Drug product:	CASODEX 150 mg	**SYNOPSIS**	(For national authority use only)
Drug substance(s):	Bicalutamide		
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A randomised, double-blind, placebo controlled, parallel-group, multicentre Phase II study to assess the dose response relationship of tamoxifen (oral tablet) in the prophylactic treatment of gynaecomastia and breast pain associated with CASODEX 150 mg (oral tablet), and to assess the tumour control efficacy of the combination in patients with prostate cancer

International co-ordinating investigator

Study centres

This study is being conducted in 4 countries (figures show the number of centres in each country that recruited patients): Canada (15), Finland (5), Norway (3), and the UK (4).

Publications

None at the time of this report.

Study dates		**Phase of development**
First patient randomised	19 November 2002	Therapeutic exploratory (II)
Last patient randomised	5 June 2003	
Data cut-off	5 December 2003	

Objectives

Primary:

To explore the relationship between the dose of tamoxifen and both the incidence of gynaecomastia and breast pain, and Prostate Specific Antigen (PSA) inhibition when co-administered with CASODEX 150 mg once daily with the aim of determining the optimal dose of tamoxifen which will reduce the breast tissue adverse effects of CASODEX without reducing the efficacy of CASODEX (as determined by assessment of PSA inhibition).

Secondary:

To describe the extent of gynaecomastia and breast pain by treatment group

To describe the relative change from baseline in sex hormone concentrations by treatment group

To describe the pharmacokinetics of tamoxifen, N-desmethyltamoxifen and R-bicalutamide when tamoxifen is co-administered at varying doses with CASODEX 150 mg once daily

To assess the tolerance of tamoxifen when co-administered at varying doses with CASODEX 150 mg once daily.

Study design

Randomised, double-blind, 6-arm, placebo controlled, parallel-group, multicentre study. Patients were randomised to receive either tamoxifen 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg or placebo as blinded treatment and to be co-administered with unblinded CASODEX 150 mg once daily.

The blinded treatment will continue for one year after which patients are to enter a follow-up period and receive unblinded CASODEX 150 mg alone for a further 1-year period.

All patients will be followed for 2 years post-randomisation.

This report describes the initial statistical analysis of the endpoints that was scheduled to take place 6 months after randomisation of the Last Subject Randomised (LSR). Subsequent analyses of each of the endpoints are to be performed at the end of the 12-month LSR treatment period and at the end of the follow up period at 24 months post-LSR. The analysis at 6 months is the one of primary interest since the incidence of gynaecomastia in patients receiving CASODEX has been seen to occur most predominantly in the first 6 months of treatment.

Target patient population and sample size

The target population comprised patients with adenocarcinoma of the prostate gland but with no evidence of distant metastasis, who had a PSA ≥4 ng/ml and for whom immediate hormonal therapy was indicated. Eligible patients included those who had received therapy of

curative intent (eg, radical prostatectomy and/or radiotherapy). Patients must have had no systemic hormonal treatment for prostate cancer, other than neoadjuvant LHRH analogue use, prior to therapy of curative intent. If a patient had received LHRH analogues prior to therapy of curative intent, there should have been at least one year between the end of the treatment and the date of randomisation. Patients were not to have had pre-existing gynaecomastia or breast pain. The study intended to recruit 240 patients to be allocated in groups of 50, 40, 40, 30 and 30 patients to the tamoxifen doses of 1, 2.5, 5, 10 and 20 mg, respectively with the remaining 50 patients to receive placebo. All patients were to receive CASODEX 150 mg.

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

Tamoxifen (1 mg, 2.5 mg, 5 mg, 10 mg or 20 mg) or placebo oral tablet co-administered with CASODEX 150 mg oral tablet both to be taken once daily. Batch numbers were:
Tamoxifen 1.0 mg, 91495I02; 2.5 mg, 91496F02; 5.0 mg, 91497C02; 10 mg, 91498K02; 20 mg, 91499H02.
Placebo to match tamoxifen, 91500K02
CASODEX 150 mg, 92147I02, 83077B01, 83078J01, 84078C01, 91504J02.

