SUMMARY

ASTRAZENECA

FINISHED PRODUCT: FASLODEX™

ACTIVE INGREDIENT: Fulvestrant

Trial title: An Open, Randomised, Multi-centre Trial Comparing the Efficacy and Tolerability of 125 mg and 250 mg FASLODEX™ (Long-acting ICI 182,780) with 1 mg ARIMIDEX™ (Anastrozole) in Postmenopausal Women with Advanced Breast Cancer (9238IL/0020)

Clinical phase: III

First patient recruited: 11 June 1997
Last patient recruited: 8 September 1999
Data cut-off date: 31 December 1999
AstraZeneca approval date: 17 January 2001

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: Originally, the primary objective of the trial was to compare the effects of 2 doses of long-acting (LA) intramuscular (im) fulvestrant (125 or 250 mg, administered every 28 ± 3 days), with oral anastrozole (1 mg daily) in terms of time to progression, in postmenopausal women with advanced breast cancer. Effective 27 April 1998, the primary objective was amended because a protocol-defined preliminary data summary showed no objective responses in the first 30 patients (across this trial and Trial 9238IL/0021[see Design below]) treated with fulvestrant 125 mg, and this treatment arm was therefore discontinued because of insufficient evidence of clinical activity. The revised primary objective was therefore amended to the following: to compare the effect of LA im fulvestrant (250 mg) with oral

anastrozole (1 mg daily) in terms of time to progression, in postmenopausal women with advanced breast cancer.
Secondary objectives: to compare objective response rate, duration of response, time to treatment failure, time to death, symptomatic response, quality of life (QOL), tolerability (local and systemic) in patients treated with fulvestrant with those of patients treated with anastrozole; and to define the pharmacokinetic profile of fulvestrant over 28 days following a single dose and to assess plasma fulvestrant levels after multiple monthly dosing.

METHODS
Design: Trial 9238IL/0020 was an open, randomised, multi-centre, parallel-group trial, conducted mainly in Europe. Another trial (Trial 9238IL/0021) of similar design (but double-blind rather than open) was conducted in North America. The efficacy and safety of treatment with the LA im formulation of fulvestrant, at a dose of 250 mg given monthly, were to be compared with treatment with anastrozole 1 mg given orally once daily.
Patients continued treatment until objective evidence of disease progression or other events required treatment withdrawal; when these occurred, trial treatment was stopped and standard therapy was initiated. Thereafter, patients were followed up for survival until death. For the final analysis, efficacy data from the 2 treatment groups were analysed (and/or summarised) when a total of at least 340 endpoint events (progression or death before progression) had occurred across the 2 groups; the number of patients required to be recruited in order to achieve this was a minimum of 392 evaluable patients across the fulvestrant 250 mg and anastrozole 1 mg treatment groups (196 patients per treatment group).
Tolerability data were also summarised and compared at this point.
Population: Postmenopausal women with advanced breast cancer who had relapsed or progressed following previous hormonal therapy were recruited into the trial.
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; requiring second-line hormonal treatment defined as (i) relapsing after adjuvant endocrine therapy with a non-steroidal anti-oestrogen, or (ii) progressing after either anti-oestrogen or progestin given as first-line treatment for advanced disease; evidence of hormone sensitivity, defined as (i) at least 12 months of adjuvant hormonal treatment before relapse, or (ii) tumour remission or stabilisation resulting from hormonal therapy for at least 3 months before progression in advanced disease, or (iii) oestrogen receptor-positive (ER+) or progesterone receptor-positive (PgR+) status; presence of at least 1 measurable or evaluable (non-measurable) lesion; World Health Organization (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) or an aromatase inhibitor; more than 1 previous endocrine treatment for breast cancer (excluding oophorectomy, ovarian radiation, or luteinizing hormone-releasing hormone [LHRH] analogue therapy); treatment with LHRH analogues within 3 months of randomisation; systemic cytotoxic therapy within 4 weeks before screening (6 weeks for nitrosoureas or mitomycin C), or treatment with strontium-90 (or other radio-pharmaceutical) within the previous 3 months; extensive radiotherapy within the previous 4 weeks; currently receiving oestrogen replacement therapy; 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: Initially, patients were given monthly, intramuscular injections of the LA formulation of fulvestrant at a dose of 125 mg (2.5 ml) or 250 mg (5 ml), or anastrozole 1 mg taken orally once daily. Following the decision to discontinue randomisation into the fulvestrant 125 mg treatment group, patients randomised to this treatment group either continued with fulvestrant 125 mg, or withdrew from the trial and received standard therapy. Increasing the dose from 125 mg to 250 mg was not permitted within the protocol, and therefore if investigators wished to do so, the patient was withdrawn from the trial and requested treatment with fulvestrant 250 mg on a named patient basis.

