AstraZeneca

Drug product:	CASODEX 150 mg	**SYNOPSIS**	
Drug substance:	Bicalutamide		
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A Randomised, Double-blind, Parallel-group Trial Comparing CASODEXTM 150 mg Once Daily with Placebo in Patients with Non-metastatic Prostate Cancer

Study centres

This study was conducted in 17 countries (figures show the number of centres in each country that recruited patients): Australia (2), Austria (5), Belgium (14), Czech Republic (6), France (22), Germany (12), Holland (14), Hungary (6), Ireland (2), Israel (5), Italy (20), Mexico (6), Poland (2), Portugal (8), South Africa (13), Spain (23), and the UK (31).

Publications

There are currently over 50 publications, including peer-reviewed journals and meeting abstracts, which describe the data from this trial and the wider EPC programme. A complete list is provided in Section 12.1.11.

Study dates		**Phase of development**
First subject enrolled	21 September 1995	Therapeutic confirmatory (IIIb)
Data cut-off	31 December 2002	

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.

Study design

This was a multicentre, international, randomised, double-blind, parallel-group study into the effects of adding CASODEX 150 mg once daily, or placebo, to the standard care regimens for patients with localised or locally advanced prostate cancer.

Following the implementation of protocol amendment number 5, all patients were to be informed of the results of the first analysis. Patients who were still taking randomised therapy could request a voluntary code-break, withdraw from randomised therapy and commence with open-label (OL) CASODEX.

Target patient 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 trial was 1 of 3 comparative Phase IIIb trials that comprised the early stage prostate cancer (EPC) clinical programme. The trials were designed and powered to enable a combined analysis to be performed. All trials were sized to investigate time to progression after 2 years follow-up (ie, the first analysis). For this trial alone, 3500 patients were required to provide 90% power (5% significance, 2-sided) to detect a 20% reduction (ie, a hazard ratio of 0.8) in the rate of progression of patients on CASODEX compared with placebo.

Investigational product and comparator: dosage, mode of administration and batch numbers

Bicalutamide (176,334; ZD7054; CASODEX™) 150 mg per day as an oral tablet or matching placebo. Batch numbers were:
CASODEX (as randomised therapy), 00040B98, 00041J98, 01390D98, 01413K98, 02911G98, 03568A98, 27088/95, 27120/95, 35394C96, 35395K96, 35396H96, 3638C96, 37074K97, 38159D96, 38474F97, 38825C97, 39829G96, 61516D99, 63295I99, 64446I99, 81258K01, 81259H01, 80824A01, 80825I01, 71323G00, 63295I99, 83526K01, 61516D99, 64446I99, 73270I00, 73273K00.

Placebo to match CASODEX, 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, 72480B00, 04699G98, 72479A00, 70533K00, 04700J98.

CASODEX (as open-label [OL] therapy), 73272C00, 73271F00, 73273K00, 81258K01, 81259H01.

Duration of treatment

Patients who received primary treatment of curative intent were to receive study therapy (including open-label [OL] CASODEX) for 5 years with extension at the discretion of the investigator, or until signs of disease progression. Patients who did not receive primary treatment of curative intent were to receive study therapy (including OL CASODEX) until signs of disease progression.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: time to objective progression (TTP).
- Secondary variables: survival (time to death [TTD]), time to treatment failure (TTF), and time to PSA doubling (TTPSA).

Safety

Standard safety assessments included adverse event reports, clinical laboratory data and physical examinations.

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, log-transformed baseline PSA, disease stage, prior therapy, and Gleason grade.

Patient population

The patient population and disposition are presented in Table S1. The 2 treatment groups were generally well balanced with regards to demography and characteristics of prostate cancer at entry to the trial (Table S2).

Table S1 Patient population demography and disposition

		Standard treatment plus CASODEX 150 mg		Placebo	
Population					
N randomised (N planned)		1798	(1750)	1805	(1750)
Demographic characteristics					
Sex (n and % of patients)	Male	1798	(100)	1805	(100)
	Female	0		0	

Table S1 Patient population demography and disposition

		Standard treatment plus CASODEX 150 mg		Standard treatment plus Placebo	
Age (years)	Mean (SD)	68.6	(7.29)	68.7	(7.13)
	Range	42 to 93		46 to 93	
Race (n and % of patients)	Caucasian	1714	(95.3)	1709	(94.7)
	Hispanic	28	(1.6)	34	(1.9)
	Mixed	29	(1.6)	32	(1.8)
	Afro-Caribbean	17	(0.9)	13	(0.7)
	Asian	6	(0.3)	9	(0.5)
	Other	3	(0.2)	7	(0.4)
	Oriental	1	(0.1)	1	(0.1)
Disposition					
N (%) of patients at data cut-off who were:					
Ongoing as randomised		636	(35.4)	556	(30.8)
Untreated with any trial therapy		8	(0.4)	10	(0.6)
Withdrawn from randomised therapy [a]		1051	(58.5)	1042	(57.7)
Withdrawn for voluntary code-break and		103	(5.7)	142	(7.9)
received no other therapy		14	(0.8)	84	(4.7)
remaining on OL CASODEX		80	(4.4)	93	(5.2)
had withdrawn from OL CASODEX		9	(0.5)	20	(1.1)
N analysed for safety [b]		1790		1795	
N analysed for efficacy (ITT)		1798		1805	

[a] Does not include those patients who withdrew as a consequence of requesting a voluntary code-break.
[b] Number of patients who took at least 1 dose of study treatment.
N, number of patients; OL, open-label; ITT, Intention to treat.