Duration of treatment

Tamoxifen once daily (1 mg, 2.5 mg, 5 mg, 10 mg or 20 mg) or placebo once daily was to be co-administered with CASODEX 150 mg once daily for one year. This was the blinded treatment period.

After one year, patients would enter a follow-up period and continue to receive CASODEX 150 mg alone for one further year.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetic

- Primary variables:
  - Incidence of breast event (either gynaecomastia or breast pain as assessed by patient questioning)
  - PSA inhibition
- Secondary variables:
  - Incidence of gynaecomastia as assessed by patient questioning
  - Incidence of breast pain as assessed by patient questioning
  - Intensity of gynaecomastia as assessed by patient questioning

- Degree of gynaecomastia, as measured by callipers
- Intensity of breast pain as assessed by patient questioning
- Relative change from baseline in hormonal parameters
- Plasma concentrations of tamoxifen, N-desmethyltamoxifen and R-bicalutamide.

Safety

- Incidence of adverse events
- Liver function test (LFT) data.

Statistical methods

The primary analyses were performed on an intention-to-treat (ITT) basis and included all patients who had at least 1 assessment in the period that included the day after they were randomised to the 6-month time-point. Supporting analyses were to be performed on a per-protocol (PP) basis that would exclude patients who had not adhered to the protocol.

The data cut-off for the first planned analysis of the study endpoints described in this report was 05 December 2003, 6 months after the last patient was randomised (for some endpoints, the data collected after 3-months were analysed at the same time as the scheduled 6-month analysis). Subsequent analyses of each of the endpoints will be performed at the end of the 12-month treatment period and at the end of the follow-up period (24 months after the last patient was randomised and entered). As the analysis at 6 months is the one of primary interest, no adjustment will be made in the level of statistical significance for multiple testing in the analyses at 12 and 24 months.

The primary endpoints of incidence of breast event and PSA inhibition were analysed using models that fitted an appropriate dose response curve to measure the effect of tamoxifen dose. Secondary supportive analyses were also performed on these endpoints. These successively compared each of the tamoxifen treatment groups with the placebo group. For the endpoint of PSA inhibition and the secondary endpoints of incidence of gynaecomastia and breast pain, this supportive analysis employed an appropriate analysis of covariance model that allowed for any important prognostic factors. For the endpoints of incidence of gynaecomastia and incidence of breast pain, this supportive analysis employed a logistic model allowing for important prognostic factors. Statistical techniques to allow for multiple testing were employed in each of these supportive analyses. All other endpoints were summarised and not subject to formal statistical analysis.

Adverse events were to be summarised by treatment received, presenting the incidence of events using the generic terminology coding system MedDRA. Gynaecomastia and breast pain were not recorded as adverse events in this study as the incidence of these events were actively monitored for the efficacy analysis. Mean levels of liver function test data, changes

in blood lipid parameters and geometric mean plasma concentrations of tamoxifen; N-desmethyltamoxifen and R-bicalutamide were to be presented by treatment received.

Patient population

A total of 282 patients were randomised into the study from 27 centres in 4 countries UK, Canada, Norway and Finland). The first patient was randomised on 19 November 2002 and the last patient was randomised on 5 June 2003. All 282 patients received CASODEX 150 mg plus placebo or tamoxifen as randomised therapy at the dose shown in Table S1. The patient disposition on the data cut-off (5 December 2003) and inclusion in the primary endpoint ITT analyses are shown in Table S1. Of the patients who had withdrawn, 5 had died and 3 had reported disease progression. The demographic properties (Table S2) and baseline disease characteristics were well balanced. The minor anomalies in terms of age range were not considered relevant to the development of gynaecomastia or breast pain.

