SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: FASLODEX

ACTIVE INGREDIENT: Fulvestrant

Trial title (number): A Double-blind, Randomised, Multi-centre Trial Comparing the Efficacy and Tolerability of 250 mg of FASLODEX™ (Long-acting ICI 182,780) with 20 mg of NOLVADEX™ (Tamoxifen) in Postmenopausal Women with Advanced Breast Cancer (9238IL/0025)

Clinical phase: III

First patient recruited: 19 November 1998
Last patient recruited: 8 June 2000
Data cut-off: 18 May 2001
AstraZeneca approval date: 26 March 2002

Principal investigator and location (centre number):

Publications: There were no publications relating to this trial at the time that this report was written.

OBJECTIVES

Primary objective: to compare time to progression in patients treated with long-acting (LA) intramuscular (im) fulvestrant (250 mg, administered every 28 ± 3 days) with that in patients treated with oral (po) tamoxifen (20 mg daily) as first-line therapy in postmenopausal women with advanced breast cancer.

Secondary objectives: to compare objective response rate, duration of response, time to treatment failure, time to death, and quality of life (QOL) in patients treated with fulvestrant with those of patients treated with tamoxifen; to assess the effect of ethnicity (ie, Japan vs. Rest of

World [ie, including USA and EU countries]) on the comparison between fulvestrant and tamoxifen for time to progression, objective response rate, duration of response, time to treatment failure, time to death, and QOL; to assess tolerability (local and systemic) of fulvestrant treatment compared with tamoxifen treatment.

METHODS

Design: Trial 9238IL/0025 was a double-blind, randomised, parallel group, multi-centre, multi-national, comparative trial conducted in postmenopausal women with advanced breast cancer. The efficacy and safety of treatment with the LA im formulation of fulvestrant, at a dose of 250 mg given monthly, were compared with treatment with tamoxifen 20 mg given orally once daily.

Trial treatment was continued until objective evidence of disease progression or other events required treatment withdrawal; when these occurred, trial treatment was stopped and further treatment was initiated at the discretion of the investigator. All patients were followed up for progression and thereafter for survival until death.

Efficacy and safety data were to be analysed (and/or summarised) when a total of 350 endpoint events (progression or death before progression) had occurred, including at least 32 events from subjects at Japanese centres. The number of patients required to be recruited in order to achieve this was a minimum of 510 evaluable patients (255 patients per group), including at least 56 patients from Japanese centres.

Population: Postmenopausal women with advanced breast cancer who had received no previous endocrine or cytotoxic therapy for advanced disease and who were oestrogen receptor-positive (ER+), progesterone receptor-positive (PgR+), or receptor status unknown.

Key inclusion criteria (ie, those pertinent to the efficacy endpoints): histological or cytological confirmation of breast cancer; objective evidence of recurrence or progression of disease not considered amenable to curative treatment (locally advanced disease was included if considered not amenable to curative therapy); postmenopausal, defined as any of the following: (i) aged 60 years or older, (ii) aged 45 years or older with amenorrhoea for longer than 12 months and an intact uterus, (iii) follicle-stimulating hormone (FSH) levels within the postmenopausal range, or (iv) bilateral oophorectomy; oestrogen-receptor-positive (ER+) or progesterone receptor-positive (PgR+) status, or receptor status unknown; presence of at least 1 measurable or evaluable (non-measurable) lesion; World Health Organisation (WHO) performance status of 0, 1 or 2; life expectancy of greater than 3 months.

Key exclusion criteria (ie, those pertinent to the efficacy endpoints): presence of life-threatening metastatic visceral disease, or any degree of brain and/or leptomeningeal involvement (past or present), or symptomatic pulmonary lymphangitic spread (patients with discrete pulmonary parenchymal metastases were eligible provided their respiratory function was not compromised as a result of disease); previous treatment with fulvestrant (for breast cancer); previous endocrine treatment for breast cancer (excluding tamoxifen as adjuvant therapy [must have been stopped 12 months before randomisation], oophorectomy, or ovarian radiation); treatment with LHRH analogues within 4 months of randomisation; systemic cytotoxic therapy for advanced breast cancer; systemic adjuvant cytotoxic therapy within 4 weeks before screening (6 weeks for nitrosoureas or mitomycin C); extensive radiotherapy within the previous 4 weeks or treatment

with strontium-90 (or other radio-pharmaceutical) within the previous 3 months; previous or current systemic malignancy within the previous 3 years (other than breast cancer or adequately treated in-situ carcinoma of the cervix uteri or basal or squamous cell carcinoma of the skin); evidence of severe or uncontrolled systemic disease.

