 has been updated with the new 120 day data to ensure consistency with Table 2 and as a result the % values have been amended. Please see marked SmPC in Appendix 3

Comment: Point addressed. The AEs above reflect those for which treatment comparisons were pre-specified or that were included on the CRF.

Points on SPC section 5.1 (Pharmacodynamic properties)

8. This section is too extensive, and should be amended to the satisfaction of the secretariat

9. The incidence of endometrial cancer should be deleted from this section, this was not a pre-defined efficacy endpoint, and can be added to section 4.8 instead

10. It is not acceptable to state here that distant disease-free survival is a surrogate for overall survival, this should be deleted

11. With regard to the sentence "…*and reduced the risk of invasive contralateral breast cancer by almost 40% but due to the relatively low power of so few events, this result was not statistically significant*" mention of lack of power should be deleted

Comment: The amended description of the BIG 1-98 study proposed is acceptable.

FINAL CONCLUSIONS

The MAH has adequately addressed all points made, and the variation can be approved

Steps Taken During Assessment

1	Receipt of Submission 12/07/2005
2	Application before Committee on Safety of Medicines 12/10/2005
3	Application Granted 01/12/2005

Regulatory History of Market Authorisation

Application type	**Scope**	**Outcome**
Variation	Change of Ownership	Determined: 21/09/1997
Variation	Extend Shelf-life to 3 years	Determined: 17/02/1999
Variation	To add the results of a clinical trial (AR/BC3) comparing letrozole with aminoglutethimide to Section 5.1 of the SmPC.	Determined: 15/06/1999
Variation	To extend the shelf-life/retest period of the active ingredient from 3 to 5 years.	Determined: 19/08/1999
Variation	To amend the active ingredient specification: to tighten the limits of particle oversize	Determined: 14/09/1999
Variation	To amend the Finished Product Specification	Determined: 10/12/1999
Variation	To amend SPC	Determined: 02/07/2000
Variation	To add new indication: First line theapy of advanced breast cancer	Determined: 10/01/2001
Variation	To update SPC in line with new indication	Determined: 15/01/2001
Variation	To extend shel-life to 5 years	Determined: 30/09/2002
Variation	To update Drug Substance Specification	Determined: 30/09/2002
Variation	To update SPC	Determined 30/09/2002
Variation	To update SPC	Determined: 06/03/2003
Variation	To update SPC	Determined: 07/03/2003
Variation	To update SPC	Determined: 05/09/2003
Variation	To add indication, treatment of early invasive breast cancer in women who have received prior standard treatment	Determined: 09/09/2004
Variation	To add indication, adjuvant treatment of post-menopausal women with hormone receptor-positive invasive early breast cancer	Determined: 01/12/2005

Summary Of Product Characteristics

1. Trade Name of the Medicinal Product

Femara®

2. Qualitative and Quantitative Composition

Active substance: 4, 4'-[(1H-1, 2, 4-triazol-1-yl)-methylene]bis-benzonitrile (INN/USAN= letrozole).

Each film-coated tablet contains 2.5 mg letrozole.

3. Pharmaceutical Form

Film-coated tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.

Treatment of early invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy.

First-line treatment in postmenopausal women with advanced breast cancer.

Advanced breast cancer in postmenopausal women in whom tamoxifen or other anti-oestrogen therapy has failed.

Pre-operative therapy in postmenopausal women with localised hormone receptor positive breast cancer, to allow subsequent breast-conserving surgery in women not originally considered candidates for breast-conserving surgery. Subsequent treatment after surgery should be in accordance with standard of care.

4.2. Posology and method of administration

Adult and elderly patients

The recommended dose of Femara is 2.5 mg once daily. In the adjuvant setting, treatment with Femara should continue for 5 years or until tumour relapse occurs, whichever comes first. Following standard adjuvant tamoxifen therapy, treatment with Femara should continue for 3 years or until tumour relapse occurs, whichever comes first. Currently there is a lack of long-term data, therefore the optimal duration of therapy has not yet been established. In patients with metastatic disease, treatment with Femara should continue until tumour progression is evident. Regular monitoring to observe progression during the pre-operative treatment period is recommended (see Section 5.1 “Pharmacodynamic properties”). No dose adjustment is required for elderly patients.

Children

Not recommended for use in children.

Patients with hepatic and/or renal impairment

No dosage adjustment is required for patients with mild to moderate hepatic impairment (Child-Pugh grade A and B) or renal impairment (creatinine clearance ≥ 10 mL/min.), (see "Pharmacokinetic properties").

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients. Premenopausal, pregnant or lactating women; patients with severe hepatic impairment (Child-Pugh grade C).

Pre-operative use of letrozole is contraindicated if the receptor status is negative or unknown.