Table S1 Patient disposition and analysis populations at data cut off

Patient status	Number (%) of patients in each category CASODEX 150 mg plus tamoxifen at indicated dose					
	1.0 mg (N=58)	2.5 mg (N=47)	5.0 mg (N=48)	10.0 mg (N=34)	20.0 mg (N=35)	Placebo (N=60)
Included in breast-event ITT	58 (100)	45 (96)	47 (98)	34 (100)	34 (97)	60 (100)
Included in PSA inhibition ITT	58 (100)	44 (94)	47 (98)	34 (100)	34 (97)	60 (100)
Ongoing and taking:						
CASODEX and randomised treatment	45 (78)	36 (77)	36 (75)	27 (79)	26 (74)	42 (70)
CASODEX only: completed 1 yr dosing[a]	4 (7)	4 (9)	3 (6)	2 (6)	3 (9)	5 (8)
CASODEX only: unscheduled[b]	0	0	0	1 (3)	1 (3)	0
randomised treatment only	0	0	0	0	0	0
Taking no medication but remaining on study for follow-up only	4 (7)	2 (4)	6 (13)	4 (12)	1 (3)	7 (12)
Withdrawn from the study	5 (9)	5 (11)	3 (6)	0	4 (11)	6 (10)

[a] Patients were to stop treatment with tamoxifen after 1 year (yr) and continue with CASODEX alone for a further year, as described in the protocol.

[b] Patients who stopped taking tamoxifen but continued with CASODEX before completion of 1-year dosing period.

N, number randomised

Data derived from Table T1, Section 11

Table S2 Patient demographic properties

Demographic characteristic		CASODEX 150 mg plus tamoxifen at indicated dose					
		1.0 mg (N=58)	2.5 mg (N=47)	5.0 mg (N=48)	10.0 mg (N=34)	20.0 mg (N=35)	Placebo (N=60)
Sex (n and %)	Male	58 (100)	47 (100)	48 (100)	34 (100)	35 (100)	60 (100)
Age (years)	Mean (SD)	74 (6)	75 (7)	74 (7)	75 (5)	74 (7)	75 (7)
	Range	59 to 88	59 to 94	56 to 87	63 to 84	47 to 85	52 to 90
Race	Caucasian	58 (100)	46 (98)	48 (100)	33 (97)	35 (100)	60 (100)
(n and %)	Black	0	1 (2)	0	1 (3)	0	0
Weight (kg)	Mean (SD)	78 (11)	78 (12)	80 (12)	80 (10)	79 (12)	81 (10)
	Range	52 to 104	52 to 105	57 to 103	61 to 97	60 to 111	63 to 102
Height (cm)	Mean (SD)	172 (7)	171 (6)	172 (7)	173 (6)	171 (7)	172 (6)
	Range	160 to 187	159 to 188	157 to 191	160 to 186	156 to 187	159 to 182
Body mass	Mean (SD)	26 (3)	26 (4)	27 (4)	27 (3)	27 (3)	27 (3)
Index	Range	18 to 31	20 to 34	21 to 34	21 to 34	20 to 33	21 to 34
Gynae or breast pain	Present at entry	0	0	0	0	0	0
PSA (ng/ml)	Median (SD)	10 (40)	10 (26)	13 (24)	13 (67)	13 (23)	12 (15)
	Range	3 to 255	4 to 160	3 to 127	3 to 387	4 to 127	3 to 87

Gynae, gynaecomastia; PSA, prostate specific antigen
Data derived from Tables T5.2.1, T5.2.2, T5.3 and T6.7.1, Section 11.

Efficacy and pharmacokinetic results

Patient questioning showed that the co-administration of tamoxifen reduced the incidence of CASODEX related breast events (gynaecomastia and/or breast pain) in a dose dependent manner (Table S3). At the 20 mg tamoxifen dose only 12% of patients (4/34) experienced a breast event compared with 97% (58/60) in the CASODEX + placebo group. Protocol-defined, pair-wise comparisons showed that all doses of tamoxifen, except the 1 mg dose, were statistically superior to placebo. The results were confirmed by objective calliper measurements of the degree of gynaecomastia. Similar dose effects were noted for the secondary endpoints of incidence of breast pain alone and gynaecomastia alone and intensity of breast pain. Tamoxifen had no detrimental effect on CASODEX-induced PSA inhibition. At 6 months 93.1% of PSA was inhibited in the CASODEX + 20 mg tamoxifen group, compared with 90.3% inhibition in the CASODEX + placebo group.

