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PROPRIETARY DRUG NAME[®]/GENERIC DRUG NAME: Exemestane

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: NCT00036270 (USA) and NCT00279448 (France)

PROTOCOL NO.: 971-ONC-0028-081 (A5999001)

PROTOCOL TITLE: Randomized Phase III Study of Exemestane for 5 Years Versus Tamoxifen for 2.5-3 Years Followed by Exemestane for A Total of 5 Years as Adjuvant Therapy for Postmenopausal, Receptor Positive, Node Negative or Node Positive Breast Cancer Patients

Study Center(s): Available upon request: this was a multi-center study, performed under 7 protocols: USA (971-ONC-0028-081), France (EXEAPO-0028-118), Germany (EXEAPO-0028-119), The Netherlands and Belgium (EXEAPO-0028-121), UK and Ireland (EXEAPO-0028-122), Greece (CTN-971-ONC-0028-120), and Japan (IG-ARM-2004-001)

Study Initiation and Completion Dates: 30 January 2002 – 03 November 2008

Phase of Development: Phase 3

Study Objectives: This interim study report presents data on the first co-primary objective of the entire TEAM study.

There are 2 co-primary objectives in this study:

1. To determine whether adjuvant treatment with exemestane, 25 mg once daily improves the Disease Free Survival (DFS) of postmenopausal, receptor positive, node negative or node positive breast cancer patients, compared with adjuvant tamoxifen, 20 mg once daily at 2.75 years.
2. To determine whether adjuvant treatment with exemestane, 25 mg once daily, improves the DFS (Disease Free Survival) of postmenopausal, receptor positive, node negative or node positive breast cancer patients at 5 years compared with adjuvant tamoxifen, 20 mg daily for 2.5-3 years, followed by treatment with exemestane, 25 mg once daily for a total of 5 years.

Secondary objectives of this study include comparison of Overall Survival (OS), time to relapse, time to new primary breast cancer, rate of new primary cancers other than breast, and the relative safety profiles

METHODS

Study Design: Postmenopausal, receptor positive, node negative or node positive breast cancer subjects were randomized to receive either 25 mg of exemestane daily for 5 years versus tamoxifen 20 mg daily for 2.5-3 years followed by 2.5-2 years of exemestane, for a total of 5 years, either as their only adjuvant therapy, or following completion of adjuvant chemotherapy and/or radiation therapy. The study medication was provided in an open-label fashion. Subjects were to be followed for a minimum of 5 years for DFS, OS, safety profiles, and the incidence of new primary breast cancers.

After randomization, subjects were to be seen by the physician every 3 months during the first year. Thereafter, during Years 2 to 5, subjects were to be seen by the physician every 6 months. See the protocols and amendments for variations in procedures and visit timings for each country.

At each visit, complaints and adverse effects were to be recorded, a physical examination was to be performed, and concomitant medications were to be recorded. Blood chemistry and hematology were to be assessed according to local policy. Table 1 presents a general study flowchart for all study centers.

Table 1. Study Flowchart

Year	1			2			3			4			5			Follow-up
Visit Month	1 0	2 3	3 6	4 9	5 12	6 18	7 24	8 30	9 36	10 42	11 48	12 54	13 60			
Medical History	X															
Clinical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Hematology and Biochemistry	X															
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Variations occurred between each country protocol.

Number of Subjects (Planned and Analyzed):

Planned: 9300 subjects.

Analyzed: 9766 subjects in the intention-to-treat (ITT) population (9779 randomized subjects).

Diagnosis and Main Criteria for Inclusion: The study population consisted of postmenopausal women diagnosed with resectable breast cancer, meeting all of the following eligibility criteria.

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1. Histologically/cytologically confirmed adenocarcinoma of the breast, followed by adequate surgical resection and/or radiotherapy, and/or adjuvant chemotherapy, if indicated.
2. ER and/or progesterone receptor (PgR) status positive (as defined by local institutional laboratory definition)
3. Post-menopausal
4. Adequate hematological, renal and hepatic function
5. Accessible for follow-up for the duration of the study.
6. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2.
7. Subjects must have been informed of the investigational nature of the study and signed an informed consent form.

Study Treatment: Randomization was done within each study, using stratification factors specific to that study. All studies, with the exception of Germany, used prior chemotherapy (yes/no) as a stratification factor; the UK used none, anthracyclines, taxanes, other and the USA used none, CMF, anthracyclines, taxanes. Four studies used center as a stratification factor.

