AstraZeneca

## Clinical Study Results Posting Template

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| **Template content reviewed** | | Select from list |
| **Study posting approved by:** | | |

**Posting Results:**

☒ Hypothesis-testing study in any indication

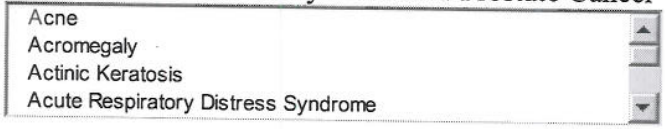
☒ Study in patients with a serious or life-threatening disease or condition

☐ Non-interventional study with an approved product.

## 1. TITLES AND BACKGROUND INFORMATION

- Protocol ID: 1839IL/0129
- Secondary ID: CAPRINO
- Official Title: **A RANDOMISED, PLACEBO-CONTROLLED STUDY TO ASSESS THE RATE OF PSA DECREASE AS WELL AS ANATOMICAL AND METABOLIC CHANGES IN THE PROSTATE AS DETERMINED BY MRI/3D-MRS AND HISTOLOGICAL CHANGES BY BIOPSY IN SUBJECTS WITH LOCALLY ADVANCED PROSTATE CARCINOMA TREATED WITH EITHER CASODEX® (BICALUTAMIDE) ALONE OR THE COMBINATION OF CASODEX® AND ZD1839 (IRESSA®)**
- Finished Product: IRESSA
- Active Ingredient: Gefitinib
- Study Phase: Phase II
- Study Status: Closed

- Select Indication: Locally Advanced Prostate Cancer




## 2. KEY STUDY DATES

- Study Start Date: 26 November 2003
- FPI: 22 December 2003
- LPLV: 28 August 2006
- Database Lock: 14 November 2007
- Approval Date: N/A

## 3. OBJECTIVES

**Primary objectives**

To detect differences in the rate of decrease of prostate-specific antigen (PSA) levels in subjects treated with Casodex® alone or Casodex® in combination with gefitinib.

**Secondary (explorative) objectives**

The secondary efficacy objectives of the study are:

1. To detect changes in prostatic metabolites such as choline, citrate and creatine, by in vivo magnetic resonance spectroscopy (MRS) in subjects receiving Casodex® alone compared with combination therapy with Casodex® and gefitinib.

2. To detect changes in the prostate gland within and between treatment arms using magnetic resonance imaging (MRI).

3. To detect changes in serum levels of chromogranin A (CgA), neuron-specific enolase (NSE), vascular endothelial growth factor (VEGF) and interleukin 8 (IL-8) between the treatment arms.

4. To study histopathological changes within and between the treatment arms based on analysis of biomarkers related to the processes of apoptosis and proliferation, as well as androgen receptor (AR) status, epidermal growth factor receptor status (EGFR [erb-1 to erb-4]) in prostatic biopsies taken before and during treatment.

### Safety objectives

1. To further characterise the safety profile of gefitinib at a 250 mg daily dose
2. To evaluate the safety and tolerability of the combination of Casodex® and gefitinib compared with Casodex® and placebo.

## 4. METHODS

### Study design

A randomised, double blind, placebo controlled two-arm study with Casodex® (150 mg) alone or Casodex® in combination with gefitinib.

Subjects were randomised to one of the following treatment arms:

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|---|---|---|
| Group 1: | Casodex® 150 mg + gefitinib 250 mg | (55 subjects) |
| Group 2: | Casodex® 150 mg + placebo | (55 subjects) |

Subjects were then randomised to one of the following biopsy times:

- Second biopsy performed 2 weeks after randomisation
- Second biopsy performed 4 weeks after randomisation
- Second biopsy performed 6 weeks after randomisation

Finally, a total of 48 subjects were randomised from each of the above six cohorts to undergo MRS and MRI 48 hours before their biopsy.

All subjects had their serum samples collected at baseline, immediately before the second biopsy, and at 3 and 6 months after randomisation, respectively.

Treatment with gefitinib or Placebo, and Casodex® was administered daily for 6 months, or until disease progression, unacceptable toxicity or withdrawal of consent. Subjects were followed up 4 weeks after the end of study treatment.

### Target subject population

A total of 110 male patients aged 18 to 80 years were included. All patients had histologically confirmed locally advanced adenocarcinoma of the prostate (T3/T4, Nx/N0-1, M0), with a WHO performance status ≤2.

### Investigational product, dosage and mode of administration

Gefitinib (Iressa) tablets 250 mg and placebo to match; one tablet orally once daily, administered continuously

Casodex® (bicalutamide) tablets 150 mg; one tablet orally once daily, administered continuously

**Comparator, dosage and mode of administration**

N/A

**Duration of treatment**

Gefitinib and Casodex® was administered daily for 6 months, or until disease progression, unacceptable toxicity, or withdrawal of consent.