Co-administration of tamoxifen at the highest dose (20 mg) had no clinically relevant effect on testosterone levels. Small, non-dose dependent increases in other sex hormones were seen relative to those seen with CASODEX + placebo. A trend to lower R-bicalutamide plasma concentrations with increasing tamoxifen dose was seen at 3 months but this was less apparent

at the 6-month time-point. The differences were small in relation to the variability observed between treatment groups and were considered to be of no clinical relevance.

Table S3 Incidence of breast event at months 3 and 6

	Number (%) of patients with a breast event CASODEX 150 mg plus tamoxifen at indicated dose					
Time-point	**1.0 mg (N=58)**	**2.5 mg (N=45)**	**5.0 mg (N=47)**	**10.0 mg (N=34)**	**20.0 mg (N=34)**	**Placebo (N=60)**
Month 3	39 (67.2)	18 (40.0)	19 (40.4)	6 (17.6)	3 (8.8)	54 (90.0)
Month 6	50 (86.2)	28 (62.2)	26 (55.3)	8 (23.5)	4 (11.8)	58 (96.7)

Data derived from Table T6.3.1, Section 11.

Safety results

The combination of CASODEX 150 mg and tamoxifen was well tolerated. Adverse event categories (AEs, SAEs, drug related AEs and AEs leading to discontinuations) were balanced across the treatment groups (Table S4). Between 66% and 79% of patients in each of the treatment groups experienced at least 1 adverse event. SAEs ranged from 7% to 17% and fatal events were sporadic. CASODEX 150 mg was well tolerated with all doses of tamoxifen such that the adverse events leading to withdrawal were reported more frequently in the CASODEX + placebo group (13%). The most common adverse events in descending order of frequency were: flushing, fatigue, dizziness, constipation, pruritus, asthenia, diarrhoea, erectile dysfunction, pain in extremity, and arthralgia (Table S5). With the exceptions of dizziness and flushing the incidence of common adverse events was consistent with the known safety profile of CASODEX 150 mg therapy and there was no indication of exacerbation due to co-administration with tamoxifen. Flushing was the most common adverse event and there appeared to be a moderate increase with increased tamoxifen dose. Dizziness was reported by 3% of patients in the CASODEX + placebo group and this increased in 3 of the active treatment groups, the greatest being 14% in the CASODEX + 20 mg tamoxifen arm. However, there was no clear dose-related trend and none of the patients who received CASODEX + 10 mg tamoxifen reported dizziness. Nonetheless, 2 patients in the CASODEX + 20 mg tamoxifen group withdrew from tamoxifen (and CASODEX in 1 case) due to dizziness. Dizziness, or light-headedness, is an expected effect of tamoxifen therapy. Fatigue, constipation, and pain in extremity appeared to be reduced in incidence or intensity at the higher tamoxifen doses.

Liver function analyses found that of those patients with normal values at baseline, 2 had a clinically significant increase in LFTs (1 each in the 1 mg and 5 mg tamoxifen groups) and both were withdrawn from treatment. One patient (placebo group) who had baseline AST and ALT values that were higher than the reference range was also withdrawn from treatment due to LFT changes. The incidence of LFT abnormalities seen in this study are in accordance with that reported previously with CASODEX 150 mg use.

Lipid analysis showed minor (generally favourable) changes that were not considered to be clinically significant and had no overt relation to tamoxifen dose.