4.4. Special warnings and precautions for use

Femara is not recommended for use in children as efficacy and safety in this patient group have not been assessed in clinical studies. There are no efficacy data to support the use of Femara in men with breast cancer.

Femara has not been investigated in patients with creatinine clearance < 10 mL/min. The potential risk/benefit to such patients should be carefully considered before administration of Femara.

As Femara is a potent oestrogen lowering agent, reductions in bone mineral density can be anticipated. The impact of Femara on long-term fracture risk remains undetermined. During adjuvant treatment with Femara, women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry e.g. DEXA scanning at the commencement of treatment. Although adequate data to show the effects of therapy in the treatment of the bone mineral density loss caused by Femara are not available, treatment for osteoporosis should be initiated as appropriate and patients treated with Femara should be carefully monitored.

4.5. Interaction with other medicinal products and other forms of interaction

Clinical interaction studies with cimetidine and warfarin indicated that the coadministration of Femara with these drugs does not result in clinically significant drug interactions, even

though cimetidine is a known inhibitor of one of the cytochrome P450 isoenzymes capable of metabolising letrozole *in vitro* (see also section 5.2, "Metabolism and elimination").

There was no evidence of other clinically relevant interaction in patients receiving other commonly prescribed drugs (e.g. benzodiazepines; barbiturates; NSAIDs such as diclofenac sodium, ibuprofen; paracetamol; furosemide; omeprazole).

There is no clinical experience to date on the use of Femara in combination with other anti-cancer agents.

Letrozole inhibits *in vitro* the cytochrome P450-isoenzymes 2A6 and moderately 2C19, however, CYP2A6 does not play a major role in drug metabolism. In *in vitro* experiments letrozole was not able to substantially inhibit the metabolism of diazepam (a substrate of CYP2C19) at concentrations approximately 100-fold higher than those observed in plasma at steady-state. Thus, clinically relevant interactions with CYP2C19 are unlikely to occur. Nevertheless, caution should be used in the concomitant administration of drugs whose disposition is mainly dependent on these isoenzymes and whose therapeutic index is narrow.

4.6. Pregnancy and lactation

There is no experience of the use of Femara in human pregnancy or lactation. Femara is contraindicated during pregnancy, lactation and in premenopausal women.

Embryotoxicity and foetotoxicity were seen in pregnant rats following oral administration of Femara, and there was an increase in the incidence of foetal malformation among the animals treated. However, it is not known whether this was an indirect consequence of the pharmacological activity of Femara (inhibition of oestrogen biosynthesis) or a direct drug effect.

4.7. Effects on ability to drive and use machines

Since fatigue and dizziness have been observed with the use of Femara and somnolence has been reported uncommonly, caution is advised when driving or using machines.

4.8. Undesirable effects

Femara was generally well tolerated across all studies as first-line and second-line treatment for advanced breast cancer, as adjuvant treatment of early breast cancer as well as in the treatment of women who have received prior standard tamoxifen therapy. Approximately one third of the patients treated with Femara in the metastatic and neoadjuvant settings, approximately 70-75% of the patients in the adjuvant setting (both Femara and tamoxifen arms), and approximately 40% of the patients treated following standard adjuvant tamoxifen (both Femara and placebo arms) experienced adverse reactions. Generally, the observed adverse reactions are mainly mild or moderate in nature, and most are associated with oestrogen deprivation.

In the metastatic and neoadjuvant settings, the most frequently reported adverse reactions in the clinical trials were hot flushes (10.8%), nausea (6.9%) and fatigue (5.0%). Many adverse reactions can be attributed to the normal pharmacological consequences of oestrogen deprivation (e.g. hot flushes, alopecia and vaginal bleeding).

After standard adjuvant tamoxifen, the following adverse events irrespective of causality were reported significantly more often with Femara than with placebo – hot flushes (49.7 %

vs. 43.3 %), arthralgia/arthritis (27.7 % vs. 22.2 %) and myalgia (9.5 % vs. 6.7 %). The majority of these adverse events were observed during the first year of treatment. The incidence of self-reported osteoporosis was higher in patients who received Femara than in patients who received placebo (6.9 % vs. 5.5 %). The incidence of clinical fractures was only slightly higher in patients who received Femara than in placebo patients (5.9 % vs. 5.5 %). The fracture rate per 1000-women years in the letrozole group (24.6) is in the range of aged-matched postmenopausal healthy women.

The following adverse drug reactions, listed in Table 1, were reported from clinical studies and from post marketing experience with Femara.

Table 1

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: *very common ≥ 10%; common ≥ 1% to <10%; uncommon ≥ 0.1% to <1%; rare ≥0.01% to < 0.1%; very rare <0.01%,* including isolated report.