Subjects were to be confirmed as being eligible for randomization into the study by the country data center and randomized in a 1:1 ratio to 1 of the following treatments:

- Exemestane (Aromasin[®]) 25 mg once daily for a minimum of 5 years.
- Tamoxifen, 20 mg once daily, until completing at least 2.5 years therapy. Before completing 3 years of tamoxifen, subjects were switched to exemestane and then were to complete a total of 5 years endocrine therapy.

Efficacy Evaluations: The following were to be completed before the subject received the first dose of study treatment.

- Subjects were to be screened against the inclusion and exclusion criteria.
- A signed consent form was to be obtained.
- A complete medical history was to be obtained.
- Hematology and blood chemistry tests were to be performed within the 10 weeks prior to randomization according to local policy.
- Documentation of concomitant medication.
- Metastatic screen: Chest X-ray/mammography was required. Additional tests/investigations (eg, liver ultrasound or computed tomography [CT] scans, bone scans), if clinically indicated (at the investigator's discretion) were to be completed prior to any adjuvant treatment.
- Baseline Quality of Life (QoL) questionnaire (Fact-B) and side effect questionnaire were to be completed either the day that treatment started (prior to treatment) or any time within 4 weeks prior to the start of study treatment. This was only required if the subject was enrolled in the QoL sub-study.

- Human epidermal growth factor receptor 2 gene (Her-2/neu) status was to be recorded (if available).

Evaluations During Treatment : The evaluations listed below were to be performed every 3 months during the first year of treatment. In Years 2, 3, 4 and 5 subjects were to be seen at least yearly and every 6 months in some countries.

- A complete medical history (relevant surgical resections, conditions that need medical intervention, like cardiac ischemia or arrhythmia, chronic obstructive pulmonary disease (COPD), gastric ulcer etc.).
- A brief clinical examination, including vital signs and body weight.
- Every 6 months, complete blood count with differential and platelet count and blood chemistry (creatinine, bilirubin, aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT], calcium and alkaline phosphatase [ALP] and glucose).
- Concomitant medications (description of other medication prescribed for more than 7 days) were to be registered and adverse events (AEs) were to be recorded.
- Drug Administration Records were to be reviewed at each visit to determine subject compliance.
- Chest X-ray yearly.
- Other tests were at the discretion of the investigator.
- During the first year only (at Months 3, 6, 9, and 12) the QoL questionnaire (FACT-B) and side effect questionnaire were to be completed.

Trial Events (Endpoints): Important information, relevant for the study (unforeseen circumstances that may have led to changes in interpretation of the results, for instance cause of death).

Events that were to be recorded included:

- Ipsilateral breast recurrence in a patient with lumpectomy;
- Chest-wall or axillary nodal recurrence in a patient with a mastectomy (locoregional recurrence);
- Distant relapse (including supraclavicular nodes) at any site;
- Contralateral breast cancer (new primary);
- Breast cancer death;
- Other second malignancies (eg, uterine, colon cancer);
- Death from any cause.

Follow-Up: Subjects who remained on study were to be followed every 3 months during the first year and every 6 months during years 2-5. Subjects who were **off study treatment** (eg,

due to toxicity, relapse, or any other reason) only needed to be followed up once yearly. All subjects were to have long-term follow-up, irrespective of whether they were withdrawn from treatment prematurely.

Safety Evaluations: The investigator obtained and recorded on the CRF/DCT all observed or volunteered AEs. The severity of the events was assessed using National Cancer Institute Common Toxicity Criteria (NCI CTC) Version 2.0, and the relationship to study treatment was reported as judged by the investigator. AEs included adverse drug reactions, illnesses with onset during the study, and exacerbation of previous illnesses. Additionally, the investigator recorded as AEs any clinically significant changes in physical examination findings and abnormal objective test findings (eg, electrocardiogram [ECG], laboratory, etc).

For all AEs, the investigator pursued and obtained information adequate to determine both the outcome of the AE and whether it met the criteria for classification as a serious adverse event (SAE). If the AE or its sequelae persisted, follow-up was required until resolution or stabilization occurred at a level acceptable to the investigator and sponsor.

Statistical Methods: There were two co-primary endpoints: (1) comparison of DFS of adjuvant exemestane versus tamoxifen at 2.75 years and (2) DFS comparison of 5 years of adjuvant exemestane versus sequential treatment with exemestane followed by tamoxifen for a total of 5 years of therapy.

