Drug product:	NOLVADEX, ARIMIDEX	**SYNOPSIS**	
Drug substance(s):	Tamoxifen, anastrozole		
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A randomised, double blind, parallel group, multicentre trial comparing the efficacy and tolerability either of NOLVADEX® or of ARIMIDEX® or of Placebo in preventing the development (worsening) of gynecomastia in patients being treated with CASODEX® 150 mg monotherapy for prostate cancer

Co-ordinating investigator

Study centre(s)

Italy 15 centres (enrolling patients).

Publications

Conti G, Cretarola E, Boccardo F, Battaglia M, Di Tonno P, Bertaccini A, et al. Tamoxifen is safe and effective in preventing gynecomastia and breast pain induced by bicalutamide monotherapy of prostate cancer and doesn't alter treatment efficacy: Eur Urol 2004; 3: S58.

Boccardo F, Rubagotti A, Battaglia M, et al. Evaluation of tamoxifen and anastrozole in the prevention of gynecomastia and breast pain induced by bicalutamide monotherapy of prostate cancer: J Clin Oncol 2005; 23: 808-815.

Study dates		**Phase of development**
First subject enrolled	23 November 2000	Therapeutic exploratory (II)
Last subject enrolled	13 December 2002	
Data cut-off	29 February 2004	

Objectives

Primary:

- To evaluate the effect of NOLVADEX or ARIMIDEX on the development or worsening of gynaecomastia and/or breast pain (breast event) in patients being treated with CASODEX 150 mg once daily for locally advanced prostate cancer.

Secondary:

- To describe the extent of gynaecomastia and breast pain by treatment group
- To evaluate the therapeutic effectiveness of CASODEX in combination either with NOLVADEX or with ARIMIDEX on prostate cancer as expressed by PSA inhibition
- To determine the pharmacodynamic profile of CASODEX in combination either with NOLVADEX or with ARIMIDEX
- To assess the effects of NOLVADEX and ARIMIDEX, each in combination with CASODEX, on sexual potency
- To assess the effects of NOLVADEX and ARIMIDEX, each in combination with CASODEX, on quality of life
- To evaluate whether the pharmacokinetic profile of CASODEX might be modified by the combination either with NOLVADEX or with ARIMIDEX
- To evaluate the safety profile of NOLVADEX and ARIMIDEX each in combination with CASODEX.

Study design

Randomised, three-arm, double-blind, multicentre, comparative trial.

Patients were randomised to receive:

- CASODEX plus NOLVADEX plus ARIMIDEX placebo
- CASODEX plus NOLVADEX placebo plus ARIMIDEX
- CASODEX plus NOLVADEX placebo plus ARIMIDEX placebo

The blinded treatment was continued for 48-weeks after which patients entered a follow-up period and received a standard hormonal therapy or continued with unblinded CASODEX 150 mg alone for a further 48-week period (protocol reported 46 weeks as refuse).

All patients were to be followed for 2 years post-randomisation.

Target subject population and sample size

The target population comprised patients with locally advanced adenocarcinoma of the prostate gland, but with no evidence of distant metastasis. Eligible patients included those who had received therapy of curative intent (eg, radical prostatectomy and/or radiotherapy). Patients already on treatment either with an LHRH analogue alone or with an LHRH analogue combined with an antiandrogen for their disease could be recruited provided that: a) antiandrogenic treatment had started less than 8 weeks before; b) patients fulfilled all other requirements before the start of androgen-suppressive treatment; c) patients were fully sexually active before androgen-suppressive treatment and desired their sexual activity to be restored. Patients were to have had no or only mild pre-existing gynaecomastia or breast pain.

The study intended to recruit 141 patients to be allocated in groups of 47 patients to the combination of NOLVADEX 20 mg and placebo or ARIMIDEX 1 mg and placebo, with the remaining 47 patients to receive placebo. All patients were to receive unblinded CASODEX 150 mg.