The formulation number for fulvestrant 250 mg used in this trial was F6521, and the various batch numbers were: P/1203/36, P1300/09B, P1300/18, P1300/19, P1300/20, P1359/04, P1359/21, P1359/22, P1359/26, P1465/22A.

The formulation number for anastrozole 1 mg used in this trial was F11292, and the batch numbers were: 9020Y and 9024A.

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; subjective symptomatology (analgesic use score, global pain score, and WHO performance status); and quality of life (Treatment Outcome Index [TOI] and time to deterioration in QOL).

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. 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. In the case of designation of CR, PR or SD for at least 24 weeks, or if the algorithm output differed from the investigator's assessment, radiological data were also reviewed by an independent radiologist.

The primary statistical analyses of the efficacy endpoints were conducted using all randomised patients on an intention-to-treat basis, and used response data as defined by the computer algorithm. Secondary (supportive) statistical analyses were conducted using a per-protocol population (according to treatment received), on an intention-to-treat basis but with a model that

excluded baseline covariates, and on an intention-to-treat basis using the data from the independent review process.

A preliminary data summary assessed objective response rates and was planned and conducted after a total of 30 patients had been treated with fulvestrant 125 mg (across both Trials 9238IL/0020 and 9238IL/0021) and had been followed up for a minimum of 3 months, in order to assess response at this dose. As a result of the preliminary data summary, which showed that no objective response had occurred in these first 30 patients, the fulvestrant 125 mg treatment group was discontinued from both Trials 9238IL/0020 and 9238IL/0021.

An interim analysis (including a formal statistical analysis of time to progression) was planned and conducted with combined data from both trials to assess whether fulvestrant treatment was less safe or efficacious than anastrozole treatment. As a result of the interim analysis, the Data Monitoring and Safety Committee (DMC) recommended that Trials 9238IL/0020 and 9238IL/0021 should continue.

Pharmacokinetics: The pharmacokinetics of fulvestrant following a single (ie, the first) injection of fulvestrant 250 mg, were assessed in a cohort of 16 patients at a number of centres. The following pharmacokinetic parameters were determined: area under the plasma concentration-time curve from time 0 to 28 days ($AUC_{(0\ to\ 28d)}$), maximum plasma concentration of fulvestrant (C_{max}), the plasma concentration of fulvestrant at 28 days after dosing (C_{min}), and the time to achieve the maximum concentration (t_{max}). In addition, trough (ie, pre-dose) samples were collected from a total of 27 patients in order to assess plasma levels after multiple monthly administration of fulvestrant 250 mg.

Safety: Adverse events were recorded throughout the treatment period and follow-up period (ie, 8 weeks after administration of the last injection of fulvestrant or 30 days after taking the last tablet of anastrozole). Health economics data (eg, duration and type of health care needed for an adverse event) were also collected.

The following clinical laboratory data were collected at baseline and throughout the treatment period: haematology; hepatic, renal, lipid, and other biochemistry; endocrinology. Blood pressure, pulse, and weight were also recorded at each visit, and electrocardiographic data were collected at baseline, if a cardiac adverse event occurred and at withdrawal of trial treatment.

RESULTS

Demography:

A total of 451 patients were randomised to trial treatment with either fulvestrant 250 mg (222 patients) or to anastrozole 1 mg (229 patients). (Ninety patients were randomised to treatment with fulvestrant 125 mg and the demographic data for these patients are listed in Appendix G of this report but the data were not summarised.)

