SUMMARY

ASTRAZENECA

FINISHED PRODUCT: FASLODEX

ACTIVE INGREDIENT: Fulvestrant

Study title (number): A double-blind, randomised, placebo-controlled trial to study the anti-tumour effects of 250 mg FASLODEX™ (fulvestrant) in oestrogen receptor-positive primary breast cancers in premenopausal women (9238IL/0041).

Clinical phase: I/II

First patient recruited: 15 January 2001
Last patient completed: 21 January 2002
AstraZeneca approval date: <Publisher to insert>

Principal investigator and location (centre number):

Publications: There were no publications at the time of writing.

OBJECTIVES

Primary objective: To compare the effect of a single 250 mg intramuscular (im) dose of fulvestrant with placebo on the oestrogen receptor (ER) index, the progesterone receptor (PgR) index, and the Ki67 labelling index in primary breast cancers in premenopausal women undergoing surgery.

Secondary objectives: To assess the safety and tolerability of single doses of fulvestrant in premenopausal women.

METHODS

Design: Study 9238/IL0041 was a double-blind, randomised, placebo-controlled, multi-centre, European study. The anti-tumour effects, safety and tolerability of single dose, long-acting (LA)

im fulvestrant 250 mg were compared with those of placebo in this ‘proof of concept’ study conducted in pre-menopausal women. Biopsy samples for measurement of tumour markers were to be taken from the tumour before treatment and at the time of surgery. Patients were to have surgery for primary breast cancer between Day 15 and Day 22 following administration of study treatment on Day 1. Patients were followed up for adverse events until 8 weeks after the injection. Tumour marker and safety data were assessed when all patients had completed the required assessments.

Population: Premenopausal women with primary oestrogen receptor-positive breast cancer. Eighty patients (40 patients per treatment group) were to be recruited

Key inclusion criteria (ie, those pertinent to the efficacy endpoints): pre-menopausal woman aged <50, with no recent change in frequency of menses and no menopausal symptoms (patients who had undergone hysterectomy with preservation of a least 1 ovary were eligible if they had follicle stimulating hormone [FSH] and oestradiol levels within the premenopausal range); histological or cytological confirmation of T1, T2 or T3 primary breast cancer (T4 was ineligible); ER-positive tumour; fit for surgery within 1 month of randomisation; tumour large enough to provide sufficient tissue for a core-cut or tru-cut biopsy.

Key exclusion criteria (ie, those pertinent to the efficacy endpoints): metastatic disease; previous treatment with tamoxifen or other hormonal therapy for breast cancer; any other treatment affecting levels of sex hormones within 4 weeks of randomisation; previous radiotherapy to the primary tumour; history of disease affecting steroid metabolism; evidence of severe or uncontrolled systemic disease.

Dosage: Patients were given either a single injection of fulvestrant 250 mg (5 ml) im or matching placebo.

The formulation number for fulvestrant 250 mg was F6521 and the batch number was 64247E99. The formulation number for the placebo was F6522 and the batch number was 64248B99.

Key assessments:

Efficacy: The primary endpoints of the study were the following biochemical tumour markers: ER index, PgR index, and Ki67 labelling index of the tumour tissue. ER and PgR indices were assessed as indicators of anti-oestrogenic effects of the study treatment, and Ki67 labelling index was assessed as an indicator of anti-proliferative effects. These markers were assessed in each patient in tumour tissue taken before study treatment was administered, and from the surgical specimen on the day of surgery. Tumour marker data were formally analysed using analysis of covariance (ANCOVA); the analysis was conducted on a per-protocol, treatment received basis. In addition, plasma levels of fulvestrant were to be assessed from a blood sample taken on the day of (but before) surgery.

Plasma levels of FSH, luteinising hormone (LH), oestradiol, and progesterone were measured at baseline (ie, on the day of administration of study treatment) and on the day of (but before) surgery, in order to identify the menstrual phase of each patient at baseline and to identify any interaction of these hormones with the anti-oestrogenic effect of fulvestrant (ie, on the tumour marker levels).