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

Bicalutamide (CASODEX) 150 mg orally one tablet daily and either tamoxifen (NOLVADEX) 20 mg orally one tablet daily or matching placebo or anastrozole (ARIMIDEX) 1 mg orally one tablet daily or matching placebo.

Batch numbers were:

a) for double blind treatment

- PO7500001088 expiry date 02/2002
- PO7500003205 expiry date 01/2004
- PO7500003208 expiry date 01/2004

b) for unblinded treatment

- PO7500002758 expiry date 08/2004
- PO718 expiry date 04/2006

Duration of treatment

NOLVADEX 20 mg or ARIMIDEX 1 mg or placebo once daily were to be co-administered with CASODEX 150 mg once daily for 48 weeks. This was the blinded treatment period.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable:
  - Incidence of breast event at the end of double blind period
- Secondary variables:
  - Incidence of breast event during the whole study period
  - Time to breast event, to gynecomastia and to breast pain during the double blind treatment period and during the whole study
  - Percentage of subjects with PSA levels in normal range, with ≥ 80% and ≥ 50% reduction in baseline PSA level at the end of double blind period and during the whole study period
  - Change from baseline in hormonal parameters: luteinising hormone, follicle stimulating hormone, testosterone, prolactin, androstenedione, 17β-oestradiol, oestrone, sex hormone binding globulin, insulin growth factor, and insulin growth factor binding proteins
  - Change from baseline in mean scores of quality of life and sexual potency
  - Plasma concentrations of R-bicalutamide, S-bicalutamide, anastrozole, tamoxifen and N-desmethyltamoxifen.

Safety

Incidence of adverse events.

Statistical methods

The primary analyses were performed on an intention-to-treat (ITT) basis and included all patients taking at least a dose of study treatment who did not have gynaecomastia at baseline and had at least 1 assessment in the period that included the day after randomisation to the 48-week time-point.

To determine if there was an overall treatment effect, a chi-square test was carried out to compare the incidence (worsening) of breast events and of PSA response across all 3 treatment groups. When the chi-square showed statistically significant differences, pair-wise comparisons were performed repeating the chi-square test, and the odds ratio with a 95% confidence interval were calculated.

The curves of time free from breast event, time free from gynecomastia and time free from breast pain were estimated according to Kaplan-Meier method. They were compared through

the log-rank test. 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 7.0 (Medical Dictionary for Regulatory Activities). Gynaecomastia and breast pain were not considered as adverse events in this study as the incidence of these events was actively monitored for the efficacy analysis.

Subject population

The enrollment of 141 subjects was originally planned. However a higher than expected incidence of breast events and a published report suggesting that ARIMIDEX might be less effective than NOLVADEX in the prevention of gynaecomastia, led to enrollment closure on 31 December 2002 when 114 Caucasian patients from 15 Italian centres had been randomised. The first patient was enrolled on 23 November 2000 and the last patient was enrolled on 13 December 2002. Of these 114 patients, 112 received at least one dose of CASODEX 150 mg plus placebo or NOLVADEX or ARIMIDEX as randomised therapy.

The patient disposition and inclusion in the primary endpoint ITT analyses are shown in Table S1.

Table S1 Subject population and disposition

	NOLVADEX		ARIMIDEX		Placebo		Total	
N randomised (planned)	37	(47)	37	(47)	40	(47)	114	(141)
No drug intake N (%)	-	-	1	(2.7)	1	(2.5)	2	(1.8)
N (%) dosed	37	(100)	36	(97.3)	39	(97.5)	112	(98.2)
No data post-baseline N (%)	-	-	-	-	1	(2.5)	1	(0.9)
N (%) analysed for safety[a]	37	(100)	36	(97.3)	38	(95.0)	111	(97.4)
Gynaecomastia at baseline N (%)	5	(13.5)	1	(2.7)	1	(2.5)	7	(6.1)
N (%) analysed for efficacy (ITT)	32	(86.5)	35	(94.6)	37	(92.5)	104	(91.2)
N (%) withdrawn from double blind treatment	3	(8.1)	8	(21.6)	10	(25.0)	21	(18.4)

[a] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing
ITT=Intention to treat; N=Number
Data derived from Tables 11.1.1, 11.1.2, 11.1.3, Section 11.

