SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: CASODEX

ACTIVE INGREDIENT: Bicalutamide

Trial title (number): A Randomised, Double-blind, Parallel-group Trial Comparing CASODEX™ 150 mg Once Daily with Placebo in Patients with Non-metastatic Prostate Cancer (SPCG-6) (7054IL/0025).

Clinical phase: IIIb

First patient recruited: 4 October 1995

Last patient recruited: 30 July 1998

Data cut-off date: 2 June 2000

AstraZeneca approval date: 1 February 2001

Publications: Wirth MP, Iversen P. A clinical programme consisting of 3 randomised, double blind, parallel-group trials comparing bicalutamide (Casodex) 150 mg once daily with placebo in patients with non-metastatic prostate cancer: preliminary demographic data from one of the largest international early prostate cancer trials. Eur Urol 1998;33:136 (Abstract 541).

Wirth MP, See WA, McLeod DG, Iversen P, Klimberg I, Gleason D, et al. Bicalutamide (Casodex) Early Prostate Cancer (EPC) programme: final demographic data from over 8000 randomised patients. Eur Urol 1999;35:13 (Abstract 52).

OBJECTIVES

Primary objectives: To compare CASODEX (bicalutamide) 150 mg once daily with placebo in terms of time to objective progression and overall survival in patients with non-metastatic (localised or locally advanced) prostate cancer; and to evaluate the tolerability of CASODEX 150 mg compared with placebo.

Secondary objectives: To compare CASODEX 150 mg once daily with placebo in terms of time to treatment failure and time to doubling of prostate specific antigen (PSA) concentration; and to assess sexual function using the Golombok Rust Inventory of Sexual Satisfaction (GRISS) questionnaire.

METHODS

Design: This trial was of a multicentre, randomised, double-blind, parallel-group design, and compared CASODEX 150 mg once daily with placebo in patients with localised or locally advanced prostate cancer. The trial was 1 of 3 comparative Phase IIIb trials central to the EPC clinical programme. The trials were designed and powered on the basis of a planned, pooled analysis. Eligible patients were randomised 1:1 to CASODEX 150 mg or placebo. Following randomisation, patients were assessed at 12-week intervals until clinical progression and, thereafter, every 12 weeks if the patient continued on randomised therapy or every 24 weeks if randomised therapy was discontinued. All patients were followed up for objective progression and survival. This report presents the first planned analysis of the trial, which is still ongoing.

Population: A total of 1218 male patients were randomised into the trial from 62 centres throughout Scandinavia. At the data cut-off date (2 June 2000) 139 patients had died, 278 had objective disease progression (including 92 who had died in the absence of objectively-confirmed progression), and 735 were continuing on randomised trial therapy.

Key inclusion criteria: Aged between 18 and 75 years; diagnosed with non-distant metastatic adenocarcinoma of the prostate gland (Stages T1b to T4, any N, M0).

Key exclusion criteria: Any previous systemic therapy for prostate cancer (other than neoadjuvant therapy prior to primary therapy of curative intent, or therapy with 5-alpha-reductase inhibitors); patients for whom long-term therapy was considered inappropriate because of their expected survival time; previous history or presence of other malignancy within the last 10 years, other than prostate cancer or treated squamous/basal cell carcinoma of the skin; serum bilirubin, aspartate aminotransferase (AST), or alanine aminotransferase (ALT) concentrations >2.5 times the upper limit of normal; treatment with any new chemical entity within the previous 3 months.

Dosage: Patients received either oral CASODEX 150 mg/day or matched placebo. CASODEX was supplied as white tablets containing 150 mg of micronised drug (formulation number F11156[1]). Placebo was supplied as matching white tablets (formulation number F11192[2]).

Key assessments:

Efficacy: The primary efficacy measures were time to objectively-confirmed progression of disease (ie, the number of days between randomisation and the earliest documented date of progression or death [from any cause]) and time to death (the number of days between randomisation and the documented date of death). The secondary efficacy measures were time

1. Batch numbers: 27088/95, 27120/95, 35396K96, 35396H96, 35394C96, 36383C96, 38159D96, 39829G96, 37074K97, 38474F97, 38825C97, 00041J98, 00040B98, 01413K98, 01390D98, 02911G98, 03568A98, 61516D99, 63295I99, 64446I99.

2. Batch numbers 34562/94, 34563/94, 59397/93, 35403D96, 35398B96, 35904I96, 35905F96, 37119E96, 37053A96, 37120F96, 36898B97, 38941C96, 36896H97, 36895K97, 36897E97, 38277G97, 38280B97, 38279A97, 38278D97, 04699G98, 04700J98, 34588/94.

to treatment failure (the number of days between randomisation and the documented date of treatment failure) and time to doubling of PSA concentration (relative to the pre-randomisation value). Treatment failure was defined as the earliest occurrence of withdrawal of therapy, addition of another systemic therapy for prostate cancer, objectively-confirmed disease progression, or death. PSA doubling was defined as the earliest occurrence of PSA doubling, disease progression, or death.