Table S2 Baseline cancer characteristics (all randomised patients)

	Standard treatment plus			
	CASODEX 150 mg (N=1798)		Placebo (N=1805)	
Tumour stage: T category (number [%])				
T1	458	(25.5)	454	(25.2)
T2	697	(38.8)	741	(41.1)
T3	597	(33.2)	564	(31.2)
T4	46	(2.6)	46	(2.5)
Gleason grade (number [%])				
Well differentiated (2,3,4)	557	(31.0)	564	(31.2)
Moderately differentiated (5,6)	728	(40.5)	742	(41.1)
Poorly differentiated (7,8,9,10)	480	(26.7)	471	(26.1)
Not known	33	(1.8)	28	(1.6)
Lymph node category (number [%])				
N-	1103	(61.3)	1091	(60.4)
N+	47	(2.6)	48	(2.7)
NX	648	(36.0)	666	(36.9)
Previous therapy of primary curative intent (number [%])				
Radical prostatectomy only	807	(44.9)	784	(43.4)
Radiotherapy only [a]	335	(18.6)	325	(18.0)
Radical prostatectomy and radiotherapy	28	(1.6)	29	(1.6)
Watchful waiting	628	(34.9)	666	(36.9)
Other [b]	0		1	(0.1)
Baseline PSA (pre-randomisation)(µg/l)	n=1734		n=1748	
Geometric mean	2.978		3.184	
Median	1.300		1.300	
Range	NQ to 477.7		NQ to 1462.0	
Baseline PSA (pre-procedure)(µg/l) [c]				
Geometric mean	12.461		11.926	
Median	12.000		11.450	
Range	0.1 to 681.0		0.1 to 204.0	

[a] Includes brachytherapy.

[b] Patient 0901/0006 received systemic therapy with flutamide plus a luteinising hormone-releasing hormone analogue.

[c] For non-watchful waiting patients only.
N=number of patients; T1 includes stages T1a, T1b, T1c; N- no regional lymph node metastasis; N+ includes categories N1, N2 and N3 (metastasis in lymph node [local or regional]); NX lymph node status not assessable; n number of observations; ITT=intention to treat; PSA prostate specific antigen; NQ non-quantifiable (below limit of quantification, 1µg/ml).

Efficacy results

The data in this report are based on a cut-off of 31 December 2002. The numbers of patients with events, and the results of this second efficacy analyses are provided in Tables S3 and S4, respectively.

Table S3 Number of efficacy events

Type of event	Number (%) of patients with each event			
	Standard therapy plus CASODEX 150 mg (N=1798)		Standard therapy plus placebo (N=1805)	
Objective progression [a]	405	(22.5)	507	(28.1)
Death [b]	320	(17.8)	316	(17.5)
Treatment failure	1066	(59.3)	1072	(59.4)
PSA doubling [c]	529	(29.4)	905	(50.1)

[a] Includes patients with objective progression and patients who died in the absence of objective progression
[b] Deaths from all causes
[c] Includes deaths and objective progression in the absence of PSA doubling,
N, Number of patients randomised. PSA, prostate specific antigen

Table S4 Analysis of efficacy results

Analysis	Estimate of hazard ratio	2-sided 95% CI	p-value
Objective progression	0.728	0.639 to 0.830	<0.001
Survival	1.026	0.878 to 1.199	0.746
Treatment failure	0.995	0.914 to 1.084	0.913
PSA doubling	0.434	0.389 to 0.483	<0.001

CI, confidence interval; PSA, prostate specific antigen

The analysis results showed that the addition of CASODEX to standard therapy significantly reduced the risk of objective progression by 27% compared with standard therapy plus placebo ($p<0.001$). These results were supported by the analysis of PSA data, which demonstrated that the addition of CASODEX significantly reduced the risk of PSA doubling compared with placebo (Table S4). Overall, 17.7% (636/3603) of patients in the study had died at the time of the data cut-off, (31 December 2002) with 4.9% (177/3603) of patients

having died of prostate cancer. There was no overall difference in survival between the 2 treatment groups (hazard ratio 1.026; 95% CI 0.878 to 1.199; p=0.746; Table S4).

Safety results

The data presented in this report are based on a data cut-off date of 31 December 2002. (Patients who requested a voluntary code-break were required to be withdrawn from randomised therapy. Safety data obtained when patients were taking OL CASODEX have been assessed independently of the randomised treatment period.)

An overview of adverse events is presented in Table S5. The majority of patients in each treatment group experienced at least 1 adverse event (AE). The proportion of patients with AEs leading to death was greater in the CASODEX group as were the proportions of patients who withdrew following an AE, and those who had drug related AEs. Many of the AEs reflected the age of the patients, the underlying prostate cancer, concomitant medical conditions and previous medical or surgical procedures.

