# SUMMARY

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**ASTRAZENECA**

**FINISHED PRODUCT:** CASODEX™

**ACTIVE INGREDIENT:** Bicalutamide

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**Trial title (number):** A randomised, double-blind, parallel-group trial to investigate the efficacy and tolerability of radiotherapy as prophylactic treatment against the development of CASODEX monotherapy induced gynaecomastia and breast pain in prostate cancer patients (7054IL/0038).

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**Clinical phase:** IIIb

**First patient recruited:** 15 November 1999
**Last patient completed:** 27 June 2001
**AstraZeneca approval date:** 5 March 2002

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**Publications:** None at the time of the preparation of this report.

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**OBJECTIVES**

**Primary objective:** To examine the efficacy of radiotherapy in reducing the incidence of CASODEX monotherapy-induced gynaecomastia as assessed by physical examination.

**Secondary objectives:** To examine the efficacy of radiotherapy in reducing the incidence and degree of CASODEX monotherapy-induced male breast pain and gynaecomastia as elicited by direct questioning and the assessment of gynaecomastia by objective measurements.

To examine the tolerability of prophylactic single fraction male breast radiotherapy.

To ensure the safety of all patients receiving CASODEX.

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**METHODS**

**Design:** Randomised, double-blind, parallel-group controlled trial. Patients received either a 10 Gy dose of radiotherapy to the breast or sham radiotherapy before commencing treatment with CASODEX 150 mg monotherapy.

Patients were assessed by the investigator before randomisation to ensure the absence of clinically detectable gynaecomastia. Two weeks after receiving radiotherapy, patients were assessed by the radiotherapist for skin irritation and other possible radiotherapy side effects. Any persistent effects as a result of the radiotherapy were followed up at 4-weekly visits until resolution. Routine assessments were scheduled at 3-monthly intervals for a total of 12 months.

**Population:** A total of 106 patients with prostate cancer were randomised into the trial from a total of 10 centres (UK, South Africa, Finland, Sweden, Norway, Belgium and Holland).

**Key inclusion criteria:** Aged 18 years and above; diagnosed with non-metastatic (M0) adenocarcinoma of the prostate gland ($T_{1b}$-$T_4$) and any N category confirmed histologically or cytologically; life expectancy of greater than 1 year.

**Key exclusion criteria:** Any known sensitivity to radiotherapy or conditions that may have led to radiation sensitivity; presence of other malignancy, other than squamous/basal cell carcinoma, or history of previous malignancy in the previous 5 years; previous history of mastectomy or radiotherapy to the chest area; any previous treatment with surgical or medical castration, anti-androgens, or oestrogen therapy at any time; any evidence of current gynaecomastia or male breast pain; concurrent treatment with drugs known to have a high potential for causing gynaecomastia.

**Dosage:** The radiotherapy was in the form of an electron beam as a single fraction of 10 Gy at 6 to 12 megaelectron-volts (MeV) (according to patient build), irradiating a 5 cm diameter circle centred around each nipple. CASODEX 150 mg/day was supplied as a white, intagliated tablet (formulation number F11156; batches 61516D99, 38159D96, 71257J00).

**Key assessments:**

**Efficacy:** Efficacy was assessed as the incidence of gynaecomastia as determined by physical examination (primary endpoint) and the incidence and severity of gynaecomastia and male breast pain elicited by direct questioning (secondary endpoints) as well as the objective measurement of gynaecomastia (secondary endpoint). For the primary endpoint (and secondary endpoints regarding gynaecomastia), normal approximation to binomial distribution was used to test the difference between groups. The odds ratio and associated 95% confidence intervals were also constructed. Data were summarised according to overall incidence and time to first incidence. For the secondary endpoints relating to breast pain, there was less emphasis on formal statistical testing as the trial was not powered on these criteria.

**Safety:** Safety was assessed by the recording of adverse events and liver function test monitoring. Any out-of-range liver function test results that were considered to be clinically significant were to be reported as an adverse event. As the efficacy objectives of this trial assessed the incidence of gynaecomastia and male breast pain, these conditions were not reported as adverse events.

