SUMMARY

ASTRAZENECA

FINISHED PRODUCT: FASLODEX™

ACTIVE INGREDIENT: ICI 182,780; ZD9238 (fulvestrant)

Trial title: A Partially-Blind, Randomised, Multi-centre Trial to Compare the Anti-Tumour Effects, Pharmacokinetics and Tolerability of 50 mg, 125 mg and 250 mg Single Doses of FASLODEX™ (Long-Acting ICI 182,780) with Tamoxifen and with Tamoxifen Placebo in Postmenopausal Women Prior to Surgery for Primary Breast Cancer (9238IL/0018).

Clinical phase: I/II

First subject recruited: 17 June 1997
Last subject completed: 6 August 1999
AstraZeneca approval date: 26 May 2000

Principal investigator and location (centre number):

Publications: Robertson JFR, Nicholson RI, Anderson E et al. The anti-tumour effects of single dose, long acting FASLODEX (ICI182780) compared with tamoxifen in post-menopausal primary breast cancer patients treated before surgery. Breast Cancer Res Treat 2000;59:99.

OBJECTIVES

The primary objective of this trial was to compare the anti-oestrogenic and anti-proliferative effects of 50 mg, 125 mg and 250 mg single doses of fulvestrant (ICI 182780; ZD9238; FASLODEX) with 20 mg daily tamoxifen and with tamoxifen placebo in primary breast tumours.

The secondary objectives of this trial were to compare the tolerability of single doses of fulvestrant with that of tamoxifen and tamoxifen placebo, and to determine the pharmacokinetic profiles of single doses of fulvestrant.

METHODS

Design: This was a randomised, partially-blind, parallel-group, multi-centre trial in which patients were randomised to receive one of the following treatments: fulvestrant 50 mg, fulvestrant 125 mg, fulvestrant 250 mg, tamoxifen 20 mg or tamoxifen placebo. All patients were to receive curative-intent surgery between 15 and 22 days following the start of randomised treatment. Tumour samples were taken before treatment and at surgery for the assessment of tumour markers. Blood samples were collected for pharmacokinetic assessments at various time points until Day 85 (following the start of treatment) from a cohort of patients who had received fulvestrant. Patients were followed up for adverse event recording until the post-surgical visit at Day 57 (or until Day 85 for those patients involved in the pharmacokinetic assessments).

Population: A total of 200 postmenopausal women (40 per treatment group) with primary breast cancer, awaiting curative-intent surgery, were to be recruited from breast cancer clinics in UK centres.

Key inclusion criteria: Postmenopausal woman; histological or cytological confirmation of T1, T2 or T3 primary breast cancer; fit for surgery within 1 month of randomisation; oestrogen receptor (ER)-positive or ER-unknown tumour that was large enough to provide sufficient tissue for 3 laboratory samples.

Key exclusion criteria: Evidence of metastatic disease; previous treatment with tamoxifen or other anti-hormonal therapy for breast cancer; treatment with hormone replacement therapy within 4 weeks of starting trial treatment; previous treatment with chemotherapy as neo-adjuvant treatment for breast cancer; previous radiotherapy to the primary tumour.

Dosage: Fulvestrant (long-acting[LA] formulation), at a dose of either 50 mg, 125 mg or 250 mg, was administered as an intramuscular (im) injection once only. Tamoxifen 20 mg or matching placebo was taken orally once a day (od) for a period of between 14 and 21 days. The formulation numbers for fulvestrant, tamoxifen and tamoxifen placebo were F6521, F6293 and F11003, respectively. The batch numbers were 39454G97, 35001G97, 36844A97 and 39452B97 for fulvestrant, NP280 for tamoxifen and 59454/93 and 38257D97 for tamoxifen placebo.

Key assessments:

Efficacy: The primary endpoints of the trial were 4 tumour marker indices. These markers were the oestrogen receptor (ER) index, progesterone receptor (PgR) index, Ki67 labelling index and the apoptotic index (AI). ER and PgR indices were assessed as indicators of anti-oestrogenic effects of the trial treatments, whereas Ki67 labelling and apoptotic indices were assessed as indicators of anti-proliferative effects. All 4 indices were assessed for each patient using sections taken from a pre-treatment tumour biopsy and from a surgical specimen after treatment.