Dosage: Patients were given either:

- fulvestrant 250 mg (5 ml) im monthly, plus placebo to match tamoxifen 20 mg (po daily), or
- tamoxifen 20 mg (po daily), plus placebo to match fulvestrant 250 mg (5 ml) im monthly.

The formulation number for fulvestrant 250 mg was F6521 and the batch numbers were P/1300/19, P/1359/24, P1359/26, P/1359/26, P/1465/22A, P/1465/23, P1465/22B, p1392/26, P1574/19, P1574/25, N83033, N83040, 983131, and 993118. The formulation number for fulvestrant placebo was F6522, and the batch numbers were P/1465/19, P/1465/20, P/1465/21, P/1359/17, P/1392/25, P/1359/19, N83082, N83070, N83099, 983132, 993003, and 993117. The formulation numbers for tamoxifen 20 mg were F6293, and, in the United States only, F12061, and the batch numbers were: LA282/2X, LA284/1X, LA276/1X, HH254, LO293/2, and in the United States, N73245A and 983112A. The formulation numbers for tamoxifen placebo were F11003, and, in the United States only, F12062, and the batch numbers were PA394X, DN354X, IM305X, and, in the United States, N73103A.

Key assessments:

Efficacy: The primary endpoint of the trial was time to disease progression. The secondary efficacy endpoints were: objective response rate, duration of response, time to treatment failure, time to death, and QOL (Treatment Outcome Index [TOI] and time to deterioration in QOL). WHO performance status was also assessed.

Objective tumour assessments were first conducted at baseline before trial treatment was administered, and were repeated at 3-month intervals during treatment until disease progression. For skin and soft tissue lesions only, assessment was every month for the first 3 months and then every 3 months. Baseline assessment involved the designation of lesions as measurable, evaluable but not measurable, or neither measurable nor evaluable. Each patient had to have at least 1 measurable or evaluable lesion to be eligible for the trial. Objective tumour assessment was categorised according to the Union Internationale Contre Le Cancer (UICC) criteria, ie, as complete response (CR), partial response (PR), stable disease (SD), or disease progression; this was determined by a computer algorithm.

The primary statistical analyses of the objective efficacy endpoints (ie, time to progression, objective response rate, and time to treatment failure) were conducted using all randomised patients on an intention-to-treat basis. Secondary (supportive) statistical analyses of these endpoints were conducted using a per-protocol population (according to treatment received). Secondary analyses (on an intention-to-treat basis) were also conducted for these endpoints using the following sub-groups: ER+ and/or PgR+ patients vs. all other patients; patients from Japanese centres vs. all other patients. Time to death and duration of response for responders was summarised in each case but not formally analysed.

In addition to a test for statistically significant difference, criteria were pre-defined for non-inferiority of the efficacy of fulvestrant 250 mg compared with that of tamoxifen 20 mg. This was assessed using the upper limit of the 95% confidence interval which was not to exceed 1.25 for the endpoints of time to progression and time to treatment failure. For objective response rate and clinical benefit, the criterion for non-inferiority was assessed using the lower limit of the 95% confidence interval for the difference in response rates which was to be no lower than -10%.
QOL was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire plus an additional Endocrine sub-scale questionnaire. TOI and time to deterioration in QOL, as well as the most bothersome endocrine symptom data, were formally analysed using all randomised patients according to treatment received. Data for the endocrine sub-scale data were summarised but not formally analysed.
WHO performance status was summarised at each visit but was not formally analysed.
Safety: Tolerability (local and systemic) was a secondary endpoint of this trial. Adverse events were recorded throughout the treatment period and follow-up period (ie, 8 weeks after administration of the last injection of fulvestrant/placebo or 30 days after taking the last tablet of tamoxifen/placebo, whichever was the latter). The following adverse events were prospectively defined and were formally compared between the treatment groups according to treatment received: hot flushes, vaginitis, gastrointestinal disturbance, and thromboembolic events. Health economics data (eg, duration and type of health care needed) were also collected.
The following clinical laboratory data were collected at baseline and throughout the treatment period: haematology; hepatic, renal, lipid, and other biochemistry. Weight was also recorded at each visit, and blood pressure and heart rate were recorded at baseline. Electrocardiographic data were collected at baseline, if a cardiac adverse event occurred and at withdrawal of trial treatment.

