Drug product:	CASODEX 150 mg	**SYNOPSIS**	
Drug substance:	Bicalutamide		
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A Randomised, Double-blind, Parallel-group Trial Comparing CASODEX™ 150 mg Once Daily with Placebo in Patients with Non-metastatic Prostate Cancer (SPCG-6)

Study centres

This study was conducted in 4 countries (figures show the number of centres that recruited patients in each country): Denmark (15 centres), Sweden (17 centres), Norway (21 centres) and Finland (9 centres).

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 patient enrolled	4 October 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 and overall survival in patients with non-metastatic (localised or locally advanced) prostate cancer; and 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 time to treatment failure and time to doubling of prostate specific antigen (PSA) concentration; and to assess sexual function using the Golombok Rust Inventory of Sexual Satisfaction (GRISS) questionnaire.

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 4, all patients were to be informed of the results of the first analysis. Patients who were still taking randomised therapy could withdraw from randomised therapy, proceed with a voluntary code-break and then commence with open-label (OL) CASODEX.

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 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, 1000 patients were required to provide 80% power (5% significance, 2-sided) to detect a 30% reduction (ie, a hazard ratio of 0.7) 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), 27088/95, 27120/95, 35396K96, 35396H96, 35394C96, 36383C96, 38159D96, 39829G96, 37074K97, 38474F97, 38825C97, 00041J98, 00040B98, 01413K98, 01390D98, 02911G98, 03568A98, 61516D99, 63295I99, 64446I99, 81258K01, 81259H01, 80824A01, 80825I01, 71323G00, 63295I99, 83526K01, 61516D99, 64446I99, 73270I00, 73273K00.

Placebo to match CASODEX, 34562/94, 34563/94, 59397/93, 35403D96, 35398B96, 35904I96, 35905F96, 37119E96, 37053A96, 37120F96, 36898B97, 38941C96, 36896H97, 36895K97, 36897E97, 38277G97, 38280B97, 38279A97, 38278D97, 04699G98, 04700J98, 34588/94, 72480B00, 04699G98, 72479A00, 70533K00, 04700J98.

CASODEX (as OL therapy), 73272C00, 73271F00, 73273K00, 81258K01, 81259H01.

Duration of treatment

For patients who remained on randomised treatment (or who changed from randomised treatment to OL CASODEX; Protocol Amendment 4), there was no recommended limit on the duration of dosing.

Criteria for evaluation (main variables)

Efficacy

- Primary variables: time to objective progression (TTP) and survival (time to death [TTD])
- Secondary variables: 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. Tolerability in terms of sexual function was assessed using the GRISS questionnaire.

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, tumour 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 the characteristics of prostate cancer at entry to the trial (Table S2).

Table S1 Patient population demography and disposition

		Standard therapy plus CASODEX 150 mg		Placebo	
Population					
N randomised (N planned)		607	(500)	611	(500)
Demographic characteristics					
Sex (n and % of patients)	Male	607	(100)	611	(100)
	Female	0		0	
Age (years)	Mean (SD)	68.5	(5.16)	68.5	(4.91)
	Range	46 to 87		52 to 77	
Race (n and % of patients)	Caucasian	606	(99.8)	607	(99.3)
	Hispanic	1	(0.2)	2	(0.3)
	Other	0		2	(0.3)
Disposition					
N (%) of patients at data cut-off who were:					
Ongoing as randomised		287	(47.3)	187	(30.6)
Untreated with any trial therapy		2	(0.3)	2	(0.3)
Withdrawn from randomised therapy [a]		309	(50.9)	400	(65.5)
Withdrawn for voluntary code-break and:		9	(1.5)	22	(3.6)
received no other therapy		0		3	(0.5)
remaining on OL CASODEX		7	(1.2)	13	(2.1)
had withdrawn from OL CASODEX		2	(0.3)	6	(1.0)
N analysed for safety [b]		605		609	
N analysed for efficacy (ITT)		607		611	