Pharmacokinetics: The following pharmacokinetic variables for fulvestrant (and both of its diastereoisomers) were the secondary endpoints of the trial: area under the plasma concentration-time curve from zero to 28 days ($AUC_{(0-28d)}$); AUC from zero to the time of the last quantifiable plasma concentration ($AUC_{(0-t)}$); plasma fulvestrant concentration at 28 days after dosing and maximum plasma fulvestrant concentrations (C_{min} and C_{max}); and the time to maximum concentration (t_{max}). In addition, the ratio of the 2 diastereoisomers of fulvestrant, ie, ZM208,926 and ZM208,927, was determined over the 28-day dosing period. Blood samples were taken before treatment and at selected times after treatment with each dose of fulvestrant.

Safety: The tolerability of fulvestrant, which was a secondary endpoint of the trial, was assessed by the recording of adverse events and clinical laboratory data.

RESULTS

Demography: Two hundred patients received randomised treatment in this trial, with 39, 38, 44, 36 and 43 patients receiving fulvestrant 50 mg, fulvestrant 125 mg, fulvestrant 250 mg, tamoxifen and placebo, respectively. The mean (SD) age in years of the patients in each treatment group was: 68.7 (7.8) for fulvestrant 50 mg, 68.8 (7.6) for fulvestrant 125 mg, 66.2 (9.2) for fulvestrant 250 mg, 68.1 (9.1) for tamoxifen, and 66.1 (9.1) for placebo. The total age range across all 5 groups was 48 to 86 years. The majority or all of the patients in each treatment group were Caucasian. Demographic and primary tumour characteristics were similar across all treatment groups. There were 11 withdrawals from the trial, comprising 1 patient from each of the 3 fulvestrant groups, 4 patients who had received tamoxifen, 3 patients who had received placebo, and 1 patient who withdrew before taking any trial treatment.
Efficacy: The analysis results of the primary endpoints are presented in Table I.

Table I Efficacy primary endpoints: analysis results (per-protocol population)

Treatment comparison/statistic	Treatment received		
	Fulvestrant 50 mg	Fulvestrant 125 mg	Fulvestrant 250 mg
ER index: comparison with placebo			
Treatment effect	-0.3041	-0.4717	-0.6012
95% confidence limits (lower, upper)	-0.5704, -0.0379	-0.7385, -0.2049	-0.8646, -0.3378
p-value	0.0255	0.0006	0.0001
ER index: comparison with tamoxifen			
Treatment effect	-0.0183	-0. 1858	-0. 3153
95% confidence limits (lower, upper)	-0.2927, 0.2562	-0.4606, 0.0890	-0.5883, -0.0423
p-value	0.8955	0.1833	0.0239
PgR index: comparison with placebo			
Treatment effect	-0.1361	-0.2795	-0.3510
95% confidence limit (lower, upper)	-0.3201, 0.0478	-0.4624, -0.0966	-0.5323, -0.1696
p-value	0.1455	0.0030	0.0002
PgR index: comparison with tamoxifen			
Treatment effect	-0. 4042	-0.5475	-0.6190
95% confidence limits (lower, upper)	-0.6026, -0.2057	-0.7510, -0.3441	-0.8186, -0.4194
p-value	0.0001	0.0001	0.0001
Ki67 index: comparison with placebo			
Treatment effect	0.7100	0.5708	0.5314
95% confidence limits (lower, upper)	0.5073, 0.9939	0.4070, 0.8005	0.3816, 0.7399
p-value	0.0460	0.0014	0.0002
Ki67 index: comparison with tamoxifen			
Treatment effect	1.1058	0.8890	0.8275
95% confidence limit (lower, upper)	0.7777, 1.5723	0.6227, 1.2691	0.5816, 1.1775
p-value	0.5725	0.5139	0.2900

(continued)

Table I Efficacy primary endpoints: analysis results (per-protocol population) (continued)