Table S4 Number (%) of patients who had an adverse event in any category (safety analysis set)

Adverse event category	Number (%) of patients in each category [a] CASODEX 150 mg plus tamoxifen at indicated dose											
	1.0 mg (N=58)		2.5 mg (N=47)		5.0 mg (N=48)		10.0 mg (N=34)		20.0 mg (N=35)		Placebo (N=60)	
Any adverse event	38	(66)	31	(66)	37	(77)	27	(79)	27	(77)	45	(75)
Serious adverse event	4	(7)	6	(13)	6	(13)	3	(9)	4	(11)	10	(17)
Serious adverse event leading to death	0		2	(4)	1	(2)	0		0		1	(2)
Serious adverse event not leading to death	4	(7)	5	(11)	6	(13)	3	(9)	4	(11)	9	(15)
Adverse events leading to withdrawal from:												
CASODEX	4	(7)	1	(2)	5	(10)	2	(6)	2	(6)	8	(13)
Tamoxifen	4	(7)	1	(2)	5	(10)	3	(9)	3	(9)	8	(13)
Study	1	(2)	0		0		0		2	(6)	3	(5)
Adverse events considered related to:												
CASODEX	20	(35)	11	(23)	18	(38)	16	(47)	10	(29)	15	(25)
Tamoxifen	14	(24)	6	(13)	13	(27)	10	(29)	8	(23)	12	(20)
Patients with no AE	20	(35)	16	(34)	11	(23)	7	(21)	8	(23)	15	(25)

[a] Patients may appear in more than 1 category.
N, number of patients; AE, adverse event
Data derived from Table T8.1, Section 11

Table S5 Incidence and intensity of common adverse events

Preferred term [a]	Number (%) of patients with each adverse event at the indicated intensity [b] CASODEX 150 mg plus tamoxifen at indicated dose																	
	1.0 mg (N=58)			2.5 mg (N=47)			5.0 mg (N=48)			10.0 mg (N=34)			20.0 mg (N=35)			Placebo (N=60)		
	Mild	Mod	Sev	Mild	Mod	Sev	Mild	Mod	Sev	Mild	Mod	Sev	Mild	Mod	Sev	Mild	Mod	Sev
Flushing	4 (7)	0	0	3 (6)	0	0	4 (8)	3 (6)	0	7 (21)	3 (9)	0	4 (11)	1 (3)	0	3 (5)	0	0
Fatigue	1 (2)	3 (5)	1 (2)	2 (4)	0	0	2 (4)	1 (2)	0	3 (9)	1 (3)	0	1 (3)	0	0	4 (7)	2 (3)	1 (2)
Dizziness	1 (2)	1 (2)	0	4 (9)	0	0	2 (4)	0	0	0	0	0	1 (3)	3 (9)	1 (3)	2 (3)	0	0
Constipation	0	1 (2)	0	3 (6)	0	0	1 (2)	0	0	2 (6)	0	0	0	1 (3)	0	3 (5)	3 (5)	0
Pruritus	1 (2)	1 (2)	0	0	1 (2)	0	1 (2)	1 (2)	0	2 (6)	0	0	0	0	0	3 (5)	1 (2)	0
Asthenia	0	0	0	3 (6)	0	1 (2)	1 (2)	2 (4)	0	1 (3)	0	0	0	0	1 (3)	0	1 (2)	0
Diarrhoea	1 (2)	1 (2)	0	0	0	1 (2)	2 (4)	1 (2)	0	0	0	1 (3)	1 (3)	1 (3)	0	1 (2)	0	0
Erectile dysfunction	1 (2)	1 (2)	0	1 (2)	1 (2)	0	1 (2)	0	0	2 (6)	2 (6)	0	0	0	0	0	1 (2)	0
Arthralgia	1 (2)	0	1 (2)	1 (2)	1 (2)	0	2 (4)	0	0	0	2 (6)	0	0	1 (3)	0	0	0	0
Pain in extremity	1 (2)	0	0	1 (2)	1 (2)	0	1(2)	0	0	0	0	0	0	0	0	3 (5)	1 (2)	1 (2)
Angina pectoris	0	1 (2)	2 (3)	0	1 (2)	0	0	1 (2)	0	0	0	0	0	0	1 (3)	1 (2)	1 (2)	0

[a] Adverse events are arranged in descending order of overall frequency (data from Table T8.2.2)

[b] Intensity data derived from Table T8.2.4, Section 11

Mod, moderate; Sev, Severe