The most common AEs were those associated with the pharmacological action of CASODEX (Table S6). Many of these such as gynaecomastia and breast pain, vasodilatation, impotence, asthenia and rash are recognized effects of CASODEX therapy. It was considered that other common events that showed a difference in incidence were due to chance findings as in most cases there is no known mechanism to explain the event as a consequence of the action of CASODEX and in several cases (back pain, pain, arthralgia, accidental injury, hernia, and haematuria), the excess was in the placebo group.

As expected in a population of elderly men, the cardiovascular system was the body system with the greatest number of AE-related deaths (61 in the CASODEX group and 50 in the placebo group). For individual events, the only imbalances of note for specific terms were death (6 cases vs 1 for CASODEX vs placebo), congestive heart failure (6 cases vs 0 for CASODEX vs placebo), heart failure (7 cases vs 1 for CASODEX vs placebo), and pneumonia (2 cases vs 8 for CASODEX vs placebo).

The most common AEs leading to withdrawal from CASODEX were gynaecomastia and breast pain. These led to the withdrawal of 12.9% (231/1790) and 11.3% (203/1790) of patients, respectively. This rate reflects the relatively high incidence of these events in the trial (67.9% and 66.3%, respectively, compared with incidences of 8.4% and 6.0% in the placebo group). The majority of the breast pain events (82.6%) and almost half of the gynaecomastia cases (46.5%) resolved on withdrawal of treatment. Other notable AEs that led to withdrawal were asthenia (20 cases vs 10 for CASODEX vs placebo), cerebrovascular accident (11 cases vs 19), myocardial infarct (23 cases vs 22), vasodilatation (16 cases vs 7), gastrointestinal carcinoma (17 cases vs 14), abnormal liver tests (14 cases vs 4), somnolence (17 cases vs 4), and impotence (13 cases vs 0).

The incidence of liver function test abnormalities was 2.1% for CASODEX compared with 0.8% for placebo.

The incidence of serious AEs (SAEs) was similar between the 2 treatment groups. The majority of SAEs that were considered related to trial therapy were reported sporadically (ie 3 or fewer cases in either group), with no clear pattern. The notable exceptions to this included diarrhoea (4 vs 2 cases for CASODEX vs placebo), gynaecomastia (70 cases vs 0), impotence (3 cases vs 4) and breast pain (14 cases vs 0). Thus the majority of SAEs were considered related to the underlying pathology and its management, or the age and general health of the population.

In all, 120 patients switched from placebo to OL-CASODEX. A review of the safety and tolerability in this cohort did not find any clinical differences from patients who received CASODEX as randomised therapy.

Table S5 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	N (%) of patients who had an adverse event in each category[a]			
	Standard therapy plus:			
	CASODEX 150 mg (n=1790)		Placebo (n=1795)	
Any adverse events	1725	(96.4)	1560	(86.9)
Serious adverse events	806	(45.0)	757	(42.2)
Serious adverse events leading to death	135	(7.5)	106	(5.9)
Serious adverse events not leading to death	763	(42.6)	708	(39.4)
Adverse event leading to withdrawal	527	(29.4)	196	(10.9)
Drug related adverse events	1573	(87.9)	591	(32.9)

a Patients may appear in more than 1 category.
N, number of patients.
Data derived from Table T8.1

Table S6 The most commonly reported adverse events that show a difference in reporting frequency of 1% or more[a]

COSTART preferred term	Number (%) of patients in each adverse event category[b]			
	Standard therapy plus:			
	CASODEX 150 mg (n=1790)		Placebo (n=1795)	
Gynaecomastia	1216	(67.9)	150	(8.4)
Male breast pain	1186	(66.3)	107	(6.0)
Back pain	186	(10.4)	239	(13.3)

Table S6 The most commonly reported adverse events that show a difference in reporting frequency of 1% or more[a]

COSTART preferred term	Number (%) of patients in each adverse event category[b]			
	Standard therapy plus:			
	CASODEX 150 mg (n=1790)		Placebo (n=1795)	
Constipation	173	(9.7)	133	(7.4)
Urinary tract infection	173	(9.7)	139	(7.7)
Vasodilatation	172	(9.6)	84	(4.7)
Arthralgia	157	(8.8)	183	(10.2)
Impotence	150	(8.4)	107	(6.0)
Asthenia	148	(8.3)	133	(7.4)
Urinary incontinence	148	(8.3)	115	(6.4)
Pain	132	(7.4)	145	(8.1)
Rash	130	(7.3)	96	(5.3)
Hernia	114	(6.4)	146	(8.1)
Peripheral oedema	112	(6.3)	99	(5.5)
Hypercholesteraemia	106	(5.9)	77	(4.3)
Accidental injury	104	(5.8)	127	(7.1)
Weight gain	104	(5.8)	53	(3.0)
Haematuria	96	(5.4)	134	(7.5)
Somnolence	95	(5.3)	57	(3.2)

[a] This table use a cut-off of 5% in either treatment group and only includes those events where the difference between treatment groups is 1% or more.

[b] A patient may be included in more than 1 category.

Data derived from Table T8.9.2