Infections and infestations	
Uncommon:	Urinary tract infection
Neoplasms, benign, malignant and unspecified (including cysts and polyps)	
Uncommon:	Tumour pain [(6)]
Blood and the lymphatic system disorders	
Uncommon:	Leucopenia
Metabolism and nutrition disorders	
Common:	Anorexia, appetite increase, raised serum cholesterol
Uncommon:	General oedema
Psychiatric disorders	
Common:	Depression
Uncommon:	Anxiety [(1)]
Nervous system disorders	
Common:	Headache, dizziness
Uncommon:	Somnolence, insomnia, memory impairment, dysaesthesia [(2)], taste disturbance, Cerebrovascular accident
Eye disorders	
Uncommon:	Cataract, eye irritation, blurred vision
Cardiac disorders	
Uncommon:	Palpitations, tachycardia
Vascular disorders	
Uncommon:	Thrombophlebitis [(3)], hypertension, ischemic cardiac events [(7)]
Rare:	Pulmonary embolism, arterial thrombosis, cerebrovascular infarction
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Dyspnoea

Gastrointestinal disorders	
Common:	Nausea, vomiting, dyspepsia, constipation, diarrhoea
Uncommon:	Abdominal pain, stomatitis, dry mouth
Hepatobiliary disorders	
Uncommon:	Increased hepatic enzymes
Skin and subcutaneous tissue disorders	
Common:	Alopecia, increased sweating, rash (4)
Uncommon:	Pruritus, dry skin, urticaria
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia
Common:	Myalgia, bone pain, osteoporosis, bone fractures
Uncommon:	Arthritis
Renal and urinary disorders	
Uncommon:	Increased urinary frequency
Reproductive system and breast disorders	
Uncommon:	Vaginal bleeding, vaginal discharge, vaginal dryness, breast pain
General disorders and administration site conditions	
Very common:	Hot flushes
Common:	Fatigue (5), peripheral oedema
Uncommon:	Pyrexia, mucosal dryness, thirst
Investigations	
Common:	Weight increase
Uncommon:	Weight loss,

*Including:

(1) including nervousness, irritability
(2) including paraesthesia, hypoaesthesia
(3) including superficial and deep thrombophlebitis
(4) including erythematous, maculopapular, psoriaform and vesicular rash
(5) including aesthenia and malaise
(6) in metastatic/neoadjuvant setting only
(7) in the adjuvant setting, irrespective of causality, the following adverse events occurred in the Femara and tamoxifen groups respectively: thromboembolic events (1.2% vs. 3.0%), angina pectoris (0.8% vs. 0.8%), myocardial infarction (0.5% vs. 0.4%), cardiac failure (0.8% vs. 0.3%).

Table 2 presents the frequency of pre-specified adverse events grades 1-5 in the BIG 1-98 study, irrespective of causality, reported in patients receiving trial therapy and up to 30 days after cessation of trial therapy.

Pre-specified event	**Letrozole N=3975 n (%)**	**Tamoxifen N=3988 n (%)**
Hot flashes/hot flushes	1367 (34.4)	1534 (38.5)
Arthralgia/arthritis	804 (20.2)	519 (13.0)
Night sweats	578 (14.5)	664 (16.6)
Nausea	394 (9.9)	424 (10.6)
Fatigue (lethargy, malaise, asthenia)	348 (8.8)	352 (8.8)
Vaginal bleeding	190 (4.8)	433 (10.9)
Myalgia	265 (6.7)	236 (5.9)
Edema	236 (5.9)	231 (5.8)
Bone fractures	252 (6.3)	187 (4.7)
Headache	148 (3.7)	139 (3.5)
Vaginal irritation	145 (3.6)	124 (3.1)
Dizziness/light-headedness	101 (2.5)	118 (3.0)
Vomiting	110 (2.8)	107 (2.7)
Total serum cholesterol > 1.5* ULN [1, 2]	174 (5.4)	36 (1.1)
Thromboembolic event	48 (1.2)	119 (3.0)
Constipation	62 (1.6)	103 (2.6)
Cerebrovascular accident/transient ischemic attack	48 (1.2)	49 (1.2)
Breast pain	45 (1.1)	50 (1.3)
Cataract	49 (1.2)	43 (1.1)
Endometrial hyperplasia or cancer [3]	10 (0.3)	62 (2.0)
Anorexia	33 (0.8)	33 (0.8)
Angina pectoris (new, or worsening or requiring surgical intervention)	30 (0.8)	30 (0.8)
Cardiac failure	32 (0.8)	13 (0.3)
Myocardial infarction	20 (0.5)	15 (0.4)
Ovarian cyst	18 (0.5)	16 (0.4)

[1] Based on number of patients with normal serum cholesterol levels at baseline, and developing at least one value greater than 1.5 times the upper limit of normal in the laboratory measuring total serum cholesterol. Approximately 90% of the measured values were non-fasting measurements.