**RESULTS**

**Demography:** A total of 106 patients were recruited: 52 in the radiotherapy + CASODEX 150 mg group and 54 in the sham radiotherapy + CASODEX 150 mg group. All 106 patients were included in the efficacy population for the intention-to-treat analysis. Two patients, both in the sham radiotherapy group, withdrew without receiving sham radiotherapy or CASODEX and were excluded from the safety summaries. One patient received sham radiotherapy but no CASODEX and was included in the safety population.

The demographic characteristics were well balanced between the treatment groups: mean age was 69.4 years (range 55 to 82) for the radiotherapy group and 69.5 years (range 52 to 80) for the sham group; mean weight was 81.5 kg and 80.0 kg for the radiotherapy and sham groups, respectively; mean height was 175.2 cm and 174.4 cm for the radiotherapy and sham groups respectively; the majority (>85%) of patients were Caucasian. At entry the majority of patients had T1c, T2 or T3 stage disease; the distribution was balanced between treatment groups.

The numbers of withdrawals were low and balanced between treatment groups (7 vs 6 for the radiotherapy and sham groups, respectively) with no treatment related pattern. There were 3 deaths, 3 patients withdrew with adverse events, 4 were unwilling to continue and 3 withdrew for other reasons.

**Efficacy:** *Incidence of gynaecomastia.* Prophylactic radiotherapy significantly reduced the incidence of gynaecomastia as assessed by the investigator or by direct questioning of the patient (Table I). In both treatment groups, the risk of developing gynaecomastia was greatest during the early part of the study: of those who would go on to have gynaecomastia, 39.6% and 86.8% of patients in the radiotherapy and sham groups, respectively, developed the condition within the first 6 months.

**Table I Summary of gynaecomastia and breast pain incidence and analysis**

| Endpoint | Number of events/patients (%) | | Difference in proportions | p-value[a] | OR | 95% CI |
|---|---|---|---|---|---|---|
| | Radiotherapy + CASODEX | Sham radiotherapy + CASODEX | | | | |
| Investigator assessed gynaecomastia (1º) | 27/52 (51.9) | 46/54 (85.2) | -0.333 | <0.001 | 0.13 | 0.04 to 0.38 |
| Direct questioning for gynaecomastia (2 º) | 26/52 (50.0) | 44/54 (81.5) | -0.315 | <0.001 | 0.20 | 0.08 to 0.50 |
| Breast pain (2 º) | 43/52 (82.7) | 49/54 (90.7) | -0.080 | 0.221 | 0.25 | 0.05 to 1.27 |

[a] p-value relates to the difference in proportions. OR, odds ratio given as radiotherapy group relative to sham. CI confidence interval. 1º/2º primary/secondary.

*Intensity of gynecomastia.* Intensity of gynaecomastia was determined by direct questioning: almost 50% of patients who received radiotherapy had no gynaecomastia compared with approximately 15% in the sham group. Of those patients who experienced gynaecomastia, radiotherapy reduced the proportion who reported a moderate or severe condition (21.2% [11/52] vs 48.2% [26/54], for radiotherapy and sham groups, respectively) and this was statistically significant (odds ratio 0.24; 95% CI, 0.111 to 0.503; p<0.001).

*Degree of gynaecomastia.* In the radiotherapy group, the degree of gynaecomastia remained relatively low and constant (median value was 1.5 cm [range 1.5 to 13.0 cm] at 3 months and 1.5 cm [range 1.5 to 12.3 cm] at 12 months). By comparison, the degree of gynaecomastia in the sham group increased by 3.6 cm over time (median value was 1.5 [range 1.5 to 7.0] at 3 months and 5.1 cm [range 1.5 to 12.3 cm] at 12 months). Further, only 11.5% (6/52) of patients in the radiotherapy group had a maximum degree of gynaecomastia >5 cm compared with 50.0% (27/54) in the sham group.

