SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT: CASODEX™

ACTIVE INGREDIENT: Bicalutamide

Trial title (number): A Multicentre, Randomised, Open-label Trial to Compare Bone Mineral Density and Fat Free Mass in Men Given Either Goserelin Acetate (ZOLADEX™) 10.8-mg Depot or Bicalutamide (CASODEX™) 150 mg for Treatment of Prostate Cancer (7054US/0004).

Clinical phase: IIIb

First patient recruited: 30 March 1998
Data cut-off date: 1 June 1999
Zeneca approval date: 17 November 1999

Publications: None at the time of writing this report.

OBJECTIVES

Primary objectives: To measure change over time compared with baseline measurements of bone mineral density (BMD) and fat free mass (FFM) within each treatment group, and to compare changes in BMD and FFM between the 2 treatment groups.
Secondary objectives: To follow changes in blood lipid levels, and to assess the safety and tolerability of ZOLADEX 10.8-mg, 3-month depot treatment and CASODEX 150 mg/day treatment, in patients with prostate cancer.

METHODS

Design: This was a multicentre, randomised, open-label, parallel-group trial in patients with histologically-confirmed adenocarcinoma of the prostate. Patients were randomly allocated to receive either CASODEX 150 mg/day or ZOLADEX 10.8-mg (ie, 3-month depot). Patients were assessed at baseline (ie, within 6 weeks before the date of randomisation but after informed

consent had been obtained), and then at 12-weekly intervals (ie, Week 12, Week 24, Week 36, etc), up to and including Week 96.

Population: A total of 100 patients were to be recruited into this trial.

Key inclusion criteria: Histologically-confirmed adenocarcinoma of the prostate; stage of disease defined as T1 to T4 NX MO, for which immediate palliative hormonal ablation was indicated; Eastern Co-operative Oncology Group performance status of 0 or 1; a life expectancy of >6 months.

Key exclusion criteria: A baseline testosterone level <194 ng/dl; currently receiving systemic steroids or a medication known to affect calcium or vitamin D metabolism (eg, anticonvulsants); history or presence of metabolic bone disease, renal disease, malabsorption (due to gastrointestinal [GI] disease or GI surgery), rheumatoid arthritis, recent fracture, or any other condition known to affect bone metabolism; baseline calcium >10.6 mg/dl; baseline thyroid-stimulating hormone (TSH) level >10 MCIU/ml or <0.4 MCIU/ml; hormonal therapy (including neoadjuvant and adjuvant therapy) within the previous 6 months before randomisation; known hypersensitivity to CASODEX, luteinising hormone-releasing hormone (LHRH), LHRH agonists or analogues, or any of the components of ZOLADEX; baseline BMD value, assessed by dual-energy x-ray absorptiometry (DEXA), of >2 standard deviations below age-matched controls performed by the site BMD centres.

Dosage: One oral dose of CASODEX 150 mg/day. One subcutaneous dose of ZOLADEX 10.8 mg, administered once every 3 months. Each CASODEX 150-mg dose was comprised of 1 CASODEX 150-mg tablet. Each ZOLADEX 10.8-mg depot was presented in a pre-filled sterile delivery device containing ZOLADEX dispersed in a cylindrical rod of biodegradable, biocompatible, 2,1-lactide-glycolide copolymer. Formulation and batch numbers were: CASODEX, white, intagliated 150-mg tablet, F11156 (batch numbers H97/2184, ADM35741K97); ZOLADEX, F6054 (batch numbers ADM AA232B, IO235A, ADM 38052G97).

Key assessments:

Efficacy: The primary endpoints for the analysis of efficacy were the percentage change from baseline to 96 weeks in BMD and FFM. The 24-week, 48-week and 72-week assessments were to be considered secondary timepoints. Data at each 24-week time point were to be analysed using an analysis of variance (ANOVA) model with treatment, centre and treatment-by-centre interaction terms included in the model. The percentage change from baseline over time in BMD and FFM were also to be analysed within and across treatment groups using a repeated measures ANOVA model. The within-group model was to include a term for centre, while the across-group model was to include terms for treatment, centre and treatment-by-centre interactions. The secondary endpoint was lipid levels (total cholesterol, high density lipids, low density lipids, very low density lipids and triglycerides); these data were to be analysed using a repeated measures analysis of covariance model with treatment, centre, the treatment-by-centre interactions, and the baseline lipid levels as terms in the model.

Safety: Safety was assessed by the recording of adverse events, routine laboratory tests and physical examinations. Safety results presented here were tabulated and summarised without formal statistical analysis.

RESULTS (at the data cut-off date [1 June 1999]):
Disposition of patients: The recruitment of patients had finished at the data cut-off date; with a total of 103 patients having been entered into the trial. Of these, 19 had been withdrawn from the trial: 5 due to non-serious adverse events, 4 refused to continue or failed to return, 8 due to protocol non-compliance, 1 withdrew his consent, and 1 due to "other" reason. Therefore, 84 patients were continuing in the trial at the data cut-off date.
Efficacy: The trial was ongoing and the results had not been analysed. No efficacy data are presented at this time.
Safety: The number of patients reporting adverse events while receiving trial treatment was 61 (59.2%). To date, there had been no deaths during the trial. Five patients (4.9%) were withdrawn due to non-serious adverse events, and 8 patients (7.8%) had serious adverse events, none of which led to withdrawal of trial treatment. Fifty-six patients (54.4%) experienced adverse events that were considered by the investigator to be related to trial treatment (either CASODEX 150 mg/day or ZOLADEX 10.8-mg). The most common adverse events related to trial treatment were vasodilation (30 patients [29.1%]), breast pain (26 patients [25.2%]) and gynaecomastia (22 patients [21.4%]).
Clinically significant, non-serious changes in laboratory parameters were observed for 5 patients. Of these, 2 were withdrawn (these patients are included in the number of withdrawals described above). There were no other clinically significant changes that were recorded as serious adverse events, or that resulted in death or withdrawal for any of the clinical laboratory assessments performed, up to and including the data cut-off date (1 June 1999).
Overall, trial treatment (either CASODEX 150 mg/day or ZOLADEX 10.8-mg) was well tolerated, with no new or clinically significant adverse events being reported.