Safety: Tolerability was a secondary endpoint of the study and was assessed by the recording of adverse events and endocrinology data. Adverse events were recorded throughout the treatment

and follow-up period (ie, until 8 weeks after the injection). Safety data were summarised for all randomised patients according to treatment received, but were not formally analysed.

RESULTS

Demography: Thirty-nine patients were randomised to receive fulvestrant 250 mg and 40 patients were randomised to receive placebo. Of these 79 patients, 13 (8 in the fulvestrant 250-mg group and 5 in the placebo group) were excluded from the per-protocol population. For the per-protocol population, the mean (SD) age of the 31 patients in the fulvestrant 250-mg group was 44.16 (3.31) years, range 35 to 49 years; and for the placebo group was 43.31 (5.82) years, range 25 to 49 years. Age distribution and weight were similar in both groups. All patients were White. Similar number of patients were found to be in either the follicular (48.4%) or luteal phase (51.6%) of their menstrual cycle in the fulvestrant 250-mg group, while slightly more patients in the placebo group were in the follicular phase (60.0%) than in the luteal phase (40.0%).

There were few withdrawals overall in both treatment groups and no withdrawals due to adverse events. Two patients in the fulvestrant 250-mg group were withdrawn: 1 due to protocol non-compliance and 1 was lost to follow up. Three patients in the placebo group were withdrawn due to being lost to follow up.

Efficacy: Results of the analyses of the 3 primary endpoints, ER index, PgR index, and Ki67 index, are presented in Table I.

Table I Tumour indices analyses results : per-protocol population

Tumour index	N	Lsmean	Treatment effect	95% confidence limits	p-value
ER Index					
Fulvestrant 250 mg	29	0.4947	0.0520	-0.0946 to 0.1986	0.4796
Placebo	31	0.4427			
PgR Index					
Fulvestrant 250 mg	26	0.6472	-0.2312	-0.4935 to 0.0311	0.0825
Placebo	26	0.8784			
Ki67 labelling index					
Fulvestrant 250 mg	30	23.9891	0.1429	-6.7374 to 7.0233	0.9669
Placebo	32	23.8461			

ER Oestrogen receptor; Lsmean least square mean; PgR Progesterone receptor.

There were no statistically significant differences between the 2 treatments for any of the tumour indices. Analysis of ER and PgR using alternative assays were supportive of the primary analysis results with no statistically significant difference detected.

Mean plasma concentration of fulvestrant 250 mg in the follicular phase was 4.572 ng/ml and in the luteal phase was 3.845 ng/ml. The overall mean (SD) for both phases combined was 4.209 (1.280) ng/ml. There was a large difference in the change from baseline in oestradiol in the luteal phase for fulvestrant 250 mg (median change = 450.0 pmol/L), compared with placebo (median change = 42.0 pmol/L). This difference between the treatment groups is of unknown clinical relevance. Differences between fulvestrant 250 mg and placebo for FSH, LH and

progesterone were small. There was no clear evidence of a trend between the size of the change in each tumour marker index and the plasma fulvestrant concentration on the day of surgery or the oestradiol/plasma fulvestrant concentration.

Safety: Approximately half of the patients in each treatment group had an adverse event: 21 patients (53.8%) in the fulvestrant 250-mg group, and 18 patients (45.0%) in the placebo group. Overall, there were few drug-related adverse events. More patients in the fulvestrant 250-mg group (10.3%) had drug-related events than in the placebo group (2.5%). There were no deaths or withdrawals due to adverse events and only 1 patient experienced serious adverse events (fulvestrant 250-mg group). This patient had pre-existing pancreatitis and cholecystitis and suffered a relapse.

Exclusion of adverse events related to surgery reduced the number of patients with adverse events in both treatment groups: 11 patients [28.2%] in the fulvestrant 250-mg group and 10 patients [25.0%] in the placebo group and resulted in the exclusion of the drug-related adverse event in the placebo group. Nausea and headache were the 2 most common events across both treatment groups following exclusion of events related to surgery.

Both fulvestrant 250 mg and placebo were well tolerated. None of the patients were considered to have had an adverse event as a result of changes in biochemical, haematologic, or hormone levels.