[2] Denominator is number of patients with baseline measurements of total serum cholesterol – letrozole, n=3207; tamoxifen, n=3228

[3] Denominator is number of patients not having undergone hysterectomy at baseline – letrozole, n=3090; tamoxifen, n=3157

4.9. Overdose

There is no clinical experience of overdosage. In animal studies, Femara exhibits only a slight degree of acute toxicity. In clinical trials, the highest single and multiple dose tested in healthy volunteers was 30 mg and 5 mg, respectively, the latter also being the highest dose tested in postmenopausal breast cancer patients. Each of these doses was well tolerated. There is no clinical evidence for a particular dose of Femara resulting in life-threatening symptoms.

There is no specific antidote to Femara. In general, supportive care, symptomatic treatment and frequent monitoring of vital signs is appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group

ATC Code: L02B G04
Non-steroidal aromatase inhibitor (inhibitor of oestrogen biosynthesis); antineoplastic agent.

Pharmacodynamic effects

The elimination of oestrogen-mediated stimulatory effects is a prerequisite for tumour response in cases where the growth of tumour tissue depends on the presence of oestrogens. In postmenopausal women, oestrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens - primarily androstenedione and testosterone - to oestrone (E1) and oestradiol (E2). The suppression of oestrogen biosynthesis in peripheral tissues and the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme.

Letrozole is a non-steroidal aromatase inhibitor. It inhibits the aromatase enzyme by competitively binding to the haem of the cytochrome P450 subunit of the enzyme, resulting in a reduction of oestrogen biosynthesis in all tissues.

In healthy postmenopausal women, single doses of 0.1, 0.5, and 2.5 mg letrozole suppress serum oestrone and oestradiol by 75-78% and 78% from baseline respectively. Maximum suppression is achieved in 48-78 h.

In postmenopausal patients with advanced breast cancer, daily doses of 0.1 to 5 mg suppress plasma concentration of oestradiol, oestrone, and oestrone sulphate by 75 - 95% from baseline in all patients treated. With doses of 0.5 mg and higher, many values of oestrone and oestrone sulphate are below the limit of detection in the assays, indicating that higher oestrogen suppression is achieved with these doses. Oestrogen suppression was maintained throughout treatment in all these patients.

Letrozole is highly specific in inhibiting aromatase activity. Impairment of adrenal steroidogenesis has not been observed. No clinically relevant changes were found in the plasma concentrations of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxy-progesterone, and ACTH or in plasma renin activity among postmenopausal patients treated with a daily dose of letrozole 0.1 to 5 mg. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0.1, 0.25, 0.5, 1, 2.5, and 5 mg did not indicate any attenuation of aldosterone or cortisol production. Thus, glucocorticoid and mineralocorticoid supplementation is not necessary.

No changes were noted in plasma concentrations of androgens (androstenedione and testosterone) among healthy postmenopausal women after 0.1, 0.5, and 2.5 mg single doses of letrozole or in plasma concentrations of androstenedione among postmenopausal patients treated with daily doses of 0.1 to 5 mg, indicating that the blockade of oestrogen biosynthesis does not lead to accumulation of androgenic precursors. Plasma levels of LH and FSH are not affected by letrozole in patients, nor is thyroid function as evaluated by TSH, T4 and T3 uptake.

Adjuvant treatment

A multicentre, double-blind study randomised over 8000 postmenopausal women with resected receptor-positive early breast cancer, to one of the following arms:

- A. tamoxifen for 5 years
- B. Femara for 5 years
- C. tamoxifen for 2 years followed by Femara for 3 years
- D. Femara for 2 years followed by tamoxifen for 3 years

Data in Table 3 reflect results from non-switching arms (arms A and B) together with data truncated 30 days after the switch in the two switching arms (arms C and D). Patients have been followed for a median of 26 months, 76% of the patients for more than 2 years, and 16% (1252 patients) for 5 years or longer.

The primary endpoint of the trial was disease-free survival (DFS) which was assessed as the time from randomisation to the earliest event of loco-regional or distant recurrence (metastases) of the primary disease, development of invasive contralateral breast cancer, appearance of a second non-breast primary tumour or death from any cause. Femara reduced the risk of recurrence by 19% compared with tamoxifen (hazard ratio 0.81; *P*=0.003). The 5-year DFS rates were 84.0% for Femara and 81.4% for tamoxifen. The improvement in DFS with Femara is seen as early as 12 months and is maintained beyond 5 years. Femara also significantly reduced the risk of recurrence compared with tamoxifen whether prior adjuvant chemotherapy was given (hazard ratio 0.72 ; *P*=0.018) or not (hazard ratio 0.84 ; *P*=0.044) and in node positive patients (hazard ratio 0.71 ; *P*=0.0002). A significant benefit of Femara over tamoxifen is not yet evident in node negative patients (hazard ratio 0.98 ; *P*=0.888).

