SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: CASODEX™

ACTIVE INGREDIENT: Bicalutamide

Trial title (number): A Randomized Double-Blind Comparative Trial of Bicalutamide (CASODEX™) Versus Placebo in Patients with Early Prostate Cancer (7054IL/0023)

Clinical phase: IIIb

First patient recruited: 01 August 1995
Last patient recruited: 29 August 1997
Data cut-off: 2 June 2000
AstraZeneca approval date: 24 January 2001

Publications: Wirth MP, Iversen P. A clinical program consisting of 3 randomized, double blind, parallel-group trials comparing bicalutamide (Casodex) 150 mg once daily with placebo in patients with non-metastatic prostate cancer: preliminary demography data from one of the largest international early prostate cancer programs. Eur Urol 1998;33:136 (Abstract 541). Wirth MP, Iversen P, McLeod DG, et al. Bicalutamide (Casodex) Early Prostate Cancer (EPC) program: final demographic data from over 8000 randomized patients. Eur Urol 1999;35:13 (Abstract 52).

OBJECTIVES

Primary objectives: To compare 2 years of adjuvant CASODEX (bicalutamide) 150-mg monotherapy with placebo in terms of time to objective progression and overall survival.

Secondary objectives: To compare 2 years of adjuvant CASODEX 150 mg with placebo in terms of time to treatment failure; to investigate the association of serial measurement of serum prostate specific antigen (PSA) and treatment outcome following 2 years of adjuvant CASODEX therapy versus placebo; to evaluate the tolerability of 2 years of CASODEX 150 mg therapy versus placebo.

METHODS

Design: This trial was of a multicenter, randomized, double-blind, parallel-group design, and compared CASODEX 150 mg once daily with placebo in patients with localized or locally advanced prostate cancer. The trial was 1 of 3 comparative Phase IIIb trials of the EPC clinical program. The trials were designed and powered on the basis of a planned, pooled analysis. Eligible patients were randomized 1:1 to CASODEX 150 mg or placebo. Following randomization, patients were assessed at 12-week intervals up to and including Month 24. For the period through month 48, patients were assessed at 12 week intervals for survival in which visits were made at 24 week intervals alternating with telephone contacts. For those patients post-month 48, phone contacts continued at 12 week intervals with visits done once annually. A minimum of 3000 patients were to be randomized at North American centers. This document is an interim report of the results from this trial, which is still ongoing.

Population: A total of 3292 male patients were randomized into the trial from 105 centers throughout North America. As of the data cut-off date (2 June 2000), patients have been followed for a median of 3.2 years.

Key inclusion criteria: Aged 18 years or older; diagnosed with non distant metastatic adenocarcinoma of the prostate gland (Stages T1b-pT4, N0-NX, M0 [N+ not allowed]) within 30 weeks of randomization. Patients were to have undergone therapy of curative intent [radiation or radical prostatectomy] within 16 weeks prior to randomization; absence of metastatic disease was to be confirmed within 30 weeks prior to randomization.

Key exclusion criteria: Any previous systemic therapy for prostate cancer (other than neo-adjuvant therapy prior to primary therapy of curative intent, or therapy with 5-alpha reductase inhibitors); previous history or presence of other malignancy, other than prostate cancer or treated squamous/basal cell carcinoma of the skin, within the last 5 years; serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) concentrations >2.5 times the upper limit of normal; any severe concomitant medical condition that would have made it undesirable, in the investigator's opinion, for the patient to participate in the trial or would have jeopardized compliance with the trial protocol.

Dosage: Patients received either oral CASODEX 150 mg/day or matching placebo. CASODEX was supplied as a white, intagliated tablet containing 150 mg of micronized drug (formulation

number F11156[1]). Placebo was supplied as a matching white tablet (formulation number F11192[2]).

Key assessments:

Efficacy: The primary efficacy measures were: time to objectively confirmed disease progression (the number of days between randomization and the earliest documented date of progression or death) and time to death (the number of days between randomization and the documented date of death). The secondary efficacy measures were: time to treatment failure (the number of days between randomization and the documented date of treatment failure; includes earliest occurrence of withdrawal of trial therapy, addition of systemic therapy for prostate cancer, objectively confirmed progression and death) and time to doubling of PSA concentration (relative to the pre-randomization value).

Statistical assessments: All patients were included in the analysis of efficacy and were analyzed as randomized on an intention-to-treat (ITT) basis. Time to progression, time to treatment failure, and PSA doubling and progression free survival were analyzed using a Cox proportional hazards regression model with randomized treatment, baseline PSA concentration, stage of prostate cancer, prior treatment for prostate cancer, and Gleason grade as covariates. From the model a hazard ratio (CASODEX:placebo) was estimated together with its associated 95% confidence interval and the data were displayed graphically using a Kaplan-Meier plot. Time to death data were summarized using a Kaplan-Meier plot. No formal statistical analyses of time to death data were performed as data were expected to be too immature.

Safety: The data presented in this report are based on a data cut-off date of 2 June 2000. An addendum to this report contains all safety data integrated up to the date of 23 February 2001. Safety was assessed by the recording of adverse events, and by the measurement of liver function parameters and physical examinations. Adverse events were summarized by Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART), preferred term and primary body system. Liver function tests were presented individually for each patient with values outside the normal reference range being highlighted. These data were also summarized for each visit. Patients with pre-defined clinically relevant changes in liver function were also identified.

