AstraZeneca

Combined Analysis Report Synopsis

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CASODEX™ 150 mg in Early Prostate Cancer Programme Report of the Final Analysis of Efficacy and Safety Data From the EPC Programme (Studies 7054IL/0023, 0024 & 0025)

This document presents the key efficacy and safety results of the fourth and final planned combined analysis of data from the 3 clinical studies in the CASODEX 150 mg EPC programme after an overall median follow-up of 9.7 years (up to a data cut-off date of 30 August 2008).

Study dates:	First patient enrolled: 01 August 1995 (Study 0023) Last patient completed: 30 August 2008 (Study 0025)
Phase of development:	Therapeutic confirmatory (III)

Study centres

The early stage prostate cancer (EPC) programme (Studies 0023, 0024 and 0025) enrolled patients at 358 centres in 23 countries.

Publications

There are currently over 50 publications, including peer-reviewed journals and meeting abstracts, which describe the data from the EPC program.

Objectives

The primary objectives of the EPC programme were:

- To determine the benefit of CASODEX as adjuvant to therapy of primary curative intent or as immediate hormonal therapy in patients with non-metastatic prostate cancer, in terms of time to objective progression (TTP; also referred to as progression-free survival) and time to death (TTD; also referred to as overall survival)

- To assess the tolerability and safety of CASODEX treatment in these patients.

Study design

The EPC programme was prospectively designed and powered on the basis of a combined analysis of data from 3 multicentre, randomised, double-blind, parallel-group, studies. In each of the 3 geographically-distinct studies, patients with localized or locally advanced prostate cancer, were randomised 1:1 to CASODEX 150 mg daily or placebo.

Target population and sample size

Male patients aged 18 years and above; diagnosed with non-distant metastatic adenocarcinoma of the prostate gland (Stages T1b to T4, any N, M0). The intended recruitment target for the EPC programme was 7500 patients to allow detection of a 15% reduction in the rate of objective clinical progression on CASODEX compared to placebo with 90% power at the 5%, 2-sided level of significance (assuming a median time to progression of 7 years and a minimum follow-up at the first analysis of 2 years).

Investigational product and comparator: dosage and mode of administration

Bicalutamide (176,334; ZD7054; CASODEX™), 150 mg once daily as an oral tablet or matching placebo.

Duration of treatment

Study 0023 patients were to receive randomized therapy for a maximum period of 2 years. Study 0024 patients were to receive randomized therapy until progression but recommended for ≤5 years in adjuvant patients. Study 0025 patients were to receive randomized therapy until progression.

Criteria for evaluation - efficacy (main variables)

Time to objective progression (TTP), also referred to as progression-free survival and time to death (TTD), also referred to as overall survival.

Criteria for evaluation - safety (main variables)

Following the 3rd analysis, protocol amendments were implemented, which reduced patient evaluations to documentation of essential data only; namely: survival, progression status and safety findings. Evaluation of safety for study 23 was reduced to reporting of Serious Adverse Events (SAEs) that: a) were believed causally related to receipt of CASODEX, b) resulted in a fatal outcome other than clinical progression of prostate cancer, or c) were pre-existing Adverse Events (AEs) that changed status to conform to SAE criteria. Evaluation of safety for studies 24 and 25 was reduced to reporting of AEs leading to cessation of CASODEX trial therapy or SAEs believed causally related to receipt of CASODEX.

Statistical methods

Efficacy data were analysed on an intention-to-treat basis (ITT: analysed as randomised). The efficacy endpoints were analysed by fitting a Cox proportional hazards model allowing for the effects of: randomised treatment, study, log-transformed baseline PSA, disease stage, prior therapy, and Gleason grade.

The first protocolled combined analysis was performed at 2 years minimum follow-up (median follow-up = 3 years). During their review of the results from the first combined analysis, several Regulatory Authorities requested analyses for the following four stage/therapy subgroups in order to assess the consistency of the benefits seen in the whole EPC programme population:

- Localised adjuvant (further sub-divided into those who had radiotherapy alone and those who had radical prostatectomy [including patients who received radiotherapy as well])
- Localised watchful waiting
- Locally advanced adjuvant (further sub-divided into those who had radiotherapy alone and those who had radical prostatectomy [including patients who received radiotherapy as well])
- Locally advanced watchful waiting

These analyses were performed for the first combined analysis, and all subsequent planned combined analyses. An analysis of time to death in these subgroups has also been performed for this 4th analysis.

Subject population

A total of 8113 male patients were recruited into the EPC programme (Studies 0023, 0024 and 0025) from 358 centres in 23 countries. The first patient was recruited on 01 August 1995 (Study 0023), and the last patient was recruited on 30 July 1998 (Study 0025). Four-thousand and fifty-two (49.9%) patients were randomised to receive CASODEX 150 mg, and 4061 (50.1%) to receive placebo. All 8113 patients were included in the efficacy analysis (ITT) population. Sixty patients (30 in each treatment arm) received no randomised therapy and were excluded from the safety population (N=8053).