*Breast pain.* There was a small reduction in the incidence of breast pain which was not significant (Table I). There was little difference between the groups for the number of patients who reported mild breast pain but the proportion who reported moderate or severe breast pain was reduced in the radiotherapy group (23.1% [12/52]) compared with the sham group (37.0% [20/54]). When considered as a whole, the difference in intensity of breast pain just reached conventional statistical significant (odds ratio 0.44; 95% CI, 0.197 to 0.974; $p<0.0429$). There was little difference between the treatment groups for the time to onset of breast pain.

*Radiotherapy side effects.* Of the patients who received radiotherapy 32% (17/52) had at least 1 radiotherapy related adverse event compared with just 1 patient in the sham group. Erythema was the most common effect, reported in 25% (13/52) of patients while skin irritation and breast tenderness were each reported by 15.4% (8/52) of patients. No radiotherapy side effects were reported as being severe in intensity and all were of short duration and resolved without intervention. There was one case of breast swelling that was considered to be related to radiotherapy; it lasted for 1 day and was mild in intensity.

**Safety:** The safety assessment was based on a median exposure to CASODEX 150 mg of 9 to 12 months and totalled 47 patient years in each treatment group. The most common adverse events were asthenia (14.4% [15/104]) and diarrhoea (10.6% [11/104]) which are recognised effects of NSAA therapy. Events in the urogenital system were also common, as would be expected in elderly men with malignant disease of the urogenital tract. The slight imbalances between treatment groups were considered to result from the small numbers of patients and events in this study. There were no differences that could plausibly be related to relatively low-dose localised radiotherapy.

Three patients died whilst on therapy and all were in the radiotherapy group. Patient 0021/0009 died from an unknown cause, patient 0031/0052 died from cardiac arrest and patient 0041/0015 died as a result of prostate cancer. None of the deaths were considered to be related to the trial therapy.

The trial therapy was well tolerated with only 3 patients withdrawing because of non-fatal adverse events: heart arrest, dyspnoea and asthenia. The dyspnoea and asthenia were considered to be related to CASODEX therapy by the investigator.

There was little difference between treatment groups in the total number of serious adverse events reported for the 2 groups (23.1% [12/52] vs 25.0% [13/52] for the radiotherapy and sham groups, respectively). The majority of adverse events were reported by only 1 patient with no emerging pattern or trend. Nine serious adverse events were reported by the whole safety population in the cardiovascular body system and a total of 12 serious adverse events were reported in the urogenital system. This was consistent with men of this age group who have malignant disease of the urogenital tract. The slight imbalances between groups were considered

to result from the small numbers in this study. On the available evidence, it was considered unlikely that the type and dose of irradiation used in this study would lead to cardiotoxicity.
The incidence of adverse events considered to be related to CASODEX plus irradiation was consistent with previous larger studies and could be predicted by the pharmacology of NSAAs (eg, asthenia [9/104], vasodilataion [5/104], constipation [4/104], diarrhoea [4/104], nausea [3/104], decreased libido [2/104], alopecia [2/104], pruritis [3/104], rash [5/104] and impotence [8/104]). Two cases of face oedema were also reported as drug-related. The incidence of adverse events considered to be related to radiotherapy plus CASODEX included urinary frequency (4/104), skin discoloration (3/104), pelvic pain (2/104) and urinary urgency (2/104).
The clinical laboratory analyses showed a tendency for the ALT and AST mean values to increase in the radiotherapy group relative to those in the sham group. However, the median values and geometric mean values were similar for both groups. The variability and increase in mean values were thought to arise from a single patient (0021/0007) who reported changes to ALT and AST values that were considered clinically relevant. There was little difference between groups for bilirubin values.
The safety data collected in this study for CASODEX-treated patients appears to be consistent with data collected in other larger studies, with no new or unexpected findings. The patient group that received radiotherapy in combination with CASODEX appeared to have an increased incidence of some events (cardiovascular SAEs and deaths) relative to those who received sham radiotherapy but there is no plausible explanation for these phenomena and they were mostly considered to result from the low number of patients and events seen in this study.