There was no significant difference between treatments in overall survival (hazard ratio 0.86; *P*=0.155).

Table 3 summarises the results.

Table 3 Disease-free survival and overall survival (ITT population)

	Femara n=4003	Tamoxifen n=4007	Hazard ratio (95% CI)	*P*-value [1]
Disease-free survival (DFS) (primary) (protocol definition)	351	428	0.81 (0.70, 0.93)	0.0030
Disease-free survival (ignoring second non-breast cancers)	296	369	0.79 (0.68, 0.92)	0.0024
Distant disease-free survival (metastases) (secondary)	184	249	0.73 (0.60, 0.88)	0.0012
Contralateral breast cancer (invasive) (secondary)	19	31	0.61 (0.35, 1.08)	0.0910
Overall survival (secondary) number of deaths	166	192	0.86 (0.70, 1.06)	0.1546

CI = Confidence interval

[1] Logrank test, stratified by randomisation option and adjuvant chemotherapy

Treatment after standard adjuvant tamoxifen

In a multicentre, double-blind, randomised, placebo-controlled study, performed in over 5100 postmenopausal patients with receptor-positive or unknown primary breast cancer patients who had remained disease-free after completion of adjuvant treatment with tamoxifen (4.5 to 6 years) were randomly assigned either Femara or placebo.

Analysis conducted at a median follow-up of around 28 months (25% of the patients being followed-up for up to 38 months) showed that Femara reduced the risk of recurrence by 42% compared with placebo (hazard ratio 0.58; *P*=0.00003), an absolute reduction of 2.4%. This statistically significant benefit in DFS in favour of letrozole was observed regardless of nodal status or prior chemotherapy.

For the secondary endpoint overall survival (OS) a total 113 deaths were reported (51 Femara, 62 placebo). Overall, there was no significant difference between treatments in OS (hazard ratio 0.82; *P*=0.29). Table 4 summarises the results:

Table 4 Disease-free and overall survival (Modified ITT population)

	Letrozole N=2582	**Placebo** N=2586	**Hazard Ratio (95 % CI)**	**P-Value**
Disease-free survival (primary)				
- events (protocol definition, total)	**92** (3.6%)	**155** (6.0%)	0.58 (0.45, 0.76) [1]	0.00003
Distant disease-free survival	**57**	**93**	0.61 (0.44, 0.84) [2]	0.003
Overall survival (secondary)				
- number of deaths (total)	**51**	**62**	0.82 (0.56, 1.19) [1]	0.291
Contralateral breast cancer (secondary)				
- including DCIS/LCIS	**19**	**30**	0.63 (0.36, 1.13) [3]	0.120
- invasive	**15**	**25**	0.60 (0.31, 1.14) [3]	0.117

CI = confidence interval, DCIS = ductal carcinoma in situ, LCIS = lobular carcinoma in situ

1 Stratified by receptor status, nodal status and prior adjuvant chemotherapy

2 Non-stratified analysis

3 Odds ratio, non-stratified analysis

The efficacy of Femara was not assessed in women who discontinued tamoxifen therapy more than 3 months earlier.

There was no difference in safety and efficacy between patients aged < 65 versus ≥ 65 years.

Preliminary results (median duration of follow-up was 20 months) from the bone mineral density (BMD) sub-study (n=222) demonstrated that, at 2 years, compared to baseline, patients receiving letrozole had a mean decrease of 3 % in hip BMD compared to 0.4 % in the placebo group (*P*=0.048). There was no significant difference in terms of changes in lumbar spine BMD. Concomitant calcium and vitamin D supplementation was mandatory in the BMD substudy. Preliminary results (median duration of follow-up was 29 months) from the lipid sub-study (n=310) show no significant difference between the Femara and placebo groups. In the core study the incidence of cardiovascular ischemic events was comparable between treatment arms (6.8% vs. 6.5%).

First-line treatment

One large well-controlled double-blind trial was conducted comparing Femara 2.5 mg to tamoxifen 20 mg daily as first-line therapy in postmenopausal women with locally advanced or metastatic breast cancer. In this trial of 907 women, Femara was superior to tamoxifen in time to progression (primary endpoint) and in overall objective response, time to treatment failure and clinical benefit (CR+PR+NC≥24 weeks).

