# SUMMARY

**ASTRAZENECA PHARMACEUTICALS**

**FINISHED PRODUCT:** CASODEX™

**ACTIVE INGREDIENT:** Bicalutamide (ICI 176,334)

**Trial title (number):** A multicentre, randomised, comparative trial to assess the tolerance (maximum well-tolerated dose), efficacy and pharmacokinetics of escalating doses of CASODEX (300 mg po daily, increasing by 150 mg intervals) versus castration (medical or surgical) in the treatment of advanced carcinoma of the prostate (7054IL/0009).

**Clinical phase:** IIIb

**First patient recruited:** 8 November 1994
**Last patient recruited:** 11 September 1996
**AstraZeneca approval date:** 28 February 2003

**Publications:** There were no publications relating to this trial at the time this report was written

## OBJECTIVES

The objectives of this trial were:

- to monitor tolerance (maximum well-tolerated dose, MWTD), efficacy, and pharmacokinetics of the enantiomers of CASODEX, starting at an oral (po) dose of 300 mg daily, and increasing by 150 mg intervals, as treatment for locally advanced (M0) or metastatic (M1) prostate carcinoma
- to compare escalating doses of CASODEX (300 mg po daily, increasing by 150 mg intervals) with castration (either medical or surgical) for tolerance, and the selected dose for efficacy, in the treatment of M0 or M1 prostate carcinoma
- to assess long-term safety data in patients receiving higher doses of CASODEX

**METHODS**

**Design:** A multicentre, randomised trial to assess tolerance (MWTD), efficacy, and pharmacokinetics of escalating doses of CASODEX (300 mg po daily, increasing by 150 mg intervals up to a possible maximum of 900 mg). If the MWTD was determined, patients were to be randomised to the MWTD of CASODEX or castration (medical or surgical) to compare the efficacy of these therapies in the treatment of locally advanced or metastatic prostate carcinoma.

**Population:** A total of 248 patients with locally advanced or metastatic prostate carcinoma were recruited from 26 centres in 9 European countries.

**Key inclusion criteria:** Histologically or cytologically confirmed locally advanced or metastatic (T3 or T4) prostate carcinoma; life expectancy >3 months; prostate-specific antigen (PSA) level of ≥5 times the upper limit of the normal reference range (20.0 mg/l); evaluable disease.

**Key exclusion criteria:** Previous or concurrent systemic therapy for prostate cancer including orchidectomy, antiandrogen therapy, oestrogen therapy, luteinising-hormone-releasing hormone (LHRH) analogue therapy, ketoconazole, or cytotoxic therapy; radiotherapy to the prostate within the 3 months before entry to the trial; invasive malignancy other than prostate cancer or squamous/basal cell carcinoma of the skin within the previous 5 years; Eastern Co-operative Oncology Group (ECOG) performance score of 3 or 4; bilirubin, aspartate aminotransferase, alanine aminotransferase, creatinine, or urea value ≥1.26 times the upper limit of centre reference range; concurrent anticoagulant therapy with warfarin; at risk of transmitting, through blood or other body fluids, the agents responsible for acquired immune deficiency syndrome, other sexually transmitted diseases, or hepatitis; myocardial infarction, coronary artery bypass graft, or angioplasty within the previous 3 months; unstable angina; decompensated heart failure; history of clinically significant dysrhythmias.

**Dosage:** Patients were to receive either CASODEX 300 mg daily (given as 150 mg tablets formulation number: F11156) in a non-random setting, or be randomly allocated to an escalating dose of CASODEX (300 mg daily, increasing by 150 mg intervals) or castration (medical [ZOLADEX™ 3.6 mg depot injection formulation number: F5589] or surgical [bilateral orchidectomy]). Batch numbers for the treatments are given at the end of the summary. Doses of CASODEX were assessed sequentially and dose escalation in individual patients was not permitted. Duration of CASODEX treatment was unrestricted, and patients continued to receive medication until they were no longer benefiting from treatment.

**Efficacy assessments:** The primary endpoint was the change in serum PSA after 12 weeks of treatment. The secondary endpoint was the objective response of disease to treatment.

**Pharmacokinetic assessments:** The primary endpoints were the steady-state plasma concentration ($C_{ss}$) and plasma elimination half-life ($t_{½}$) of (R)-bicalutamide.

**Safety assessments:** The primary safety endpoints were adverse events, haematological variables, biochemical variables (except PSA), pulse rate, blood pressure, and electrocardiogram (ECG) measurements.

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**RESULTS**

**Demography:** A total of 248 patients were randomised, 21 to CASODEX 300 mg, 94 to CASODEX 450 mg, 43 to CASODEX 600 mg, and 90 to castration (8 surgical and 82 medical).