The treatment groups were well balanced in terms of demographic and disease characteristics both in the individual studies and in the combined analysis.

Summary of efficacy results

The data in this report are based on a cut-off of 30 August 2008. Table S1 summarises the analyses of TTP (combined and individual study data).

Table S1 Analysis of time to progression for the combined data and individual studies

Analysis population	Events (%) in CASODEX arm	Events (%) in placebo arm	HR (95% CI)	p-value
Combined	1483/4052 (36.6)	1549 /4061 (38.1)	0.847 (0.788 to 0.910)	0.001
Study 0023	353/1647 (21.4)	333/1645 (20.2)	1.05 (0.90 to 1.22)	0.531
Study 0024	735/1798 (40.9)	807/1805 (44.7)	0.82 (0.74 to 0.90>)	<0.001
Study 0025	395/607 (65.1)	409/611 (66.9)	0.75 (0.65 to 0.86)	<0.001

The analysis of TTP shows significant differences in favour of CASODEX in terms of a reduction in the risk of disease progression, both in the combined data, and in Studies 0024 and 0025. No significant difference was seen in Study 0023. These results are in agreement with those obtained from the earlier planned analyses.

The results of the analysis of TTP in the 4 stage/therapy subgroups are presented in Table S2. The clearest benefits for CASODEX therapy in terms of improved progression-free survival were seen in patients at highest risk of disease progression ie, those with locally advanced disease. In patients at less risk of progression (ie, those with localised disease), CASODEX lead to only a small non-significant numerical improvement in progression-free survival.

Analysis of TTD (combined and individual study data) is summarised in Table S3. The combined and individual study data reveal no significant differences in overall survival between patients receiving CASODEX and those receiving placebo. These results are in agreement with those obtained from the previous planned analyses.

Table S2 Analysis of time to progression for the 4 stage/therapy subgroups

Analysis population	Events (%) in CASODEX patients	Events (%) in placebo patients	HR (95% CI)	p-value
Locally advanced disease				
Watchful waiting	245/335 (73.1)	252/322 (78.3)	0.67 (0.56 to 0.80)	<0.001
Adjuvant therapy	334/1031 (32.4)	360/993 (36.3)	0.78 (0.67 to 0.91)	0.001
Radiotherapy	89/161 (55.3)	103/144 (71.5)	0.62 (0.47 to 0.83)	0.001
Radical prostatectomy	245/870 (28.2)	257/849 (30.3)	0.85 (0.71 to 1.01)	0.065
Localised disease				
Watchful waiting	443/779 (56.9)	469/848 (55.3)	0.93 (082 to 1.06)	0.261
Adjuvant therapy	458/1903 (24.1)	467/1896 (24.6)	0.92 (0.81 to 1.05)	0.215
Radiotherapy	207/538 (38.5)	211/527 (40.0)	0.90 (0.74 to 1.09)	0.259
Radical prostatectomy	251/1365 (18.4)	256/1369 (18.7)	0.94 (0.79 to 1.12)	0.516

Table S3 Analysis of time to death for the combined data and individual studies

Analysis population	Events (%) in CASODEX arm	Events (%) in placebo arm	HR (95% CI)	p-value
Combined	1289/4052 (31.8)	1261/4061 (31.1)	1.012 (0.94 to 1.09)	0.765
Study 0023	308/1647 (18.7)	286/1645 (17.4)	1.07 (0.91 to 1.25)	0.429
Study 0024	633/1798 (35.2)	643/1805 (35.6)	0.99 (0.89 to 1.11)	0.90
Study 0025	348/607 (57.3)	332/611 (54.3)	0.98 (0.84 to 1.14)	0.79

As was the case with the third combined analysis, the fourth combined analysis demonstrated opposing trends in the subgroups of watchful waiting patients receiving CASODEX (Table S4). Patients with locally advanced disease tended towards improved survival, while those with localised disease tended towards decreased survival. For patients in the adjuvant group overall, no difference between the treatment groups was seen in patients with either locally advanced disease or localised disease. In patients with locally advanced disease, those patients treated initially with radical prostatectomy showed no difference in overall survival between the treatment groups (p=0.817). However, those treated initially with radiotherapy showed a statistically significant (p=0.031) improvement in survival in favour of CASODEX.

