SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT: CASODEX™

ACTIVE INGREDIENT: Bicalutamide

Trial title (number): A Treatment Protocol to Monitor the Safety of a 200-mg Daily Dose of CASODEX™ in Patients with Advanced Prostate Cancer (7054IL/0014).

Clinical phase: II

First patient recruited: 14 December 1994
Data cut-off date: 1 June 1999
Zeneca approval date: 6 October 1999

Publications: Scher HI, Liebertz C, Kelly WK, Mazumdar M, Brett C, Schwartz L et al. Bicalutamide for advanced prostate cancer: The Natural Versus Treated History of Disease. Journal of Clinical Oncology 1997;15(8):2928-2938.

OBJECTIVES

To monitor the safety of a 200-mg daily dose of CASODEX in patients with advanced prostate cancer.

METHODS

Design: This was an open, single-centre, non-randomised trial in patients with histologically- or cytologically-confirmed advanced prostate cancer. All patients were to receive CASODEX 200 mg/day for as long as both the investigator and patient considered that it was in the patient's best interest.

Population: Approximately 120 patients were to be recruited into this trial.

Key inclusion criteria: Male, aged >18 years; histologically- or cytologically-confirmed advanced prostate cancer.

Key exclusion criteria: An Eastern Co-operative Oncology Group performance status of 4; previous history or presence of another malignancy other than prostate cancer or treated squamous or basal cell carcinoma of the skin within the previous 5 years; previous participation in any other CASODEX trial other than in Trial 176334/0005.
Dosage: CASODEX 200 mg/day, composed of 4 x 50-mg CASODEX tablets. Formulation and batch numbers were CASODEX, film-coated, round, green tablets, F6625 (batch numbers ADM 59482/93; ADM 59481/93); and CASODEX, film-coated, round, white tablets F11168 (batch numbers ADM 59339/93); F11284 (batch number A70448).
Key assessments:
Safety: The primary endpoint was safety, which was assessed by the recording of adverse events, subjective symptomology, routine laboratory tests and physical examinations.
Safety results presented here were tabulated and summarised without formal statistical analysis.

RESULTS (at data cut-off date [1 June 1999]):
Disposition of patients: The number of patients quoted by Scher (1997) was 105. However, only 101 of these patients had received investigational CASODEX as part of the trial protocol. The other 4 patients were treated at the investigator's descretion and therefore, were outside the jurisdiction of Zeneca's IND. Safety data for these 4 patients was not collected by Zeneca.
The recruitment of patients had finished at the data cut-off date; with a total of 101 patients having entered the trial. Of these, 88 patients had been withdrawn from the trial: 6 due to adverse events, 1 died due to an adverse event, and 81 due to disease progression. Therefore, 13 patients were continuing in the trial at data cut-off date.
Safety: This was an investigator-initiated trial conducted under a Zeneca investigational new drug (IND) application. The principal investigator had conducted an interim analysis and published the results (Scher et al 1997). However, only safety data collected by Zeneca from this trial are presented here for the assessment of the safety of CASODEX.
The number of patients reporting adverse events whilst receiving trial treatment was 89 (88.1%). One patient (1%) died due to a serious adverse event, 6 patients (5.9%) were withdrawn due to adverse events, 1 of which was serious, and 15 patients (14.9%) had serious adverse events not leading to withdrawal.
One patient (1%) had non-serious adverse events of bilirubinaemia and elevated AST/SGOT levels and was subsequently withdrawn (this patient is included in the number of withdrawals described above). There were no other clinically significant changes recorded as serious adverse events, deaths or withdrawals for any of the clinical laboratory parameters assessed during the trial.
The majority of adverse events reported in the patients in this trial are those to be expected for the general population in this age group. Adverse events that were associated with trial treatment, were those that are expected as a result of the pharmacological effects of this class of anti-androgen. Thus, gynaecomastia and/or breast pain were the commonest of such adverse events. No new safety concerns were raised in this trial.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

(1) Abbreviations

Abbreviation	Term
AST/SGPT	aspartate aminotransferase
GI	gastrointestinal
IND	investigational new drug
mg	milligrams

(2) Definitions

(i) Adverse events

Adverse events were recorded on specifically designed case report forms and were submitted to Zeneca Pharmaceuticals as directed by the protocol. Certain adverse experiences were to be reported within 24 hours of obtaining first knowledge of the event. These included: all fatal experiences; all life-threatening experiences associated with the use of the drug; any other adverse experience that was both serious and unexpected and associated with the use of the drug.

The definitions of serious adverse experiences, unexpected adverse experiences, and experiences associated with the use of the drug are described below:

- a serious adverse experience was any experience that was fatal or life-threatening, was permanently disabling, required in-patient hospitalisation, or was a congenital anomaly, cancer, or overdose
- an unexpected adverse experience included any adverse experience that was not identified in nature, severity, or frequency in the investigator brochure (available at the time that the protocol was written and finalised)
- an adverse experience that was associated with the use of the drug, was any experience where there was a reasonable possibility that the experience could have been caused by the drug

At the time of writing and finalising the protocol (15 October 1994), the definitions as described above were in use as part of normal standard operating procedures. However, the standard definitions of adverse events and serious adverse events have been updated since the initiation of the trial. Consequently, the above definitions were superseded by those presented below and came into operation for this trial on 1 April 1998.

(ii) Adverse events

An adverse event was defined as the development of a new medical condition or the deterioration of a pre-existing medical condition, following or during exposure to a medicine. A "medical condition" could be symptoms (such as nausea or chest pains), signs (such as a rash or enlarged liver), or abnormal results on investigation (including blood tests, X-rays or scans of various types). Where there was deterioration in the condition for which the medicine is being used, there may have been uncertainty as to whether this was normal disease progression (resulting from a lack of efficacy) or an adverse event. In these circumstances, if the investigator felt the medicine did not contribute to the deterioration, then this was considered as a lack of efficacy. However, if the investigator felt that the medicine may have contributed to the deterioration, then it was treated as an adverse event.

Adverse events were recorded on specifically designed case report forms. A description of the event was recorded together with its severity and duration, any action taken, its outcome, and the investigator's assessment of the relationship of the event to trial treatment. If a diagnosis of the patient's condition had been made, then the diagnosis was to be recorded as the adverse event in instances of well recognised syndromes (eg, fever, runny nose, cough could be recorded as "flu"). However, if a diagnosis of the patient's condition had not been made, or if the individual symptoms were not well recognised, then the individual symptoms were to be recorded separately.

(iii) Serious adverse events

A serious adverse event was defined as an adverse event that was fatal; was life-threatening; resulted in or prolonged hospitalisation; resulted in disability or incapacity; required medical or surgical intervention to prevent permanent impairment or damage; was a congenital abnormality.