The mean age for patients randomised to fulvestrant 250 mg was 63 years (range 35 to 86 years), and the mean age for patients randomised to anastrozole 1 mg was 64 years (range 33 to 89 years). The age distribution was also similar in the 2 groups, with 48.2% and 51.5% of patients randomised to fulvestrant 250 mg and anastrozole 1 mg, respectively, being 65 years or older. The mean weight and weight range were similar between the 2 treatment groups. Over 95% of patients in both groups were white.

The incidence and types of abnormalities found at the physical examination at trial entry were similar between the 2 groups. Breast cancer history and baseline characteristics of breast cancer status were all similar in each of the 2 treatment groups, as were baseline data for analgesic use, global pain score, and WHO performance status.
Withdrawal rates were similar between the 2 groups, with 177 (80.8%) patients treated with fulvestrant 250 mg and 182 (79.1%) patients treated with anastrozole 1 mg withdrawing from trial treatment. The main reason for withdrawal in both groups was disease progression (over 70% of patients withdrew for this reason).

Efficacy:

At the time of data cut-off for this trial, the median duration of follow-up (ie, from randomisation to date of death or the date at which the patient was known to be alive) was 439 days, with a total of 374 (82.9%) randomised patients having progressed.
The median time to progression was 10 days longer for the fulvestrant 250 mg group compared with the anastrozole 1 mg group (166 and 156 days, respectively), and the primary analysis of time to progression showed no statistically significant difference (p=0.8402) between the 2 treatments (hazard ratio of 0.98, 95.14% confidence interval of 0.80 to 1.21).
The estimated difference in objective tumour response rates for the 2 treatments was 4.78% (95.14% confidence interval of -2.19 to 14.23), indicating a higher response rate for fulvestrant 250 mg. The results of the primary analysis demonstrated that fulvestrant 250 mg was not statistically significantly different in terms of objective response rate (p=0.2010) when compared with anastrozole 1 mg (odds ratio of 1.38, 95.14% confidence interval of 0.84 to 2.29).
The median duration of objective response for all patients who had a complete or partial response, when measured from randomisation until disease progression or death, was 434 days for fulvestrant 250 mg patients and 425 days for anastrozole 1 mg patients. When measured from the date of first response, the median duration of objective response was 280 days and 274 days for the fulvestrant 250 mg group and anastrozole 1 mg group, respectively.
The proportion of patients who had gained clinical benefit by the time of data cut-off was very similar in each treatment group, being approximately 45%.
A difference between the 2 treatment groups of 13 days in favour of fulvestrant 250 mg was seen in the median time to treatment failure, with the results of the primary analysis showing that fulvestrant 250 mg was not statistically significantly different (p=0.8053) from anastrozole 1 mg in terms of time to treatment failure (hazard ratio of 0.97, 95% confidence interval of 0.80 to 1.19).
At the time of data cut-off, 36.9% and 36.2% of patients in the fulvestrant 250 mg and anastrozole 1 mg groups, respectively, had died. Because this did not meet the pre-specified death rate of half of the patients across both groups, no analysis of time to death was undertaken.
Symptomatic response, as judged by analgesic use, global pain score and WHO performance status, was similar for the 2 treatment groups throughout the trial period, with most patients in both groups requiring no analgesia, having either no pain or only mild pain, and being either fully active or only restricted by strenuous exercise.
Insufficient data on quality of life were collected beyond disease progression to enable these data to be included in the statistical analyses of QOL, ie, TOI and time to deterioration of QOL.
Using data from time-points occurring before progression of disease, the primary analysis

showed no statistically significant difference (p=0.3846) between the treatment groups in the TOI (estimated difference of -0.94, 95% confidence interval of -3.08 to 1.19).
The difference between treatment groups in median time to deterioration in quality of life was 37 days in favour of anastrozole 1 mg, and the primary statistical analysis showed no statistically significantly difference (p=0.3698) between treatments in this variable (hazard ratio of 1.17, 95% confidence interval of 0.83 to 1.66).
For all of the efficacy endpoints where formal statistical analyses were conducted, the results of each of the secondary analyses supported the findings of the primary analyses. The intention-to-treat and per-protocol analyses gave similar results in each case, indicating that the data from patients who were excluded from the per-protocol analyses had no significant effect on the outcome. The results of the analyses without covariates were also similar to the primary analyses. Furthermore, the time to progression and objective response rate analyses which used data from the independent review gave results that supported the conclusions of the respective primary analyses.
In summary, no statistically significant difference was seen between treatment with fulvestrant 250 mg and with anastrozole 1 mg for any of the efficacy endpoints that were analysed, indicating that fulvestrant 250 mg is at least as effective as anastrozole 1 mg in the second-line treatment of advanced breast cancer in postmenopausal women.