Table S4 Analysis of time to death for the 4 main patient subgroups

Analysis population	Deaths (%) in CASODEX patients	Deaths (%) in placebo patients	HR (95% CI)	p-value
Locally advanced disease				
Watchful waiting	226/335 (67.5)	222/322 (68.9)	0.89 (0.74 to 1.07)	0.206
Adjuvant therapy	260/1031 (25.2)	261/993 (26.3)	0.93 (0.78 to 1.10)	0.386
Radiotherapy	72/161 (44.7)	82/144 (56.9)	0.70 (0.51 to 0.97)	0.031
Radical prostatectomy	188/870 (21.6)	179/849 (21.1)	1.03 (0.84 to 1.26)	0.817
Localised disease				
Watchful waiting	396/779 (50.8)	388/848 (45.8)	1.15 (1.00 to 1.32)	0.054
Adjuvant therapy	404/1903 (21.2)	388/1896 (20.5)	1.01 (0.87 to 1.16)	0.943
Radiotherapy	191/538 (35.5)	185/527 (35.1)	0.98 (0.80 to 1.20)	0.854
Radical prostatectomy	213/1365 (15.6)	203/1369 (14.8)	1.03 (0.85 to 1.25)	0.759

Summary of safety results

Across the whole programme, at the data cut-off for the fourth analysis, 32.0% (1286) of patients in the CASODEX group had died compared with 31.1% (1254) of patients in the placebo group (Table S5).

Table S5 Incidence of deaths in the EPC clinical programme

	Number (%) of patients	
	Bicalutamide 150 mg (n=4022)	**Placebo (n=4031)**
All deaths	1286[a] (32.0)	1254 (31.1)
Related to prostate cancer	370 (9.2)	401 (9.9)
Other causes (total)	916 (22.8)	853 (21.2)

Table S6 summarises deaths by body system for the combined data. There were no notable imbalances in the incidence of death in any body system.

Other than prostate cancer itself, the most frequently reported causes of death were "cause unknown" (122 [3.0%] deaths in the CASODEX group vs 106 [2.6%] deaths in the placebo group) and myocardial infarction (103 [2.6%] vs 85 [2.1%]) (Table S7). At the time of the third analysis there was an apparent imbalance in the incidence of death due to heart failure (1.2% vs 0.6%) and gastrointestinal (GI) carcinoma (1.3% vs 0.9%), each being greater in the CASODEX arm. Following the fourth analysis the apparent difference between the treatment groups in the incidence of death due to heart failure had declined (1.5% vs 1.2%) while the difference in the incidence of death due to GI carcinoma remained unchanged (1.6% vs 1.1%).

Table S6 Summary of deaths by body system for the combined data

	Number (%) of patients	
	Bicalutamide 150 mg (n=4022)	**Placebo (n=4031)**
Body as a whole	206 (5.1)	180 (4.5)
Cardiovascular	341 (8.5)	316 (7.8)
Digestive	96 (2.4)	80 (2.0)
Endocrine	1 (0.0)	5 (0.1)
Haemic/Lymphatic	30 (0.7)	18 (0.4)
Metabolic	9 (0.2)	11 (0.3)
Nervous	23 (0.6)	27 (0.7)
Respiratory	183 (4.5)	185 (4.6)
Skin/appendages	5 (0.1)	4 (0.1)
Urogenital	392 (9.7)	427 (10.6)

Table S7 Summary of most common causes of death for the combined data

	Number (%) of patients	
	Bicalutamide 150 mg (n=4022)	**Placebo (n=4031)**
Prostate cancer	370 (9.2)	401 (9.9)
Myocardial infarction	103 (2.6)	85 (2.1)
Gastrointestinal carcinoma	66 (1.6)	46 (1.1)
Cause unknown	122 (3.0)	106 (2.6)
Lung carcinoma	66 (1.6)	66 (1.6)
Cerebrovascular accident	60 (1.5)	60 (1.5)
Heart arrest	49 (1.2)	49 (1.2)
Heart failure	60 (1.5)	47 (1.2)
Pneumonia	53 (1.3)	65 (1.6)

The most common adverse events were those that could be predicted from the pharmacology of CASODEX 150 mg. These included breast pain, gynaecomastia, asthenia, rash, constipation, vasodilatation and impotence which were all reported at a higher incidence in the CASODEX 150 mg group compared with the placebo group (Table S8).

Table S8 Summary of most common AEs for the combined data

	Number (%) of patients	
	Bicalutamide 150 mg (n=4022)	**Placebo (n=4031)**
Breast pain	2963 (73.7)	308 (7.6)
Gynaecomastia	2766 (68.8)	334 (8.3)
Pharyngitis	448 (11.1)	470 (11.6)
Asthenia	442 (11.0)	315 (7.8)
Back pain	420 (10.4)	490 (12.2)
Rash	404 (10.0)	337 (8.4)
Constipation	380 (9.4)	314 (7.8)
Impotence	375 (9.3)	263 (6.5)
Vasodilatation	370 (9.2)	216 (5.4)

A total of 655 patients randomised to CASODEX and 253 patients randomised to placebo subsequently switched to open-label CASODEX. After switching, 352/655 (53.7%) patients originally randomised to CASODEX and 211/253 (83.4%) patients originally randomised to placebo experienced at least 1 AE with an onset during the open-label treatment period. The most common AEs experienced by patients randomised to placebo after switching to CASODEX were gynaecomastia (107/253; 42.3%) and breast pain (138/253; 54.6%).