RESULTS

Demography: A total of 587 patients were randomised to trial treatment with either fulvestrant 250 mg (313 patients) or to tamoxifen 20 mg (274 patients). Thirty-five (11.2%) patients in the fulvestrant group and 25 (9.1%) patients in the tamoxifen group were resident Japanese.. The mean age for patients randomised to fulvestrant 250 mg was 66 years (range 43 to 93 years), and the mean age for patients randomised to tamoxifen 20 mg was 65 years (range 43 to 92 years). The age distribution was also similar in the 2 groups, with 57.5% and 54.7% of patients randomised to fulvestrant and tamoxifen, respectively, being 65 years or older. The majority of patients in both groups (79.7% in total) were white.
Breast cancer history and disease baseline characteristics were all similar between the 2 treatment groups, as was baseline data for WHO performance status.
Withdrawal rates were similar in each treatment group, with 220 (71.0%) patients treated with fulvestrant and 191 (70.5%) patients treated with tamoxifen being withdrawn from trial treatment. The main reason for withdrawal in both groups was disease progression (61.3% and 63.5% in the fulvestrant and tamoxifen groups, respectively).

Efficacy:
At the time of data cut-off for this trial, the median overall duration of follow-up was 441 days, with a total of 434 (73.9%) randomised patients, including 47 patients from Japanese centres, having progressed. It is considered that these results indicate that adequate data were available for obtaining clinically meaningful information for the primary efficacy endpoint of time to disease progression.
Table I summarises the results of the objective efficacy endpoints in this trial.

Table I Results of the objective efficacy endpoints

Endpoint	Outcome		Hazard ratio or odds ratio[a]	95%CI for hazard/odds ratio	Estimated treatment group difference	95% CI for treatment difference	p-value
	Fulvestrant 250 mg	Tamoxifen 20 mg					
Time to progression (median)	206 days	252 days	1.18	0.98 to 1.44	NA	NA	0.0876
Objective response rate	31.6% of patients	33.9% of patients	0.87	0.61 to 1.24	-2.98	-9.99 to 5.03	0.4508
Clinical benefit rate	54.3% of patients	62.0% of patients	0.68	0.48 to 0.95	-9.43%	-17.96 to -1.11	0.0257
Duration of response from randomisation (median)	527 days	602 days	NA	NA	NA	NA	NA
Duration of response from date of response (median)	420 days	423 days	NA	NA	NA	NA	NA
Duration of clinical benefit (median)	422 days	419 days	NA	NA	NA	NA	NA
Time to treatment failure (median)	179.5 days	238.5 days	1.24	1.03 to 1.50	NA	NA	0.0256
Time to death (median)	24.6% of patients died	19.7% of patients died	NA	NA	NA	NA	

CI Confidence interval. NA Not applicable.
[a] Hazard ratio for time to progression and time to treatment failure, and odds ratio for response rate and clinical benefit.