Femara treatment in the first line therapy of advanced breast cancer patients is associated with an early survival advantage over tamoxifen. A significantly greater number of patients were alive on Femara versus tamoxifen throughout the first 24 months of the study. As the study design allowed patients to cross-over upon progression to the other therapy the long-term survival could not be evaluated.

Pre-operative treatment:
A double blind trial was conducted in 337 postmenopausal breast cancer patients randomly allocated either Femara 2.5mg for 4 months or tamoxifen for 4 months. At baseline all patients had tumours stage T2-T4c, N0-2, M0, ER and/or PgR positive and none of the patients would have qualified for breast-conserving surgery. There were 55% objective responses in the Femara treated patients versus 36% for the tamoxifen treated patients ($p<0.001$) based on clinical assessment. This finding was consistently confirmed by ultrasound ($p=0.042$) and mammography ($p<0.001$) giving the most conservative assessment of response. This response was reflected in a statistically significantly higher number of patients in the Femara group who became suitable for and underwent breast-conserving therapy (45% of patients in the Femara group versus 35% of patients in the tamoxifen group, $p=0.022$). During the 4 month pre-operative treatment period, 12% of patients treated with Femara and 17% of patients treated with tamoxifen had disease progression on clinical assessment.

5.2. Pharmacokinetic properties

Absorption
Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99.9%). Food slightly decreases the rate of absorption (median t_{max}: 1 hour fasted versus 2 hours fed; and mean C_{max}: 129 ± 20.3 nmol/L fasted versus 98.7 ± 18.6 nmol/L fed) but the extent of absorption (AUC) is not changed. The minor effect on the absorption rate is not considered to be of clinical relevance and therefore letrozole may be taken without regard to mealtimes.

Distribution
Plasma protein binding of letrozole is approximately 60%, mainly to albumin (55%). The concentration of letrozole in erythrocytes is about 80% of that in plasma. After administration of 2.5 mg ^{14}C-labelled letrozole, approximately 82% of the radioactivity in plasma was unchanged compound. Systemic exposure to metabolites is therefore low. Letrozole is rapidly and extensively distributed to tissues. Its apparent volume of distribution at steady state is about 1.87 ± 0.47 L/kg.

Metabolism and elimination
Metabolic clearance to a pharmacologically inactive carbinol metabolite is the major elimination pathway of letrozole (CL_m= 2.1 L/h) but is relatively slow when compared to hepatic blood flow (about 90 L/h). The cytochrome P450 isoenzymes 3A4 and 2A6 were found to be capable of converting letrozole to this metabolite *in vitro*, but their individual contributions to letrozole clearance *in vivo* have not been established. In an interaction study co-administration with cimetidine, which is known to inhibit only the 3A4 isoenzyme, did not result in a decrease in letrozole clearance suggesting that *in vivo* the 2A6 isoenzyme plays an important part in total clearance. In this study a slight decrease in AUC and increase in C_{max} were observed.

Formation of minor unidentified metabolites and direct renal and faecal excretion play only a minor role in the overall elimination of letrozole. Within 2 weeks after administration of 2.5 mg ^{14}C-labelled letrozole to healthy postmenopausal volunteers, 88.2 ± 7.6% of the

radioactivity was recovered in urine and 3.8 ± 0.9% in faeces. At least 75% of the radioactivity recovered in urine up to 216 hours (84.7 ± 7.8% of the dose) was attributed to the glucuronide of the carbinol metabolite, about 9% to two unidentified metabolites, and 6% to unchanged letrozole.

The apparent terminal elimination half-life in plasma is about 2 days. After daily administration of 2.5 mg steady-state levels are reached within 2 to 6 weeks. Plasma concentrations at steady state are approximately 7 times higher than concentrations measured after a single dose of 2.5 mg, while they are 1.5 to 2 times higher than the steady-state values predicted from the concentrations measured after a single dose, indicating a slight non-linearity in the pharmacokinetics of letrozole upon daily administration of 2.5 mg. Since steady-state levels are maintained over time, it can be concluded that no continuous accumulation of letrozole occurs.

Age had no effect on the pharmacokinetics of letrozole.

Special populations
In a study involving volunteers with varying degrees of renal function (24 hour creatinine clearance 9-116 mL/min) no effect on the pharmacokinetics of letrozole or the urinary excretion of the glucoronide of its carbinol metabolite was found after a single dose of 2.5 mg. The C_{max}, AUC and half-life of the metabolite have not been determined. In a similar study involving subjects with varying degrees of hepatic function, the mean AUC values of the volunteers with moderate hepatic impairment was 37 % higher than in normal subjects, but still within the range seen in subjects without impaired function.