Statistical assessments: All patients were included in the analysis of efficacy and were analysed as randomised on an intention-to-treat (ITT) basis. Time to objective progression, time to treatment failure, and PSA doubling-free progression were analysed using a Cox proportional hazards regression model with randomised treatment, logarithm of 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 summarised using a Kaplan-Meier plot; no formal statistical analyses were performed as these data were immature. However, the data were compared in a combined analysis of survival data from all 3 trials in the EPC clinical programme.

Safety and tolerability: Safety was assessed by the recording of adverse events and by the measurement of liver function parameters. Adverse events were presented both individually for each patient and were summarised by COSTART-preferred term and primary body system (ie, Coding Symbols for Thesaurus of Adverse Reaction Terms). Liver function test results were presented individually for each patient and any values outside the normal reference range were highlighted. These data were also summarised for each visit. Patients with pre-defined clinically relevant changes in liver function were also identified. Tolerability, in terms of sexual function, was assessed using the GRISS questionnaire.

RESULTS

Demography: Demographic data at entry were well balanced across the treatment groups. The majority (>99%) of patients were Caucasian with an overall mean age of 68.5 years.

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

Table I Numbers of events

Analysis	Number (%) of patients with event			
	CASODEX 150 mg (N=607)		Placebo (N=611)	
Objective progression[a]	99	(16.3)	179	(29.3)
Death[b]	69	(11.4)	70	(11.5)
Treatment failure	196	(32.3)	293	(48.0)
PSA doubling-free progression	131	(21.6)	335	(54.8)

[a]Includes patients with objectively-confirmed disease progression and patients who had died in the absence of an objectively-confirmed progression.

[b]Values represent total number of deaths, not just those patients who died as a result of prostate cancer.

N Number of patients randomised.

PSA Prostate specific antigen.

Table II Analysis results

Analysis[a]	Estimate of hazard ratio (CASODEX:placebo)	2-sided 95% CI	p-value
Objective progression	0.430	0.336 to 0.552	<<0.0001
Treatment failure	0.565	0.471 to 0.679	<<0.0001
PSA doubling-free progression	0.243	0.197 to 0.299	<<0.0001

[a]No analysis was performed on survival data as the data were considered to be immature.
CI confidence interval.
PSA Prostate specific antigen.

The analysis results showed that CASODEX 150 mg significantly reduced the risk of objective disease progression by 57% compared with placebo (p <<0.0001). These results were supported by an analysis of PSA data, which demonstrated that CASODEX 150 mg significantly reduced the risk of PSA doubling compared with placebo. CASODEX also significantly reduced the risk of treatment failure by 43% compared with placebo (p<<0.0001). Overall, 11.4% (139/1218) of patients in the trial had died by the time of data cut-off (69 randomised to CASODEX and 70 to placebo), 4.3% (52/1218) as a result of prostate cancer (24 randomised to CASODEX and 28 to placebo). The immaturity of these data prevented a meaningful formal statistical analysis of survival.

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 similar in both the CASODEX 150 mg and placebo groups (6.0% [36/605 patients] and 4.3% [26/609 patients], respectively), with the majority of deaths being the result of cardiovascular events. A larger proportion of patients randomised to CASODEX 150 mg compared with placebo withdrew from trial therapy as a result of adverse events (15.9% [96/605 patients] and 6.9% [42/609 patients], respectively). The most commonly reported adverse events leading to the withdrawal from treatment with CASODEX 150 mg were gynaecomastia (2.6% [16/605 patients]) and male breast pain (2.8% [17/605 patients]). These events are predictable pharmacological effects of CASODEX and the withdrawal rate reflects the relatively high incidence of these events observed in the trial: 53.9% (326/605 patients) and 61.3% (371/605 patients), respectively, compared with incidences of 2.6% (16/609 patients) and 3.8% (23/609 patients) in the placebo group. The proportion of patients with serious adverse events was similar in each of the treatment groups (44.1% [267/605 patients] in the CASODEX 150 mg group and 39.6% [241/609 patients] in the placebo group). The majority of these serious adverse events were not considered to be related to trial therapy and reflected the age and disease status of the patient population or that hospitalisation and/or medical intervention was required for concomitant conditions. Other non-serious adverse events were widely distributed across body systems with many events being those commonly experienced by elderly male patients with malignant disease.

The incidence of clinically relevant changes in total bilirubin, ALT, or AST was relatively low with 26/605 (4.3%) patients who received CASODEX 150 mg and 7/609 (1.1%) patients who received placebo reporting clinically relevant changes in 1 or more of these laboratory parameters.

Tolerability: After a year of treatment, sexual function in relation to frequency of intercourse and sexual potency was maintained (relative to baseline) in 40% and 36% of CASODEX-treated patients, respectively, compared with 54% of placebo-treated patients.