Data from this trial have shown that fulvestrant 250 mg has anti-tumour activity as demonstrated by a 32% response rate. However, neither superiority (tested at the 5% level) nor non-inferiority of fulvestrant 250 mg relative to tamoxifen 20 mg can be concluded for the primary endpoint of time to progression. For the secondary endpoints of time to treatment failure and clinical

benefit, the data favoured tamoxifen, with differences between the treatment groups being statistically significant. The criterion for non-inferiority of fulvestrant relative to tamoxifen was satisfied for the secondary endpoint of objective response rate.
The sub-group analyses for receptor-positive patients showed that no statistically significant differences were observed for fulvestrant 250 mg relative to tamoxifen for any of the endpoints, although the criteria for non-inferiority was satisfied for objective response rate. The separate analyses for receptor status 'other' (ie, negative or status unknown) patients showed that non-inferiority of fulvestrant relative to tamoxifen could not be concluded for any endpoint; all analyses favoured tamoxifen, with fulvestrant being statistically significantly different to tamoxifen for time to treatment failure and objective response rate.
The sub-group analyses for Japanese patients showed that fulvestrant 250 mg was statistically significantly different to tamoxifen, being in favour of tamoxifen (with the criteria for non-inferiority not being fulfilled) for time to progression, time to treatment failure, objective response rate and clinical benefit. The analyses of Rest of World patients showed that the criterion for non-inferiority of fulvestrant relative to tamoxifen was satisfied for the secondary endpoint of objective response rate, although neither statistical significance nor non-inferiority could be concluded for the other endpoints.
Duration of clinical benefit, duration of response from randomisation and duration of response from the date of response were also similar for the 2 treatment groups.
At the time of data cut-off, 77 (24.6%) patients in the fulvestrant 250 mg group and 54 (19.7%) patients in the tamoxifen group had died. Since this did not meet the pre-specified number of deaths, ie, half of the patients across both groups, no analysis of time to death was undertaken.
WHO performance status was similar for the 2 treatment groups throughout the trial period.
Insufficient data on quality of life were collected beyond progression to enable these data to be included in the statistical analyses of QOL, ie, Treatment Outcome Index and time to deterioration of QOL. Therefore, no conclusions can be drawn from this trial on the effect of the 2 trial treatments on quality of life once progression has occurred. Analysis of data up to disease progression showed that the QOL was maintained over time, and that there were no statistically significant differences between the 2 treatment groups (p=0.4989). In terms of time to deterioration in QOL, fulvestrant 250 mg was not statistically significantly different from tamoxifen (p=0.1513).
For the analysis of the most bothersome endocrine response, vaginal discharge was the only symptom to obtain statistical significance at the 5% level (p=0.0493) with the odds ratio indicating that patients in the fulvestrant 250 mg group had decreased odds of having vaginal discharge as their most bothersome endocrine symptom by 47% compared with those in the tamoxifen group, and the 95% confidence interval indicating that the odds for fulvestrant could be between 73% lower and the same as tamoxifen. Of the other symptoms, vaginal dryness (p=0.0542) and feel bloated (p=0.0546) were marginally statistically significant, with the incidence of being the most bothersome symptom being in favour of tamoxifen (ie, a lower incidence in the tamoxifen group).
All secondary analyses conducted supported the results of the primary analyses.
Safety:

A total of 86.8% of patients in the fulvestrant treatment group and 88.2% of patients in the tamoxifen treatment group reported at least 1 adverse event within the treatment or follow-up period. The events were mostly of mild intensity.

In general, the numbers of patients with serious adverse events (17.7% vs. 20.3%), events leading to withdrawal (2.9% vs. 5.2%), and events leading to death (2.3% vs. 4.8%) were fewer in the fulvestrant group than in the tamoxifen group. Serious adverse events were reported by approximately one-fifth of patients in each treatment group, with pathological fracture being the only event with an incidence exceeding 2% in either of the groups (in this case in the tamoxifen group). Serious drug-related events occurred in 1.9% of patients in the fulvestrant group and 2.2% of patients in the tamoxifen group. Of the patients with adverse events leading to death, only 1 patient in the fulvestrant treatment group and none in the tamoxifen group had an event considered to be related to trial treatment.

Approximately 42% of fulvestrant–treated patients and 51% of tamoxifen–treated patients experienced a drug-related adverse event, with vasodilatation, injection site pain, and nausea being the most common of this type of event in both of the groups. Overall, the profile of most frequently reported adverse events such as nausea, vasodilatation, asthenia, headache and pain is not dissimilar to previous clinical trial experience with fulvestrant and tamoxifen.