Pharmacokinetics:

Continuous exposure to fulvestrant over the 28-day dosing interval was seen in all patients from whom pharmacokinetic samples were obtained. Following the first 250 mg dose of fulvestrant, release of fulvestrant from the injection site was prolonged, with t_{max} being approximately 7 days (range 2 to 8 days). Following C_{max}, plasma concentrations declined slowly in a bi-exponential fashion to beyond 28 days after dosing. The Gmean $AUC_{(0 \text{ to } 28d)}$ value of 148 ng.d/ml was similar to exposure values obtained in previous trials. The plasma concentration profiles demonstrated some inter-subject variability, and this was reflected in the value for the coefficient of variation of $AUC_{(0 \text{ to } 28d)}$, ie, 45.3%.
Geometric mean trough plasma concentrations increased steadily from 2.62 ng/ml after the first injection to 6.15 ng/ml after the sixth dose. After this time, the trough plasma concentrations remained fairly constant at approximately 6 to 7 ng/ml, indicating that steady-state kinetics had been achieved after 6 injections given once a month.
The single- and multiple-dose pharmacokinetics of fulvestrant were predicted for this patient population using a 2-compartment pharmacokinetic model. A comparison of $AUC_{(0 \text{ to } 28d)}$ after the first injection with that at steady state, as predicted from the fitted model, indicated that there was approximately a 2-fold increase in plasma exposure due to accumulation of fulvestrant. However, there was no evidence of a change in the pharmacokinetic behaviour of fulvestrant on repeated dosing.

Safety:

The median duration of exposure to trial treatment was 169 days (range 28 to 888 days) and 168 days (range 19 to 773 days) for the fulvestrant 250 mg and anastrozole 1 mg groups, respectively. A wide variety of concomitant treatments was taken by patients in both of the groups, with similar incidences in each group for the various treatments.
The majority of patients in both of the treatment groups (83.6% in the fulvestrant 250 mg group and 85.2% in the anastrozole 1 mg group) experienced 1 or more adverse events during the trial.

The most common events to be reported overall were nausea, asthenia, vasodilatation, bone pain, pain, headache, and vomiting (in descending order of incidence). The incidences of these events were similar between the 2 treatment groups (fulvestrant 250 mg and anastrozole 1 mg, respectively), ie, 21.9 and 18.3% for nausea, 15.1 and 18.7% for asthenia, 16.0 and 13.0% for vasodilatation, 12.8 and 11.3% for bone pain, 9.6 and 12.2% for pain, and 10.0 and 10.9% for headache.

Gastro-intestinal disturbance events (nausea, vomiting, constipation, diarrhoea, and anorexia) were experienced by a broadly similar number of patients in each group for each category of event, although vomiting was reported by more patients in the fulvestrant 250 mg group than in the anastrozole 1 mg group.

The incidence of venous thromboembolic events was low in both groups, ie, thrombophlebitis was reported by 3 (1.4%) patients in the fulvestrant 250 mg group and by 2 (0.9%) patients in the anastrozole 1 mg group, and pulmonary embolus was reported by 3 (1.4%) fulvestrant 250 mg patients and by none of the anastrozole 1 mg patients. Two (0.9%) and 1 (0.4%) of the cases(s) of thrombophlebitis in the fulvestrant 250 mg and anastrozole 1 mg groups, respectively, were considered to be drug-related. None of the cases of pulmonary embolism were considered to be drug-related. All patients with thromboembolic events had additional risk factors for the development of these conditions.

Urinary tract infections (including cases of cystitis and dysuria) occurred in 10 (4.6%) patients in the fulvestrant 250 mg group and in 7 (3.0%) patients in the anastrozole 1 mg group.

