SUMMARY

ZENECA

FINISHED PRODUCT: FASLODEX™

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

Trial title (number): A Randomised, Placebo-Controlled, Dose-Ranging Trial Comparing ICI 182,780 with ZOLADEX™ in Patients with Uterine Fibroids Awaiting Hysterectomy (9238IL/0019)

Clinical phase: II

First patient recruited: 23 October 1997
Last patient completed: 15 March 1999
Zeneca approval date: 22 March 2000

Principal investigator and location (centre number):

Publications: Audebert A, Anderson K. A randomised placebo-controlled, dose-ranging trial comparing ZM 182,780 with ZOLADEX in patients with uterine fibroids awaiting hysterectomy. Annual Regional International Society for Gynaecologic Endoscopy Meeting 1998, Abs 78.

OBJECTIVES

The primary objective of this trial was:

- to determine which of 3 intramuscular (im) doses of fulvestrant, when given over a 3-month period, was the most effective at inhibiting endometrial growth and shrinking uterine fibroids when compared with placebo, and caused less bone resorption, as measured by cross-linked N-telopeptide, when compared with goserelin

The secondary objectives were:

- to assess the effect of each of the 3 doses of fulvestrant when given over a 3-month period on ovarian stimulation (ovarian ultrasound, follicular size), hypothalamus

pituitary axis (sex hormones), uterine volume, endometrial biopsy, bone resorption (free deoxypyridinoline), and vaginal bleeding when compared with goserelin and placebo

- to assess the effect of each treatment on haematology and biochemistry parameters including antithrombin III (coagulation) and lipoprotein levels
- to assess the effect of each treatment on the severity of pelvic pain, pressure symptoms, and patient tolerability in terms of adverse events
- to assess dose proportionality and the pharmacokinetic profile of fulvestrant following im administration in a cohort of patients over a 5-month period (3 doses plus 3 months' follow-up after the last dose)

METHODS

Design: This was a phase II, multicentre, randomised, active- and placebo-controlled, parallel-group, dose-ranging trial in pre-menopausal women with uterine fibroids awaiting hysterectomy. Treatments were administered in 3 doses at 4-week intervals and patients were assessed every 4 weeks for 16 weeks.

Population: A total of 250 evaluable patients (50 patients per treatment arm).

Key inclusion criteria (ie, criteria that differentiate this trial population from those typically recruited to clinical trials): Pre-menopausal women; diagnosed uterine fibroids requiring hysterectomy and which were measurable.

Key exclusion criteria (ie, those of particular relevance to the safety of the volunteers): Patients having previously undergone bilateral ovariectomy; positive for any malignancy or cervical cancer; previously received more than 3 months' treatment with a gonadotrophin releasing hormone (GnRH) agonist or had finished treatment within 3 months before entry; use of sex-hormone therapy within 4 weeks before entry; history of hypersensitivity or any other severe reaction to GnRH agonists; history of disease affecting bone or steroid metabolism; metabolic bone disease, or having received calcitonin, biphosphonate, or sodium fluoride within the previous 2 years; a bone fracture with 6 months; history of coagulation or haemostatic disorder (platelets $<100 \times 10^9$/l, decrease in antithrombin III levels compared with normal), or an abnormal prothrombin time; definite recent change in menstrual frequency, unrelated to the diagnosis of fibroids; recent appearance or increased frequency of hot flushes; any other reason to suspect onset of menopause.

Dosage: Patients received 50, 125, or 250 mg of fulvestrant, or a goserelin 3.6 mg depot, or placebo to match these doses. For fulvestrant treatments (including placebo), patients received an im injection once every 4 weeks. Goserelin or sham goserelin (ie, placebo to goserelin) was administered as a subcutaneous (sc) injection, once every 4 weeks. The first dosing took place on Day 1 to 4 of the patient's menstrual cycle. Patients were to receive 3 injections of active or placebo treatment. Formulation and batch numbers were as follows: fulvestrant (long-acting) (F6521, 3945G97, 39455D97, 39452B97, 36843D97, and 36844A97) and matching placebo (F6522, 39453J97, 36839A97, 40156H96, and 01184F98); goserelin (F5589, SN450XA, and 37654A96) and matching sham (F6328, 39795F97, and 37550G96).

Key assessments:
Efficacy: Primary endpoints were: endometrial thickness and fibroid volume. Secondary endpoints were uterine volume, size and presence of follicular cystic-like structures, subjective symptomatology (pelvic pain, lower abdominal pressure), vaginal blood loss, and endometrial biopsy.
Pharmacokinetic: Pharmacokinetic parameters were: area under the plasma concentration-time curve (AUC) from time 0 to 28 days ($AUC_{(0-28)}$), maximum plasma concentration (C_{max}), and time of the maximum plasma concentration (t_{max}) after the first and third doses, AUC from time 0 to the time of the last quantifiable plasma concentration ($AUC_{(0-t)}$) after the third dose, and plasma concentration at the end of the 28-day dosing interval (C_{min}) after the first, second, and third doses.
Safety: The primary safety endpoint was bone resorption index (cross-linked N-telopeptide); secondary safety endpoints were bone resorption index (free deoxypyridinoline), haematology and clinical chemistry (including sex hormones, plasma lipoproteins, and antithrombin III), and adverse events/tolerability. Other safety assessments were: post-operative complications; vital signs; and electrocardiogram.