Of the pre-defined adverse event categories (hot flushes, vaginitis, gastrointestinal disturbances, thromboembolic events), fewer patients in the fulvestrant group than in the tamoxifen group experienced gastrointestinal disturbance (37.1% vs. 43.2%) or vaginitis (3.9% vs. 6.3%, mainly leukorrhea), although these differences did not achieve statistical significance. A lower frequency of leukorrhea (ie, vaginal discharge) is noteworthy because in the QOL component of the trial 8.6% of fulvestrant patients compared with 16.8% of tamoxifen patients were bothered by vaginal discharge. Furthermore, fewer patients in the fulvestrant group experienced hot flushes than those in the tamoxifen group (17.7% vs.24.7%), the difference reaching borderline statistical significance in favour of fulvestrant (p=0.0501). There was no statistically significant difference between the treatment groups for incidence of thromboembolic events (5.8% for fulvestrant and 3.3% for tamoxifen).

A number of adverse events, which were reported with lower incidences, are discussed in this report either because they were medically important, mechanistically could have been caused by either trial treatment, or are associated with treatment with hormonal therapies for breast cancer. Thus the following events were reviewed: fever, infection, leukopenia, urinary tract infection, alopecia, visual disturbances (amblyopia, cataracts), cardiac events including chest pain, rash, pathological fractures, and osteoporosis. No obvious casual relationship was seen between occurrence of any of these events and exposure to fulvestrant. Assigning a definitive cause for these events was often confounded by the presence of many concurrent conditions, concomitant treatments and other treatments for breast cancer (chemotherapy, radiotherapy, other hormonal therapy).

The fulvestrant injections were well tolerated locally, with none of the injection site events being reported as severe, serious, or leading to withdrawal.

Venous and arterial thromboembolic events were more common in the fulvestrant group than in the tamoxifen group, although the incidence in both groups was relatively low. A detailed analysis of all data from this and other clinical trials revealed insufficient evidence to conclude a

causal relationship between treatment with fulvestrant and the development of thromboembolism.

Clinical laboratory data were similar between the 2 treatment groups for most variables. For the haematological variables, haemoglobin and platelets median values decreased more over time in the tamoxifen group than in the fulvestrant group. For other variables, changes were observed in alkaline phosphatase, lipids and SHBG levels. Mean and median serum levels of alkaline phosphatase were elevated at entry to the study in both groups but decreased subsequently, although the reduction in the fulvestrant group was smaller and occurred later in comparison to the tamoxifen group.

The observed changes in lipids behaviour in the tamoxifen group are concordant with previous experience with this drug which, due to its agonist properties, reduces levels of total cholesterol, LDL cholesterol, and lipoprotein A. Fulvestrant, which is devoid of agonist action, was not shown to alter levels of cholesterol and lipoprotein A. However, a review of cardiovascular events occurring in patients treated with fulvestrant did not reveal an excess in incidence in this treatment group compared with the tamoxifen group.

The rise over time in sex-hormone binding globulin (SHBG) level in the tamoxifen group was expected and reflects the effects of its agonist properties in postmenopausal women. In this trial, mean values of SHBG remained steady over time in the fulvestrant group, supporting evidence of its lack of agonist properties.

No significant trends were apparent when adverse event data were summarised according to demographic characteristics or to duration of trial treatment. In general adverse events were reported by similar proportion of patients in each group over a defined period of exposure.

It was difficult to assess any race differences because mostly white patients took part in this trial. However, Japanese patients reported a higher rate of all adverse events (97.1%of fulvestrant patients and 96% of tamoxifen patients) and a lower rate of serious adverse events (16% of tamoxifen patients and 11.4% of fulvestrant patients) in comparison to the Rest of World patients, which possibly could be attributed to a different profile of concurrent diseases in this population.

No significant differences were observed in patients with abnormal hepatic values in comparison with a group of patients with normal hepatic values.

In summary, both treatments were well tolerated. A numerical advantage in favour of fulvestrant was shown in the incidences of gastrointestinal disturbances and vaginal symptoms in comparison with tamoxifen. Furthermore, hot flushes achieved almost statistical significance in favour of fulvestrant.

The incidences of adverse events in the fulvestrant group did not increase with longer exposure of the drug and the fulvestrant safety profile appears to support previous clinical experience.