Of these patients, 139 had M0 prostate cancer and 109 had M1 prostate cancer. One patient randomised to CASODEX 600 mg received medical castration in error and 1 patient randomised to castration received CASODEX 450 mg in error. In addition, 3 patients randomised to CASODEX 450 mg did not receive any trial treatment. Thus, the number of patients receiving trial treatment was 21, 92, 42, and 90 for CASODEX 300 mg, 450 mg, 600 mg, and castration, respectively.

The age of patients ranged from 46 years to 89 years with a mean age range of 69.5 to 72.1 years across all groups. The majority (241/248 [97.2%]) of patients were White.

**Efficacy:** Pharmacokinetic (PK) assessments showed that 300 mg, 450 mg, and 600 mg dose of CASODEX all gave similar plasma steady-state concentrations ($C_{ss}$) indicating that systemic exposure had reached a plateau. Therefore, the dose of CASODEX was not increased above 600 mg and hence the MWTD was not identified and so no formal statistical analyses on protocolled endpoints have been included in this report. The percentage decrease in geometric mean PSA from pre-trial screen for all patients at 12 weeks was 93% (CASODEX 300 mg), 95% (CASODEX 450 mg), 96% (CASODEX 600 mg), and 95% (castration). A summary of objective response to treatment is given in Table I.

**Table I Summary of best objective response of disease to treatment**

| Best objective response[a] | Number (%) of patients | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | CASODEX | | | | | | Castration | |
| | 300 mg (n=21) | | 450 mg (n=91) | | 600 mg (n=41) | | (n=86) | |
| Partial response | 14 | (66.7) | 52 | (57.1) | 20 | (48.8) | 34 | (39.5) |
| Stable disease | 1 | (4.8) | 4 | (4.4) | 6 | (14.6) | 10 | (11.6) |
| Progression | 4 | (19.0) | 17 | (18.7) | 6 | (14.6) | 16 | (18.6) |
| Not assessable | 2 | (9.5) | 18 | (19.8) | 9 | (22.0) | 26 | (30.2) |

[a] 'Best response' was defined as the best response a patient had across visits.

The nature of this study is such that the response by dose of CASODEX cannot easily be interpreted due to the inclusion of patients at different phases of the trial, and the non-random allocation of patients to the 300 mg dose group. Non-protocolled analyses of time to death showed that there were no statistically significant differences between CASODEX 450 mg and castration or between CASODEX 600 mg and castration in the risk of death.

**Pharmacokinetics:** Pharmacokinetic data suggest that (R)-bicalutamide $C_{ss}$ reached a plateau at an approximate dose of 300 mg; a similar observation was made for the (S)-bicalutamide enantiomer. These findings indicate that escalating the dose of CASODEX above 300 mg daily is unlikely to substantially increase systemic exposure. $C_{ss}$ values at the 300 mg and 600 mg doses appeared to differ with metastatic status, with higher values seen in M0 patients compared with M1 patients. However, the observed difference may have been as a result of low patient numbers. Plasma $t_{½}$ values were similar for all doses of CASODEX.

**Safety:** The majority of patients reported at least 1 adverse event (21/21 [100%] patients who were given CASODEX 300 mg, 90/92 [97.8%] patients who were given CASODEX 450 mg, 40/42 [95.2%] patients who were given CASODEX 600 mg, 81/90 [90.0%] patients treated with castration). For patients who were given CASODEX, the most commonly reported adverse

events were gynaecomastia (88/155 [56.8%] patients) and breast pain (81/155 [52.3%] patients), known pharmacological effects of CASODEX. The most frequently reported adverse event in the castration group, vasodilatation (48/90 53.3%] patients), was also related to the pharmacological effects of the treatment. There was no clinically relevant increase in the incidence of any adverse event with increasing daily dose of CASODEX. Thirty-nine patients died whilst receiving trial therapy, 15 of whom died from prostate cancer. None of these deaths was categorised as probably or definitely related to CASODEX. No major differences were observed in the reason for withdrawals between different groups; individual adverse events, with the exception of events associated with the pharmacological profile of CASODEX (breast pain and gynaecomastia), resulted in the withdrawal of a maximum of 2 people in any treatment group. The most frequently reported serious adverse events were urinary retention and gynaecomastia in patients given CASODEX (reported by 11 and 8 patients, respectively) and pneumonia in patients who underwent castration (5 patients). There were no major concerns regarding clinical laboratory data and electrocardiography. Although a small decrease in mean heart rate was observed at 600 mg, the decrease was too small to be of any clinical significance.