RESULTS
Demography: A total of 313 patients were randomised to either fulvestrant 50 mg (59 patients), fulvestrant 125 mg (66 patients), fulvestrant 250 mg (62 patients), goserelin 3.6 mg (66 patients), or placebo (60 patients); 15 patients were included in each of the placebo sub-groups. The groups were comparable for the demographic characteristics. Twelve patients were withdrawn.
Efficacy: The analyses of the changes in endometrial thickness and fibroid volume after 13 weeks of treatment are shown in Tables I and II respectively.

Table I Endometrial thickness: estimated treatment effects at Week 13 (PP population)

Treatment comparison	Fulvestrant		Placebo/goserelin					
	n	glsmean (mm)	n	glsmean (mm)	Estimate of treatment effect	Lower 95% CL	Upper 95% CL	p-value
Fulvestrant:								
50 mg vs placebo	38	1.90	35	2.16	0.88	0.61	1.28	0.4980
125 mg vs placebo	36	2.23	35	2.16	1.03	0.71	1.51	0.8676
250 mg vs placebo	39	2.04	35	2.16	0.94	0.65	1.37	0.7553
50 mg vs goserelin 3.6 mg	38	1.90	44	1.27	1.50	1.05	2.12	0.0249
125 mg vs goserelin 3.6 mg	36	2.23	44	1.27	1.75	1.23	2.50	0.0021
250 mg vs goserelin 3.6 mg	39	2.04	44	1.27	1.60	1.13	2.28	0.0091

glsmean Least squares geometric mean.

Table II Fibroid volume: estimated treatment effects at Week 13 (PP population)

Treatment comparison	Fulvestrant		Placebo/goserelin					
	n	glsmean (mm)	n	glsmean (mm)	Estimate of treatment effect	Lower 95% CL	Upper 95% CL	p-value
Fulvestrant:								
50 mg vs placebo	38	51.28	34	49.06	1.05	0.69	1.58	0.8330
125 mg vs placebo	36	49.86	34	49.06	1.02	0.67	1.54	0.9383
250 mg vs placebo	39	42.69	34	49.06	0.87	0.58	1.31	0.5064
50 mg vs goserelin 3.6 mg	38	51.28	44	27.33	1.88	1.28	2.76	0.0015
125 mg vs goserelin 3.6 mg	36	49.86	44	27.33	1.82	1.24	2.68	0.0023
250 mg vs goserelin 3.6 mg	39	42.69	44	27.33	1.56	1.06	2.30	0.0235

glsmean Least squares geometric mean.

There were no statistically significant differences in endometrial thickness or fibroid volume between any dose of fulvestrant and placebo; however, there were significant differences between each dose of fulvestrant and goserelin. There was no evidence of a dose-response relationship for either primary efficacy endpoint. Analysis of the secondary endpoints were consistent with those of the primary endpoints, with no evidence of any effect for fulvestrant.

Pharmacokinetics: After a single dose, release of fulvestrant into the systemic circulation was slow: t_{max} was typically 7 days after injection (range: 2 to14 days). C_{max} of 2.79, 2.21, and 8.06 ng/ml and $AUC_{(0-28)}$ of 39.5, 38.3, and 147.5 ng.d/ml were achieved with doses of 50, 125, and 250 mg fulvestrant, respectively. After the peak, plasma levels declined slowly falling to concentrations of 0.55, 0.73, and 3.33 ng/ml after 28 days. After 3 doses, C_{max} of 1.23, 4.76, and 9.77 ng/ml and $AUC_{(0-28)}$ of 24.5, 73.6, and 163.6 ng.d/ml occurred with doses of 50, 125, and 250 mg. Median t_{max} occurred after 5 to 7 days; plasma concentrations subsequently declined slowly to C_{min} of 0.80, 1.94, and 3.96 ng/ml after 28 days. In some patients, circulating levels of drug were still measurable at 84 days post-dose. There was evidence of limited accumulation between the first and third doses, with geometric mean $AUC_{(0-28)}$ values showing an increase in exposure of between 21% and 92% at doses of 125 and 250 mg. These results were based on low patient numbers and insufficient AUC data were available to perform a formal analysis of dose-proportionality. However, plasma profiles generated by pharmacokinetic modelling suggested that the increase in exposure was dose-related.

Safety: There was no statistically significant difference between any dose of fulvestrant and placebo in N-telopeptide excretion; however, there was a statistically significant difference between each dose of fulvestrant and goserelin. The estimated increase in bone marker from baseline to Week 13 was 47%, 41%, and 41% lower for fulvestrant 50 mg, 125 mg, and 250 mg, respectively, than for goserelin ($p<0.0001$). All trial treatments were generally well tolerated. Adverse events were reported by 27/55 (49.1%) patients receiving fulvestrant 50 mg, 37/65 (56.9%) receiving fulvestrant 125 mg, 33/67 (49.3%) receiving fulvestrant 250 mg, 51/66 (77.3%) receiving goserelin, and 32/60 (53.3%) receiving placebo. The most frequent events occurred with goserelin and were vasodilatation (28/66 patients [42.4%]) and sweating (13/66 patients [19.7%]). The incidence of these events was lower with fulvestrant (6.0% to 7.7%; 0.0% to 4.5%) and placebo (11.7%; 3.3%). Headache was also frequently reported across the treatment groups, although the incidence was higher with goserelin (24.2%) than fulvestrant (9.2% to 14.9%) or placebo (15.0%). Fulvestrant was associated with lower free

deoxypyridinoline excretion than goserelin; otherwise, there were no major differences across the treatment groups with respect to specific safety endpoints (haematology, biochemistry, antithrombin III, and lipoproteins).