The demographic properties (Table S2) and baseline disease characteristics were well balanced. The population was wholly representative of patients with locally advanced prostate cancer. The minor anomalies in terms of age range were not considered relevant to the development of breast events.

Table S2 Demographic and clinical characteristics (safety population)

		NOLVADEX		ARIMIDEX		Placebo	
Gender	N (%) male	37	(100)	36	(100)	38	(100)
Age (years)	Mean (SD)	71	(6)	71	(8)	72	(7)
	Range	58 to 83		56 to 87		53 to 87	
Weight (kg)	Mean (SD)	78	(11)	80	(9)	79	(15)
	Range	61 to 105		62 to 97		54 to 137	
PSA (ng/ml) (ITT population)	Median (SD)	2.7	(23.9)	6.6	(47.1)	5.6	(22.0)
	Range	0.33 to 106		0.009 to 272		0.19 to 106	
Gleason grade* (differentiated) N (%)	Well (2 to 4)	1	(2.7)	3	(8.3)	4	(10.5)
	Moderate (5 or 6)	13	(35.1)	13	(36.1)	14	(36.8)
	Poor (7 to 10)	21	(56.7)	18	(50.0)	16	(42.1)
	Missing	1	(2.7)	2	(5.6)	4	(10.5)
T stage	T1	1	(2.7)	1	(2.8)	0	-
N (%)	T2	8	(21.6)	6	(16.7)	8	(21.0)
	T3	16	(43.2)	20	(55.5)	21	(55.2)
	T4	1	(2.7)	1	(2.8)	0	-
	Tx	2	(5.4)	1	(2.8)	3	(7.9)
	Missing	9	(24.3)	7	(19.4)	6	(15.8)
N stage	N0	22	(59.5)	20	(55.6)	20	(52.6)
N (%)	N1	0	-	1	(2.8)	1	(2.6)
	Nx	4	(10.8)	5	(13.9)	8	(21.1)
	Missing	11	(29.7)	10	(27.8)	9	(23.7)
Treatment of primary tumour N (%)	Prostatectomy	18	(48.6)	12	(33.3)	15	(39.5)
	Radiotherapy	5	(13.5)	5	(13.9)	5	(13.2)
	LHRH	10	(27.0)	6	(16.7)	7	(18.4)

LHRH, luteinising hormone releasing hormone; PSA, prostate specific antigen; TNM tumor nodes metastasis classification
*A patient of NOLVADEX group reported 1 as Gleason Grade score and was excluded
Data derived from Tables 11.1.4, 11.1.6, 11.1.8, 11.2.18, 11.3.8.4, Section 11.

Efficacy and pharmacokinetic results

Calliper and ultrasound measurements and patient questioning showed that the co-administration of NOLVADEX with CASODEX 150 mg reduced the incidence of breast events. During double blind treatment only 9.4% of patients (3/32) on NOLVADEX

experienced a breast event compared with 89.2% (33/37) in the CASODEX + placebo group (odds ratio NOLVADEX vs placebo for having a breast event 0.0125, 95% confidence interval 0.0026 to 0.0607, p<0.0001). ARIMIDEX also reduced the incidence of the primary outcome (22/35, 62.9%, odds ratio ARIMIDEX vs placebo 0.2051, 95% confidence interval 0.0591 to 0.7115, p=0.0086). However ARIMIDEX determined a 16-fold increase in the risk of breast event when compared to NOLVADEX (odds ratio ARIMIDEX vs NOLVADEX 16.359, 95% confidence interval 4.148 to 64.523, p<0.0001).

Table S3 Incidence of breast events at study time points

	Number (%) of patients with breast event							
Time-point	**NOLVADEX (n=32)**		**ARIMIDEX (n=35)**		**Placebo (n=37)**		**Total (n=104)**	
Double blind treatment period	3	(9.4)	22	(62.9)	33	(89.2)	58	(55.8)
Whole study period	14	(43.8)	22	(62.9)	34	(91.9)	70	(67.3)

Data derived from Tables 11.2.2, 11.2.3, Section 11.