[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 therapy plus CASODEX 150 mg		Placebo	
Tumour stage: T category (number [%])				
T1	120	(19.8)	137	(22.4)
T2	241	(39.7)	233	(38.1)
T3	236	(38.9)	226	(37.0)
T4	9	(1.5)	14	(2.3)
TX	1	(0.2)	1	(0.2)
Gleason grade (number [%])				
Well differentiated (2,3,4)	259	(42.7)	264	(43.2)
Moderately differentiated (5,6)	265	(43.7)	276	(45.2)
Poorly differentiated (7,8,9,10)	72	(11.9)	68	(11.1)
Not known	11	(1.8)	3	(0.5)
Lymph node category (number [%])				
N-	132	(21.7)	122	(20.0)
N+	28	(4.6)	26	(4.3)
NX	447	(73.6)	463	(75.8)
Previous therapy of primary curative intent (number [%])				
Radical prostatectomy only	77	(12.7)	76	(12.4)
Radiotherapy only [a]	39	(6.4)	26	(4.3)
Radical prostatectomy and radiotherapy	2	(0.3)	4	(0.7)
Watchful waiting	486	(80.1)	505	(82.7)
Other [b]	3	(0.5)	0	
Baseline PSA (pre-randomization)(µg/l)	n=607		n=611	
Geometric mean	12.03		11.85	
Median	12.60		13.75	
Range	NQ to 3107.3		NQ to 291.4	
Baseline PSA (pre-procedure)(µg/l) [c]				
Geometric mean	17.10		17.54	
Median	17.0		16.0	
Range	1.5 to 190.0		3.9 to 102.0	

[a] Includes brachytherapy.
[b] Other includes cryotherapy/cryosurgery.
[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 Table S3 and Table S4, respectively.

Table S3 Number of efficacy events

Type of event	Number (%) of patients with each event			
	Standard therapy plus CASODEX 150 mg (N=607)		Standard therapy plus placebo (N=611)	
Objective progression [a]	215	(35.4)	282	(46.2)
Death [b]	163	(26.9)	158	(25.9)
Treatment failure	319	(52.6)	406	(66.4)
PSA doubling [c]	267	(44.0)	456	(74.6)

[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	0.571	0.477 to 0.683	<0.001
Survival	0.990	0.794 to 1.234	0.929
Treatment failure	0.599	0.516 to 0.696	<0.001
PSA doubling	0.318	0.272 to 0.372	<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 43% 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. CASODEX also significantly reduced the risk of treatment failure by 40% compared with placebo (p<0.001). Overall, 26.4% (321/1218) of patients in the study had died at the time of the data cut-off, (31 December 2002) with 13.8% (168/1218) of patients having died of prostate cancer. There was no overall difference in survival between treatment groups for the whole study population. However, a significant interaction was found between disease stage and survival. When analysed, a trend towards increased survival was seen in patients with locally advanced disease (T3/T4 or N+) who were treated with CASODEX compared with those who received placebo (hazard ratio, 0.675; 95% confidence interval [CI], 0.495 to 0.920; p=0.013). Conversely a trend for decreased survival was seen in

those with localised disease (T1/T2, N- or Nx) who were treated with CASODEX compared with those who received placebo (hazard ratio, 1.469; 95% CI, 1.064 to 2.028; p=0.019). This trend was also seen when the treatment effect was examined as a function of PSA at baseline: patients with high PSA (ie at high risk of progression) showed increased survival when treated with CASODEX compared with placebo, whilst the opposite was seen in patients with low PSA at baseline. However, due to the absence of an overall survival difference, the trends indicated in these exploratory analyses cannot be considered statistically significant per se. Accepted practice would require significance levels lower than the conventional 5% to be applied to counter the increased risk of false positives in such subgroup analyses.

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 from patients taking OL CASODEX have been assessed independently of the randomised treatment period.)

An overview of adverse events (AEs) is presented in Table S5. The majority of patients in each treatment group experienced at least 1 AE. The proportion of patients with AEs leading to deaths 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, impotence, arthralgia, asthenia, nausea and depression 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 such events were sporadic with no clear effects in any given body system.