5.3. Preclinical safety data

Femara showed a low degree of acute toxicity in rodents exposed up to 2000 mg/kg. In dogs Femara caused signs of moderate toxicity at 100 mg/kg.

In repeated-dose toxicity studies in rats and dogs up to 12 months, the main findings can be attributed to the pharmacological action of the compound. Effects on the liver (increased weight, hepatocellular hypertrophy, fatty changes) were observed, mainly at high dose levels. Increased incidences of hepatic vacuolation (both sexes, high dose) and necrosis (intermediate and high dose females) were also noted in rats treated for 104 weeks in a carcinogenicity study. They may have been associated with the endocrine effects and hepatic enzyme-inducing properties of Femara. However, a direct drug effect cannot be ruled out.

In a 104-week mouse carcinogenicity study, dermal and systemic inflammation occurred, particularly at the highest dose of 60 mg/kg, leading to increased mortality at this dose level. Again it is not known whether these findings were an indirect consequence of the pharmacological activity of Femara (i.e. linked to long-term oestrogen deprivation) or a direct drug effect.

Both *in vitro* and *in vivo* investigations on Femara's mutagenic potential revealed no indication of any genotoxicity.

In the carcinogenicity studies no treatment-related tumours were noted in male animals. In female animals, treatment-related changes in genital tract tumours (a reduced incidence of

benign and malignant mammary tumours in rats, an increased incidence of benign ovarian stromal tumours in mice) were secondary to the pharmacological effect of the compound.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Silica aerogel, cellulose, lactose, magnesium stearate, maize starch, sodium carboxymethyl starch, hydroxypropyl methylcellulose, polyethylene glycol, talc, titanium dioxide, iron oxide yellow

6.2. Incompatibilities

None known.

6.3. Shelf life

Five years.

6.4. Special Precautions for Storage

Do not store above 30°C. Store in the original package.

6.5. Nature and Contents of Container

PVC/PE/PVDC blister packs of 14 or 28 tablets.

6.6. Instructions for Use, Handling and Disposal

No specific instructions for use/handling.

7. MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals UK Ltd
Frimley Business Park
Frimley Camberley
Surrey GU16 5SG

Trading style Ciba Laboratories
Frimley Business Park
Frimley Camberley
Surrey GU16 5SG

8. MARKETING AUTHORISATION NUMBER(S)

PL 00101/0493

9. DATE OF FIRST AUTHORISATION /RENEWAL OF THE AUTHORISATION

21 September 1997

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

01/12/2005

Labelling and Product Information Leaflet for Femara

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Femara® 2.5 mg Tablets

Ciba

letrozole

Information for Patients

WHAT YOU NEED TO KNOW ABOUT FEMARA

Please read this leaflet carefully before you start to take your medicine. It contains important information. If you have any questions or are not sure about anything ask your doctor or pharmacist (chemist).

WHAT'S IN YOUR MEDICINE

FEMARA contains 2.5 mg letrozole in each tablet.

The film-coated tablets also contain the following inactive ingredients: Silica aerogel, cellulose, lactose, magnesium stearate, maize starch, sodium carboxymethyl starch, hydroxypropyl methylcellulose, polyethylene glycol, talc, titanium dioxide (E171) and iron oxide yellow (E172).

The tablets come in blister packs of 14 or 28.

WHO MAKES YOUR MEDICINE

Manufactured by:
Novartis Pharma AG, CH 4332, Stein, Switzerland.

Released onto the market by:
Novartis Pharmaceuticals UK Limited,
Wimblehurst Road, Horsham, West Sussex, RH12 5AB, England.

Product licence/authorisation holder:
Novartis Pharmaceuticals UK Limited
trading as Ciba Laboratories,
Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR, England.

WHAT IS THIS MEDICINE USED FOR?

FEMARA blocks the production of oestrogens. It is used in the treatment of advanced breast cancer in women who are post-menopausal.

FEMARA is used in post-menopausal women with hormone receptor positive early invasive breast cancer.

FEMARA is also used in post-menopausal women with early breast cancer after they have received standard tamoxifen therapy.

It can also be used to treat localised breast cancer in post-menopausal women before breast surgery. Your doctor will arrange regular check-ups during this treatment period before surgery as there is a risk that your disease could progress even whilst taking this medicine.

BEFORE TAKING YOUR MEDICINE ASK YOURSELF THE FOLLOWING QUESTIONS

- Have you ever had an allergic reaction to letrozole or any of the inactive ingredients (see "What's in your medicine")?
- Is there any possibility that you might be pregnant?
- Do you suffer from any serious liver disease?

If the answer to any of these questions is YES, do not take the tablet without talking to your doctor again.