RESULTS

Demography: The majority of patients were white in both treatment arms (83.1% CASODEX, 84.6% placebo) with a mean age of 64.5 years (CASODEX) and 64.4 years (placebo). The treatment groups were well-balanced in terms of patient demographics and disease characteristics at entry into the trial.

Efficacy:

The numbers of patients with events and the results of each of the efficacy analyses are shown in Tables I and II, respectively.

[1] Batch numbers ADM49288/92, ADM59338/93, ADM27178/95, ADM35393F96, ADM36384K96, H96/2146, ADM35741K97, H97/2184.

[2] Batch numbers ADM59396/93, ADM28100/95, ADM35402G96, ADM34561/94, ADM35828E96, ADM35807E96, ADM37118H96, ADM37120F96, ADM38940F96.

Table I Numbers of events

Analysis	Number (%) of patients with event			
	CASODEX 150 mg (N=1647)		Placebo (N=1645)	
Time to objective progression	83	(5.0)	87	(5.3)
Time to treatment failure	638	(38.7)	347	(21.1)
Time to PSA doubling-free progression	270	(16.4)	394	(24.0)

N Number of randomized patients.

Table II Analysis results

Analysis	Estimate of hazard ratio[a] (CASODEX:placebo)	2-sided 95% CI	p-value
Time to objective progression	0.933	0.691 to 1.261	0.653
Time to treatment failure	2.083	1.827 to 2.374	<<0.0001
Time to PSA doubling-free progression	0.619	0.530 to 0.722	<<0.0001

[a] Hazard ratio (HR) <1 = difference in favor of CASODEX; hazard ratio >1 = difference in favor of placebo.
CI Confidence interval.

There was no significant difference between the two treatment arms in terms of time to objective progression (HR: 0.933; 95% CI, 0.691 to 1.261; p-value 0.653). Of the 170 progression events in the analysis, only 63 were actually objective disease progression, the remainder being deaths in the absence of progression. Therefore, the observed result is probably reflective of the relative immaturity of this trial for this endpoint. CASODEX significantly reduced the risk of PSA doubling compared to placebo (HR: 0.619, 95% 0.530 to 0.722; p-value <<0.0001). A statistically significant difference was seen in favor of placebo for time to treatment failure (HR: 2.083, 95% 1.827to 2.374; p-value <<0.0001) which reflected the difference in withdrawals rates between the two arms. Survival data were considered immature with less than 0.5% prostate mortality.

Safety:

The data presented in this report are based on a data cut-off date of 2 June 2000. An addendum to this report contains all safety data integrated up to the date of 23 February 2001.

The proportion of patients with adverse events leading to death was low in both the CASODEX 150 mg and placebo treatment groups (1.0% [17/1627 patients] and 1.4% [22/1627 patients], respectively) with the majority of these deaths being the result of cardiovascular events. A greater number of patients in the CASODEX 150 mg group were withdrawn from treatment as a result of an adverse event (31.0% [505/1627 patients] compared with 9.0% [147/1627 patients] of placebo-treated patients). The most commonly reported adverse events were gynecomastia and male breast pain, both predictable pharmacological effects of antiandrogens. The

withdrawal rate of CASODEX-treated patients as a result of these events (11.7% [190/1627 patients] and 17.5% [285/1627 patients], respectively) reflected their high incidence in the trial (72.6% [1182/1627 patients] and 85.4% [1390/1627 patients], respectively, compared with incidences of 10.1% [164/1627 patients] and 10.6% [173/1627 patients] in the placebo group). The proportion of patients with serious adverse events was more balanced between treatment groups with a slightly higher incidence reported in placebo-treated patients (18.5% [301/1627 patients]) than CASODEX-treated patients (17.0% [277/1627 patients]). The majority of the serious adverse events were not considered to be related to trial therapy and reflected the age and disease status of the patient population, or resulted from hospitalization and/or medical intervention for concomitant conditions.

Higher rates of withdrawal due to asthenia, vasodilatation, weight gain, libido decreased, depression, headache, and emotional lability were seen in the CASODEX treatment group (1.9% [31/1627 patients], 1.0% [17/1627 patients], 0.9% [14/1627 patients], 0.9% [14/1627 patients], 0.5% [8/1627 patients], 0.3% [5/1627 patients], and 0.3% [5/1627 patients], respectively) than in the placebo group (0.4% [7/1627 patients], 0.3% [5/1627patients], 0.1% [2/1627 patients], 0.5% [8/1627 patients], 0.2% [4/1627 patients], 0.1% [1/1627 patients], and 0% [0/1627 patients], respectively). The majority of these adverse events on the CASODEX arm were considered by the investigator to be related to study drug.

The incidence of liver function test abnormalities, as assessed by the number of adverse event reports and clinically relevant changes in liver function tests, was relatively low (4.2% [68/1627 patients] in CASODEX-treated patients; 3.7% [60/1627 patients] in placebo-treated patients) and appears consistent with that observed in other studies.