SUMMARY

ASTRAZENECA

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 (7054IL/0024).

Clinical phase: IIIb

First patient recruited: 21 September 1995
Last patient recruited: 27 July 1998
Data cut-off date: 2 June 2000
AstraZeneca approval date: 25 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, 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 in patients with non-metastatic (localised or locally advanced) prostate cancer. 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 overall survival and time to treatment failure; to investigate the role of serum prostate-specific antigen (PSA) as a predictor of outcome.

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 to enable a combined analysis to be performed. Eligible patients were randomised 1:1 to CASODEX 150 mg or placebo. Following randomisation, patients were assessed at 12-week intervals until clinical progression (objective or subjective) 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 death. This report presents the first planned analysis of this trial which is still ongoing.

Population: A total of 3603 male patients were recruited into the trial from 191 centres throughout Europe, Israel, Mexico, South Africa, and Australia. At the data cut-off date (2 June 2000) 260 patients had died, 474 patients had objective progression (including 188 patients who had died in the absence of objectively-confirmed progression), and 2197 patients were continuing with randomised trial therapy.

Key inclusion criteria: Aged 18 years and above; 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); previous history or presence of other malignancy within the last 5 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 matching 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 measure was time to objectively-confirmed progression of disease (the number of days between randomisation and the earliest documented date of objective progression or death [from any cause]). The secondary efficacy measures were: the time to death (the number of days between randomisation and documented date of death), time

1. Batch numbers 00040B98, 00041J98, 01390D98, 01413K98, 02911G98, 03568A98, 27088/95, 27120/95, 35394C96, 35395K96, 35396H96, 3638C96, 37074K97, 38159D96, 38474F97, 38825C97, 39829G96, 61516D99, 63295I99, 64446I99.

2. Batch numbers 04699G98, 04700J98, 34558/94, 34562/94, 34563/94, 35398B96, 35403D96, 35904I96, 35905F96, 36895K97, 36896H97, 36897E97, 36898B97, 37053A96, 37119E96, 37120F96, 37121C96, 38277G97, 38278D97, 38279A97, 38280B97, 38941C96, 59397/93.

to treatment failure (the number of days between randomisation and the documented date of treatment failure), and the time to doubling of prostate specific antigen (PSA) concentration (relative to the pre-randomisation value). Treatment failure was defined as the earliest occurrence of withdrawal of trial therapy, addition of 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 displayed graphically using a Kaplan-Meier plot. Time to death data were summarised using a Kaplan-Meier plot. No formal statistical analyses of time to death data were performed as the data were too immature. However, the data were compared in a combined analysis of survival data from all 3 trials in the EPC clinical programme.

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. Adverse events were presented both individually for each patient and were summarised by Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) preferred term and primary body system. Liver function test results were presented individually for each patient and any value outside the normal reference range was highlighted. These data were also summarised for each visit.

RESULTS

Demography: The majority of patients (3423/3603: 95.0%) were Caucasian with a mean age of 68.7 years. In each treatment group the majority of patients were aged between 65 and 74 years. The treatment group were well balanced in terms of patient demographics and disease characteristics at entry into the trial.

Efficacy: The number 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 = 1798)		Placebo (N = 1805)	
Objective progression[a]	181	(10.1)	293	(16.2)
Death[b]	123	(6.8)	137	(7.6)
Treatment failure	735	(40.9)	690	(38.2)
PSA doubling-free progression	272	(15.1)	600	(33.2)

[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	Estimate of hazard ratio (CASODEX:placebo)	2-sided 95% CI	p value
Objective progression	0.574	0.477 to 0.692	<<0.0001
Treatment failure	1.095	0.986 to 1.215	0.089
PSA doubling-free progression	0.369	0.320 to 0.426	<<0.0001

CI Confidence interval.
PSA Prostate specific antigen.
No analysis was performed on the survival data because the data were considered too immature.

The analysis results showed that CASODEX 150 mg significantly reduced the risk of objective disease progression by 43% 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. No statistically significant difference was seen in the analysis of the proportion of patients with treatment failure. Overall, 7.2% (260/3603) of patients in the trial had died at the time of the data cut-off, (2 June 2000) with 1.8% (64/3603) of patients having died as a result of prostate cancer. 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 treatment groups (3.7% [67/1790 patients] and 3.1% [56/1795 patients], respectively), the majority of these 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 (24.4% [437/1790 patients] and 7.6% [136/1795 patients], respectively). The most commonly reported adverse events leading to the withdrawal from treatment with CASODEX 150 mg were gynaecomastia (10.7% [191/1790 patients]) and male breast pain (10.5% [188/1790 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 (64.9% [1161/1790 patients] and 65.1%

[1165/1790 patients], respectively, compared with incidences of 7.4% [132/1795 patients] and 5.2% [93/1795] patients in the placebo group). The proportion of patients with serious adverse events was similar in each of the treatment groups (33.2% [595/1790 patients] in the CASODEX 150 mg group and 32.6% [586/1795 patients] in the placebo group). Only the pharmacologically expected adverse event of gynaecomastia was reported as being serious with a relative incidence of more than 1% in the CASODEX group (1.7% [30/1790 patients]) compared with the placebo group (0/1795 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 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 49/1790 (2.7%) patients who received CASODEX 150 mg and 18/1795 (1.0%) patients who received placebo reporting clinically relevant changes in 1 or more of these laboratory parameters. These results are consistent with those observed in other studies.