**Outcome variables**

The following variables have been used in this study:

**Outcome variables**

**Efficacy**

**Primary outcome variable:**

- PSA level 3 months after randomisation

**Secondary outcome variables:**

- Decrease of the [(choline + creatine)/citrate] ratio, as measured by MRS, indicative of metabolic changes in the prostate
- Morphological changes in the prostate gland, assessed by MRI.
- Changes in serum tumour markers
- Changes in prostate biopsies related to:
  - Microscopic tumour morphology, including Gleason grading
  - Biomarkers related to apoptosis, proliferation and neuroendocrin differentiation

**Safety**

- Nature, incidence and severity of adverse events (AEs) and serious adverse events (SAEs)

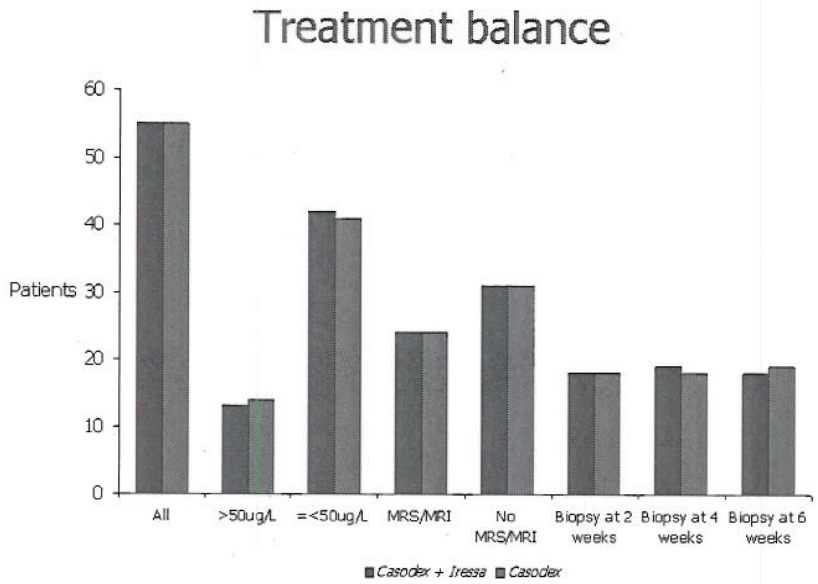
**Sample size and power calculation**

- The percentage of patients with PSA level < 2 mg/L at 3 months was expected to be 50% with Casodex alone, and 80% with the combination Casodex + Iressa

- Two-sided significance level = 5%
- Power = 90%
- Number of patients required = minimum 102 patients

## 5. RESULTS

The groups were well balanced for all pre-specified factors. With respect to the primary endpoint, we found no significant difference with regards to PSA measured 3 months after initiation of treatment. Mean PSA at 3 months was 4.6 µg/L (95% CI [15.6;41.0) in the Casodex group and 5.7 µg/L (95% CI [27.6;55.0]) in the combination group, respectively. In general, more AEs were reported in the combination group than in the group treated with Casodex alone. Also, more patients interrupted study treatment or discontinued the study due to AEs in the combination treatment group. Dry skin (53% vs 16% for the combination group vs Casodex alone, respectively), skin rash (24% vs 4%) and diarrhea (16% vs 0%) were the most frequently reported AEs. In the Casodex alone group, 9% of the patients experienced nipple tenderness vs none in the combination treatment group.
The outcomes for explorative endpoints are still of considerable interest in spite of neutral efficacy result. Analysis of explorative endpoints is ongoing and the results will be published subsequently as data becomes available.




Excellent balance at baseline with respect to all pre-specified factors (no confounding)

## Primary efficacy endpoint

| Number of patients | | Casodex + Iressa N=55 | Casodex N=55 | All N=110 |
|---|---|---|---|---|
| PSA at end of month 3 (µg/L) | Mean | 5.7 | 4.6 | 5.1 |
| | Std | 6.9 | 5.5 | 6.2 |
| | Median | 3.7 | 2.5 | 3.1 |
| | Range | 1-39 | 1-35 | 1-39 |
| | N | 52 | 54 | 106 |
| Patients with PSA <=2µg/L | | 14 (27%) | 22 (41%) | 36 (34%) |
| 95% CI: | | [15.6;41.0] | [27.6;55.0] | [25.0;43.8] |

Primary efficacy endpoint shows no significant difference between treatment groups

## Safety endpoints

| Number of patients | Casodex + Iressa N=55 | Casodex N=55 | All N=110 |
|---|---|---|---|
| Number of patients with at least one AE | 51 (93%) | 30 (55%) | 81 (74%) |
| Number of patients with at least one SAE | 8 (15%) | 3 ( 5%) | 11 (10%) |
| Patients who discontinued study drug due to AE | 13 (24%) | 2 ( 4%) | 15 (14%) |
| Patients who interrupted study drug due to AE | 11 (20%) | 2 ( 4%) | 13 (12%) |

Safety endpoints show less favorable toxicity profile of the combined therapy

## 6. REFERENCE:

None