SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT(S): ICI 182,780

Study title (number): An Open, Phase II Study to Determine if Partial or Complete Responses can be achieved with the Slow Release formulation of a Pure Anti-oestrogen (ICI 182,780) in Post-menopausal Women with Advanced Breast Cancer who have Relapsed on Tamoxifen Therapy (9238IL/0004)

Clinical phase: II

First patient entered: 28 October 1992

Last patient completed: 17 November 1993

Principal investigator(s), location and centre number:

Publications: DeFriend DJ, Blamey RE, Robertson JF, Walton P, Howell A (1993), Response to the pure antioestrogen ICI 182780 after tamoxifen failure in advanced breast cancer, 16th Annual San Antonio Breast Cancer Symposium, San Antonio, 5-6 November. Breast Cancer Research and Treatment 27 (1/2): 136 Abstract 21.

OBJECTIVES: Primary objective: to determine if partial or complete responses could be achieved with the slow release formulation of ICI 182,780 in post-menopausal women with advanced breast cancer who had relapsed on tamoxifen therapy.

Secondary objectives: to assess the systemic and local tolerability of the slow release formulation of ICI 182,780 in post-menopausal women with advanced breast cancer who had relapsed on tamoxifen therapy; to monitor serum concentrations of ICI 182,780 following treatment with the slow release formulation.

ZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT(S): ICI 182,780

METHODS:

Design: Two-centre, open, Phase II, 2-part study; Part 1: 1 month with assessments at entry (Day 0) and Days 1, 3, 7, 10, 14, 21, and 28; Part 2: 6 months with assessments at entry and monthly thereafter.

Population: Part 1: 4 patients who were receiving tamoxifen and exhibiting a stable condition; Part 2: 19 patients who had relapsed on tamoxifen.

Key inclusion criteria: Part 1: no menstrual periods for the last 12 months, or follicle-stimulating hormone-proven menopause; histologically-verified/cytologically-verified breast cancer; stable disease and receiving tamoxifen therapy.

Part 2: no menstrual periods for the last 12 months, or follicle-stimulating hormone-proven menopause; histologically-verified/cytologically-verified breast cancer; relapsed on tamoxifen therapy; evidence of progressive disease.

Key exclusion criteria: Part 1: aged 81 years or over; history or presence of conditions known to interfere with absorption, distribution, metabolism or excretion of drugs; weighed <40 kg or >110 kg; performance status (WHO) scale ≥ 3, and life expectancy ≤ 3 months; history of disease associated with or affecting steroid metabolism; clinical chemistry or haematology outside the normal range and considered to be clinically significant for reasons other than breast cancer.

ZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT(S): ICI 182,780

Key exclusion criteria (continued):
Part 2: as for Part 1 and - for patients previously treated with endocrine therapy: oestrogen receptor and/or progesterone receptor negative and no response to prior endocrine therapy (mixed receptor status was acceptable, as was unknown receptor status providing the relapse-free interval was ≥2 years); only manifestation of disease was one of the following: lymphoedema, pleural effusions, ascites, or osteoblastic skeletal lesions, or liver metastases as the only site of recurrent disease; received chemotherapy for advanced or metastatic disease (adjuvant chemotherapy was acceptable); received radiotherapy to the indicator lesion(s); absence of measurable lesions; brain or leptomeningeal disease.

Dosage: By im injection of ICI 182,780, administered once a month;
Part 1: 1 ml (50 mg);
Part 2: either 1 x 2 ml (100 mg) + 5 x 5 ml (250 mg) or 6 x 5 ml (250 mg).

Key assessments: Demographic and baseline characteristics.

Clinical efficacy: objective overall response evaluations - comprising best response (as assessed at any 2 visits ≥4 weeks apart) and overall response rates, for responders and for stable disease; pharmacokinetic analysis of ICI 182,780; endocrinology parameters - follicle-stimulating hormone (FSH), luteinising hormone (LH), sex hormone binding globulin (SHBG).

Tolerability: subjective WHO performance status and toxicity symptom scores.

Safety: adverse events, haematology and clinical chemistry laboratory evaluations.

ZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT(S): ICI 182,780

Statistical considerations: Evaluable patients were defined as those who remained in the study after 2 months of treatment as assessed at their third visit (Month 2), regardless of whether they received a third dose of study medication.

Population response rate estimates were based on the number of responders in the study, expressed as a percentage of all evaluable patients in the study sample (including any not assessed for overall response); 95% confidence intervals incorporated a continuity correction because of the small sample size.

RESULTS:

Demography: Demography results were based on Part 2 patients.

The age of the participants ranged from 48 to 78 years with a mean of 61.6 years; 18 patients (94.7%) were white and one patient (5.3%) was black. The mean weight at study entry was 61.6 kg; mean height was 158.4 cm.

The time since the first diagnosis of primary breast cancer up until the date of first dose of study medication ranged from 8 months to 22.7 years with a mean of 7.1 years. Of the 19 Part 2 patients, 15 (78.9%) had undergone prior surgery for breast cancer, comprising mastectomy and/or wide local excision or lumpectomy; these procedures were sometimes accompanied by axillary node sampling and/or clearance. In one patient, bilateral oophorectomy was subsequently performed. Nine patients (47.4%) had received prior radiotherapy. All 19 patients had received tamoxifen treatment. One patient had also received concomitant treatment with prednisolone.

ZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT(S): ICI 182,780

RESULTS, Demography (continued):
One patient had received goserelin acetate for 6 months prior to oophorectomy and then received tamoxifen on further progression of the disease. Of the 19 patients, 12 had received tamoxifen as adjuvant therapy for breast cancer; the duration of treatment ranged from 7 months to 78 months. The remaining seven patients had received tamoxifen for advanced disease.

A total of six patients withdrew from the study, all as a result of progressive disease (PD).

RESULTS, Efficacy: Except for the pharmacokinetic results, efficacy results were based only on Part 2 patients. All patients in Part 2 of the study fulfilled the pre-defined criteria for evaluability.

Best overall response: evaluable patients

Best response	Patients N	Patients %
Complete response (CR)	0	0.0
Partial response (PR)	7	36.8
No change (NC, stable disease)	7	36.8
Progressive disease (PD)	4	21.1
Not assessed (NA)	1	5.3
Total	19	100.0

The overall population response rate to ICI 182,780 was estimated to be 36.8%, with a standard error of 11.1%; the corresponding 95% confidence interval was

ZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT(S): ICI 182,780

RESULTS, Efficacy (continued):

12.5% to 61.2%. The population response rate for stable disease was estimated to be 63.2%, with a standard error of 11.1%; the corresponding 95% confidence interval was 38.8% to 87.5%. This was based on 12 of the 19 evaluable patients in the study sample being identified either as having best overall response assessments of PR or CR, or of having consistent assessments of NC or better for all 6 months in the study.

Remission was ongoing in 11 of the 19 patients (57.9%) at the Month 6 visit.

In Part 1 of the study mean serum concentrations ranged from non-detectable (<0.68 ng/ml) 1 day after dosing to a maximum serum concentration (C_{max}) of 2.0 ng/ml 9 days after dosing. In these patients, exposure to the drug throughout the 1-month dosing interval was not shown, with three of the four patients having non-detectable concentrations (<0.68 ng/ml) by 21 days after dosing. In patients who received either a 100 mg or 250 mg dose at entry, mean C_{max} was 2.7 ng/ml and 10.5 ng/ml, respectively, and occurred 8 and 7 days after dosing, respectively. Following both dose levels, continuous release of drug was shown throughout the 1-month dosing interval. Corresponding mean area under the serum concentration versus time profile (AUC) and total body clearance values were 39.4 ng.d/ml and 140.5 ng.d/ml, and 2077 ml/min and 1534 ml/min for doses of 100 mg or 250 mg, respectively. Comparison of data after the first and sixth monthly 250-mg doses of ICI 182,780 showed that mean C_{max} increased from 10.5 ng/ml to 12.8 ng/ml, accompanied by increases in mean end-of-month concentrations from 3.1 ng/ml to 5.6 ng/ml and AUC values from 140.5 ng.d/ml to 206.8 ng.d/ml, respectively, in the 11 patients in this group. This resulted in a 1.2-fold increase in C_{max} and a 1.5-fold increase in

ZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT(S): ICI 182,780

RESULTS, Efficacy (continued):
AUC, suggesting a degree of accumulation upon multiple dosing of the 250 mg dose in this particular group of patients.

Endocrine parameters showed shifts in individual values and group means during treatment that were generally compatible with the anti-oestrogen actions of ICI 182,780. Mean FSH and LH levels increased from low post-menopausal levels, presumably as a result of the oestrogenic effect of tamoxifen at the pituitary level. During treatment with ICI 182,780, FSH and LH rose to more normal values, with concomitant individual reductions in SHBG. These data suggest that ICI 182,780 does not affect the hypothalamo-pituitary axis.

RESULTS, Tolerability: Tolerability results were based on Part 2 patients.

No patient had a WHO performance status score of ≥ 3 (on a scale of 0 to 4) assigned to them during the study period. Patients were subjectively assessed for each of 12 symptoms related to the primary diagnosis (breast cancer) and/or its treatment; this analysis revealed no problems of an unexpected nature or severity: cutaneous symptoms, transient lethargy (state of consciousness), pain symptoms, and stiffness were reported frequently.

RESULTS, Safety: Safety results were based on Part 1 and Part 2 patients.

A total of 17 patients (73.9%) experienced 55 adverse events during the study, but in only five patients (21.7%) were the events considered to be related to study medication. There were no fatal adverse events and none necessitated withdrawal.

ZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT(S): ICI 182,780

RESULTS, Safety (continued):

The most common events, each occurring in 17.4% of patients, were pain and infection (not unexpected in patients treated for breast cancer) and nausea and vomiting, which could be related to pharmacological effects of the study drug, although they were not considered by the investigators to be related to study medication. Three patients (13.0%) experienced six serious adverse events: cough and breathlessness in one patient, bile duct obstruction in another, and pleural effusion in the third. None was attributed to study medication.

Local reactions at the injection site occurred in four patients, on one occasion each. One patient had a change in body odour, and another patient had a pinkish vaginal discharge and depersonalisation which was thought by the investigator to be drug-related.

Laboratory analysis of haematological and biochemical parameters, revealed no clinically significant changes in group mean or individual values attributable to study medication or which could give rise to concerns regarding drug safety.

There were no unexpected changes in body temperature, blood pressure and heart rate or physical examination that gave rise to concern.