Hot flushes consisted of vasodilatation and sweating; vasodilatation was experienced by 35 (16.0%) and 30 (13.0%) patients in the fulvestrant 250 mg and anastrozole 1 mg groups, respectively, whilst sweating was reported by 9 (4.1%) and 11 (4.8%) patients, respectively. A proportion (2.5%) of the cases in the fulvestrant 250 mg group were reported after withdrawal of trial treatment.

A higher number of patients treated with anastrozole 1 mg experienced joint pain (arthralgia, arthrosis, arthritis, and joint disorder) compared with those treated with fulvestrant 250 mg, ie, 20 (8.7%) patients compared with 5 (1.9%) patients, respectively.

Vasodilatation and nausea were the most commonly-reported adverse events which were considered by the investigator to be related to trial treatment. For both events, the incidences of drug-related cases were similar in each of the treatment groups, ie, 11.9 and 12.6% for vasodilatation (for fulvestrant 250 mg and anastrozole 1 mg, respectively) and 8.7% in both groups for nausea. Weight gain that was attributed to treatment with the trial drug occurred in 1 (0.5%) and 3 (1.3%) patients in the fulvestrant 250 mg and anastrozole 1 mg groups, respectively; all these events were of mild intensity. A small and similar number of patients in each group (less than 2% in each case) reported cases of vaginitis, vulvovaginitis, or vaginal bleeding that were considered to be related to trial treatment; again, all cases were of mild or moderate intensity. The majority of all drug-related adverse events were of mild or moderate intensity, and many of the events, eg, hot flushes (ie, vasodilatation and sweating), vaginitis, and weight gain, would be expected because of the mode of action of the trial drugs, ie, resulting from a change in the hormonal environment.

Sixteen (7.3%) patients in the fulvestrant 250 mg treatment group reported injection site adverse events (comprising injection site pain, inflammation, haemorrhage, hypersensitivity, and reaction) following the administration of trial medication. Of the 1898 injections given,

20 injections resulted in an injection site event (with a median duration of 3 days), equating to an event rate of 1.1%. All injection site events were of mild intensity and non-serious, and none of them led to withdrawal of trial treatment.

A small percentage of patients in each treatment group, ie, 1.8% and 1.3% in the fulvestrant 250 mg and anastrozole 1 mg groups, respectively, suffered an adverse event that led to death. No trends were apparent. None of the events leading to death in the fulvestrant 250 mg group were considered to be related to trial treatment, although 1 death in the anastrozole 1mg group resulted from a cerebral thrombosis which was considered by the investigator to be related to the trial drug.

The percentage of patients that were withdrawn from trial treatment due to adverse events was small in each group (3.2% and 1.3% in the fulvestrant 250 mg and anastrozole 1 mg groups, respectively).

More patients treated with fulvestrant 250 mg experienced a serious adverse event compared with patients treated with anastrozole 1 mg (ie, 16.9% compared with 13.0%), although all types of serious event were reported with a low incidence (less than 2%) in each of the groups. A wide range of serious adverse events was reported in both treatment groups, but most of the events were considered by the investigator not to be related to trial treatment. No underlying trends or patterns were observed.

As expected in a large group of patients with advanced breast cancer, haematology and biochemistry laboratory results were commonly above and/or below the reference ranges, occurring as isolated events or persistently within individual patients. Many of these abnormal results were present at entry to the trial and were possibly related to the disease, previous treatments for breast cancer (radiotherapy or chemotherapy), or to other concurrent conditions.

FSH and LH levels rose during treatment with each of the trial drugs to more normal postmenopausal levels (ie, levels were low at trial entry probably because of previous tamoxifen treatment), with a concomitant decrease in SHBG levels, supporting previous findings that fulvestrant does not affect the hypothalamo-pituitary axis and is devoid of agonist action.

Oestradiol levels remained constant following treatment with fulvestrant 250 mg but, as expected with an aromatase inhibitor, oestradiol levels decreased during treatment with anastrozole 1 mg.

In general, both treatments were well tolerated by the patients in this trial. As expected in a group of patients with advanced breast cancer there was a large number of adverse events and abnormal clinical laboratory data, many of which were related to the disease, disease progression, to other concurrent conditions, or to concomitant medications.

Safety data from patients treated with fulvestrant 125 mg were consistent with those from patients treated with fulvestrant 250 mg. Although not formally tested, no evidence was apparent of any dose-related toxicities.