- If you suffer from any serious kidney disease, tell your doctor

IS THERE ANYTHING ELSE YOU NEED TO KNOW BEFORE TAKING YOUR MEDICINE?

- If you feel dizzy or drowsy when you start to take FEMARA, do not drive or work with machinery.
- Your doctor may want to measure your bone density before and during your treatment. This is because drugs of this class lower the levels of female hormones and this may lead to a loss of the mineral content of bones, which might decrease their strength (osteoporosis).

HOW TO TAKE YOUR MEDICINE

It is important to take your tablets as instructed by your doctor. The usual dose of FEMARA is 1 tablet once a day.

WHAT IF YOU MISS A DOSE?

If you forget to take a dose, take it as soon as you remember. Then go on as before.

WHAT IF YOU TAKE TOO MANY?

If you accidentally take too many FEMARA tablets, tell your doctor at once or contact your nearest hospital casualty department. Take your medicine with you.

AFTER TAKING YOUR MEDICINE

These tablets sometimes cause unwanted effects in some people. These effects are often mild and may wear off after a few days' treatment. However, if they are severe or last for more than a few days, tell your doctor.

Some of these unwanted effects may also be due to your illness.

In studies of people treated with FEMARA, the following side-effects have been reported:

Very Common Side-effects, reported in more than 1,000 people in every 10,000

- Hot flushes
- arthralgia (pain in your joints)

Common Side-effects, reported in between 100 and 1,000 people in every 10,000

- appetite problems (loss of appetite or increased appetite)
- raised cholesterol levels
- depression
- headache

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- dizziness
- problems with the digestive system (feeling sick, vomiting, indigestion, constipation, diarrhoea)
- loss or thinning of the hair
- increased sweating
- skin rash
- pain in your muscles
- bone problems (pain, bone thinning (osteoporosis), fractures)
- fatigue (feeling tired)
- swelling of the legs or feet due to fluid retention
- weight gain.

Uncommon side-effects, reported in between 10 and 100 people in every 10,000

- urinary tract infections
- pain (in the breast including in the tumour, in the stomach)
- general swelling due to fluid retention
- decreased white blood cells which can lead to infections (leucopenia)
- mental problems (anxiety, nervousness, irritability, memory impairment)
- sleep problems (sleepiness or difficulty in sleeping)
- changes in sensation (including touch sensation (pins and needles), taste changes)
- eye problems (cataract (loss of transparency of the lens of the eye), eye irritation, blurred vision, dry eyes)
- heart problems (fluttering in the chest (palpitations), fast heart beat (tachycardia) irregular heart beat (arrhythmia), angina and heart attack (ischemic cardiovascular disease))
- stroke
- inflamed blood vessels
- hypertension (raised blood pressure)
- breathlessness
- mouth problems (ulcers, dryness)
- liver problems
- skin problems (wheals or itching, dryness)
- joint problems inflammation of the joints (arthritis)
- urinary and vaginal problems (urinating more often, vaginal bleeding, vaginal discharge, vaginal dryness)
- fever
- thirst
- weight loss.

Rare side effects, reported in between 1 and 10 people in every 10,000

- thrombosis (clotting in the blood vessels e.g. legs)
- pulmonary embolism (a blood clot in the lungs)

WHEN YOU SHOULD SEEK URGENT MEDICAL HELP

A few of the uncommon and rare side effects of FEMARA (occurring in 1 to 100 people in every 10,000) need immediate medical attention. These are angina, heart attack, thrombosis, pulmonary embolism and stroke. The symptoms which might suggest that you are developing this problem are shown below.

- Chest tightness or heaviness
- Pain in the chest, spreading to your arms or shoulders, neck, teeth or jaw, abdomen or back
- Coughing blood
- Unusual pains or swelling of your arms or legs
- Sudden shortness of breath
- Fainting
- Numbness or weakness in arm or leg or any part of the body
- Loss of coordination
- Vision changes
- Sudden severe headache
- Loss of coordination
- Difficulty in speaking or breathing

If you develop any of the symptoms above, you should stop taking FEMARA and contact your doctor or your local accident and emergency department IMMEDIATELY.

Also, if your medicine upsets you in any other way, tell your doctor.

HOW TO STORE YOUR MEDICINE

- The expiry date for these tablets is given on the carton. Do not take the tablets after this date.
- Store your tablets in a cool (below 30°C), dry place, out of the reach of children. Keep in the original package. Return any unused medicines to your pharmacist.

REMEMBER: This medicine is for you. Only a doctor can prescribe it for you. Never give it to somebody else. It may harm them even if they have the same symptoms as you.

The information in this leaflet applies only to FEMARA. If you have any questions or are not sure about anything ask your doctor or pharmacist.

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November 2005

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