As expected in a population of elderly men, the cardiovascular system was the body system with the greatest number of AE-related deaths (25 cases in the CASODEX group and 19 in the placebo group). For individual events, the only imbalances of note for specific terms were death (6 cases vs 0 for CASODEX vs placebo), heart arrest (6 cases vs 1), GI carcinoma (7 cases vs 3), and carcinoma of the lung (7 cases vs 1). Because of the imbalance in survival in patients with localised or locally advanced disease, the incidence of deaths was examined further according to these subgroups. No specific clinical cause for the survival deficit was found, rather there were a number of small imbalances in unrelated events. In addition, whilst there was a significant reduction in prostate cancer deaths in locally advanced patients who received CASODEX, the number of prostate cancer deaths in the localised group was similar for the 2 treatment groups. Further, there was no difference in the relative incidence of liver AEs which would indicate direct toxicity.

The most common AEs leading to withdrawal from CASODEX were gynaecomastia and breast pain. These led to the withdrawal of 2.6% (16/605) and 3.1% (19/605) of patients, respectively. This rate reflects the relatively high incidence of these events in the trial (57.5% and 63.3%, respectively, compared with incidences of 3.1% and 4.1% in the placebo group). The majority of the breast pain events (59.7%) and a quarter of the gynaecomastia cases (26.1%) resolved on withdrawal of treatment. Other notable AEs that led to withdrawal were asthenia (5 cases vs 1 case for CASODEX vs placebo), heart arrest (6 cases vs 1), myocardial infarct (8 cases vs 10), abnormal liver tests (10 cases vs 0), nausea (11 cases vs 3) carcinoma of the lung (7 cases vs 1), and impotence (6 cases vs 0).

The incidence of liver function test abnormalities was 3.1% 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 1 to 3 cases in either group), with no clear pattern. The exceptions to this included liver function tests (6 vs 0 cases for CASODEX vs placebo), gynaecomastia (46 vs 0), impotence (5 vs 0) and breast pain (13 vs 1). 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, 20 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.

The GRISS questionnaire found that CASODEX therapy led to a small reduction in the frequency of sexual intercourse and a small increase in impotence compared with placebo.

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=605)		Placebo (n=609)	
Any adverse events	601	(99.3)	544	(89.3)
Serious adverse events	359	(59.3)	312	(51.2)
Serious adverse events leading to death	63	(10.4)	37	(6.1)
Serious adverse events not leading to death	340	(56.2)	307	(50.4)
Adverse event leading to withdrawal	119	(19.7)	52	(8.5)
Drug related adverse events	564	(93.2)	161	(26.4)

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 of more than 1% in reporting frequency[a]

COSTART preferred term	Number (%) of patients in each adverse event category[b]			
	Standard therapy plus:			
	CASODEX 150 mg (n=605)		Placebo (n=609)	
Male breast pain	383	(63.3)	25	(4.1)
Gynaecomastia	348	(57.5)	19	(3.1)
Impotence	102	(16.9)	43	(7.1)
Back pain	73	(12.1)	81	(13.3)
Urinary tract infection	63	(10.4)	45	(7.4)
Arthralgia	62	(10.2)	44	(7.2)
Asthenia	62	(10.2)	31	(5.1)
Pneumonia	56	(9.3)	40	(6.6)
Pelvic pain	47	(7.8)	33	(5.4)
Constipation	45	(7.4)	31	(5.1)
Bronchitis	43	(7.1)	33	(5.4)
Pain	41	(6.8)	48	(7.9)
Vertigo	39	(6.4)	20	(3.3)
Heart failure	34	(5.6)	18	(3.0)
Nausea	34	(5.6)	23	(3.8)

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

COSTART preferred term	Number (%) of patients in each adverse event category[b]			
	Standard therapy plus:			
	CASODEX 150 mg (n=605)		Placebo (n=609)	
Depression	33	(5.5)	18	(3.0)
Flu syndrome	32	(5.3)	24	(3.9)
Urinary retention	32	(5.3)	44	(7.2)
Urinary tract disorder	26	(4.3)	39	(6.4)

[a] This table uses 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.