The results of the primary analysis were supported by the secondary efficacy end points and indirectly confirmed during the follow-up period by the substantial increase in the rate of breast events observed following withdrawal of NOLVADEX.

NOLVADEX had no detrimental effect on CASODEX-induced PSA inhibition. At 48 weeks 93.8% of patients showed PSA within normal ranges in the NOLVADEX group, compared with 86.5% in the placebo group. Conversely, PSA inhibition was observed in a lower proportion of patients in the ARIMIDEX arm (78.8%).

Co-administration of NOLVADEX had no clinically relevant effect on testosterone levels, while ARIMIDEX was associated with mild increases in free testosterone. 17βestradiol levels moderately increased relative to placebo on NOLVADEX and were unchanged on ARIMIDEX.

Co-administration of both NOLVADEX and ARIMIDEX had no detrimental effects on quality of life; a trend to improvement in sexual functioning scores in particular was observed in the NOLVADEX arm.

In the subset of 7 patients from each treatment group who had plasma concentrations measured, concentrations of R-bicalutamide and S-bicalutamide were similar in all treatment arms.

Safety results

The incidence of adverse events (AEs, SAEs, drug related AEs and AEs leading to discontinuations) was similar across the treatment groups (Table S4). Between 27% and 44% of patients in each of the treatment groups experienced at least 1 adverse event. SAEs ranged from 11% to 19% and fatal events were sporadic. CASODEX 150 mg was well tolerated with both NOLVADEX and ARIMIDEX such that the adverse events leading to withdrawal were not different in the CASODEX + placebo group (5%).

Table S4 Number (%) of subjects 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 subjects who had an adverse event in each category[a]							
	NOLVADEX (N=37)		ARIMIDEX (N=36)		Placebo (N=38)		Total (n=111)	
Any adverse events	10	(27.0)	16	(44.4)	12	(31.6)	38	(34.2)
Serious adverse events	5	(13.5)	7	(19.4)	4[b]	(10.5)	16	(14.4)
Serious adverse events leading to death	-	-	1	(2.8)	1	(2.6)	2	(1.8)
Serious adverse events not leading to death	5	(13.5)	6	(16.7)	4[b]	(10.5)	15	(13.5)
Discontinuations of study treatment due to adverse events	1	(2.7)	2	(5.6)	2	(5.3)	5	(4.5)
Adverse events considered related to study drug	2	(5.4)	3	(8.3)	5	(13.2)	10	(9.0)
Patients with no AE	27	(73.0)	20	(55.6)	26	(68.4)	73	(65.8)

a Subjects with multiple events (excluded gynecomstia and breast pain) in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

b Subject 66 in placebo group died and reported other serious adverse events not leading to death.

Data derived from Table 11.3.2.4, Section 11.

No adverse event was reported by more than 2 subjects in any treatment group (Table S5). The most common adverse events in descending order of frequency were: urinary tract infections, dizziness, nipple pain, flushing, and acute myocardial infarction. The incidence of common adverse events was similar to placebo and there was no indication of exacerbation due to co-administration with NOLVADEX or ARIMIDEX.

Table S5 **Number (%) of subjects with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)**

Preferred term	NOLVADEX (n=37)		ARIMIDEX (n=36)		Placebo (n=38)		Total (n=111)	
Urinary tract infection	-	-	2	(5.6)	2	(5.3)	4	(3.6)
Dizziness	1	(2.7)	2	(5.6)	-	-	3	(2.7)
Nipple pain	-	-	1	(2.8)	2	(5.3)	3	(2.7)
Hot flush	1	(2.7)	1	(2.8)	1	(2.6)	3	(2.7)
Acute myocardial infarction	1	(2.7)	1	(2.8)	1	(2.6)	3	(2.7)

[a] Events with a total frequency of ≥2% across all treatment groups are included in this table.
Data derived from Table 11.3.2.1, Section 11.