Treatment comparison/statistic	Treatment received		
	Fulvestrant 50 mg	Fulvestrant 125 mg	Fulvestrant 250 mg
Apoptotic index: comparison with placebo			
Treatment effect	0.9044	0.9201	0.9281
95% confidence limit (lower, upper)	0.7593, 1.0774	0.7736, 1.0943	0.7833, 1.0996
p-value	0.2581	0.3436	0.3853
Apoptotic index: comparison with tamoxifen			
Treatment effect	1.1170	1.1363	1.1462
95% confidence limit (lower, upper)	0.9372, 1.3312	0.9532, 1.3546	0.9648, 1.3617
p-value	0.2144	0.1525	0.1196

Analysis of the ER index showed a significant overall treatment effect (p=0.0003). Following treatment with either fulvestrant or tamoxifen, there was a fall in the ER index. In the case of fulvestrant, this reduction in ER expression occurred in a dose-dependent manner and was statistically significantly different, when compared with placebo, for all 3 doses of fulvestrant investigated. In addition, the 250 mg dose of fulvestrant resulted in a statistically significant greater decrease in ER index than tamoxifen.

Analysis of PgR index showed a significant overall treatment effect (p=0.0001). All doses of fulvestrant resulted in a decrease in PgR index, whereas tamoxifen treatment caused an increase in PgR expression. The decreases seen with the 125 and 250 mg doses of fulvestrant were significantly different from placebo, and all 3 doses of fulvestrant were significantly diffferent when compared with tamoxifen.

Analysis of the Ki67 labelling index showed a statistically significant overall treatment effect (p=0.0029). All doses of fulvestrant and tamoxifen resulted in a decrease in Ki67 labelling index. There was evidence of a dose response for fulvestrant and all 3 doses resulted in a statistically significant effect compared with placebo. However, no statistically significant effects were seen in the comparisons between fulvestrant and tamoxifen.

There was no statistically significant overall treatment effect for the analysis of apoptotic index and no statistically significant effects between any of the individual treatment comparisons.

Pharmacokinetics: Following intramuscular injection of fulvestrant, there was slow absorption of fulvestrant, with a median t_{max} of 7 days. The individual concentration-time profiles of fulvestrant were very similar to each other, showing a slow, approximately bi-exponential decrease from C_{max} beyond 28 days after dosing.

The plasma concentration data up to 84 days following dosing confirm that release of fulvestrant from the injection site was sustained over a considerable period of time following dosing, owing to the properties of the formulation. Plasma concentrations that were well above the lower limit of quantification were achieved over the entire intended dosing interval for FASLODEX, ie, 28 days, in all dose groups, and it appeared that fulvestrant was still being released even beyond 84 days.

$AUC_{(0\text{-}28d)}$, C_{max} and C_{min} values were shown to increase approximately proportionally with dose.

The pharmacokinetic data confirmed that fulvestrant plasma concentrations were similar in this trial to those seen in other trials with this formulation.
The 2 diastereoisomers of fulvestrant, ie, ZM208,926 and ZM208,927, were present in approximately equal amounts, with the ratios of their concentrations being approximately 50:50. These observations confirmed previous findings that, following intramuscular injection, the absorption and disposition processes for the 2 diastereoisomers of fulvestrant are achiral.
Safety: The majority of patients had 1 or more adverse events during the trial, with most of the events not being drug related. The most frequently reported adverse event was skin pain (ie, wound pain), generally occurring following breast surgery. Other commonly reported adverse events were sepsis (usually wound infection relating to the surgical scar), nausea, and insomnia, all of which occurred with similar incidence across the 5 treatment groups. There was 1 death, which was due to disease progression and occurred in the placebo group. A total of 3 patients had adverse events that led to withdrawal from treatment: 1 patient in the fulvestrant 50 mg group due to thrombophlebitis, 1 patient in the tamoxifen group due to vomiting and 1 patient in the placebo group due to paraesthesia and a rash. A total of 18 (9.0%) patients had 1 or more serious adverse events: 5 (12.8%) of the fulvestrant 50 mg patients, 4 (10.5%) of the fulvestrant 125 mg patients, 4 (9.1%) of the fulvestrant 250 mg patients, 3 (8.3%) of the tamoxifen patients and 2 (4.7%) of the placebo patients. The most frequently reported serious adverse event across all treatment groups was sepsis (wound infection).
No trends in haematological or biochemistry variables were seen in any of the treatment groups during the trial.