The sample size estimate was based on both co-primary endpoints. To maintain an overall α of 0.05, two adjustments were made. First, based on a correlation between the test statistics of the 2 co-primary endpoints of 0.75, a nominal α of 0.0302 was used for each of the endpoints separately. Second, accounting for 1 planned interim analysis, the levels of significance at the interim and final analyses for the first co-primary endpoint were 0.0012 and 0.0298, respectively. Assuming a hazard ratio (HR) of 1.28, 723 DFS events were required to achieve 87% power to detect statistically significant differences in DFS with a two-sided significance level of 0.0302, requiring a sample size of 9300 subjects (4650 in each arm).

DFS was defined as the time from randomization to the earliest documentation of disease relapse or death from any cause. Disease relapse was defined as primary tumor recurrence (locoregional or distant) and ipsilateral/contralateral breast cancer (CBC). Intercurrent death was defined as death without disease relapse. Secondary endpoints were overall survival, RFS, defined as all breast events minus deaths without relapse, time to CBC, and occurrence of new primary cancer other than breast cancer. Time to distant disease was included as an exploratory analysis. Efficacy analyses were performed on the ITT population. All subjects were censored at 2.75 years post-randomization, the midpoint of the switching window. A pre-planned supportive analysis censored subjects at treatment discontinuation, at switch, or at 2.75 years (whichever occurred first). This analysis is referred to as DFS on study drug.

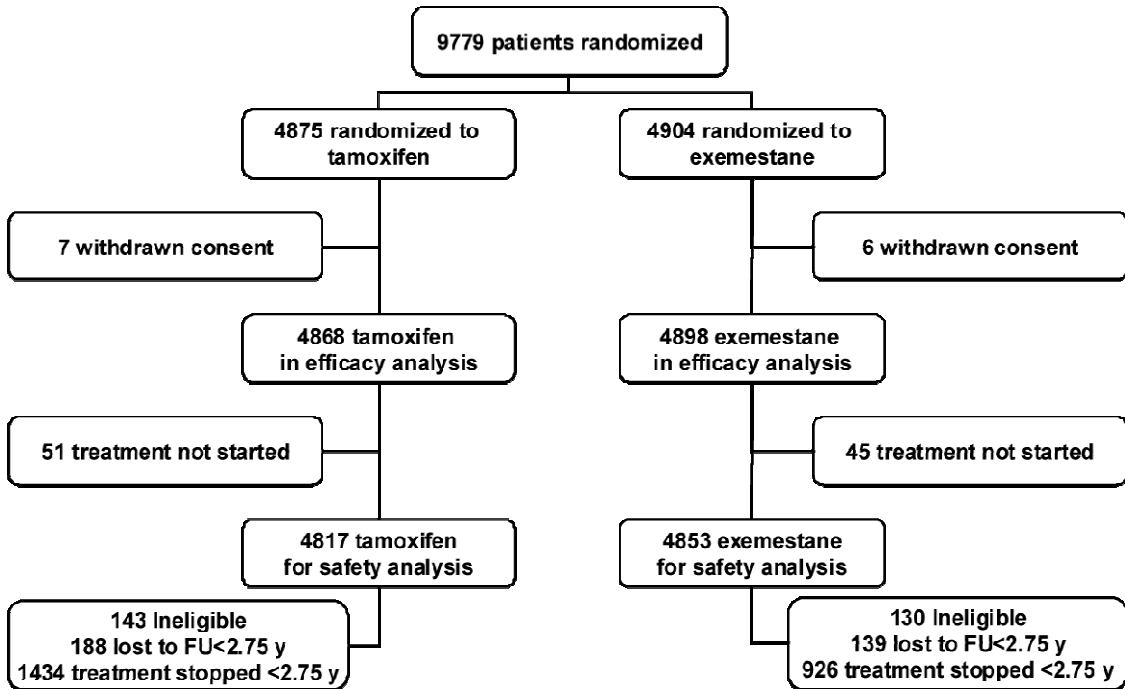
Subjects receiving ≥ 1 dose of study drug were included in safety/tolerability analyses. All AEs (worst ever by subject) occurring < 2.5 years post-randomization were reported; AEs occurring > 30 days after discontinuation were censored unless the AE was treatment related or graded as severe, life threatening, or fatal.

All tests were two-sided, and comparisons of efficacy endpoints were performed using log-rank tests stratified by study with additional stratification factors nested in each study. Stratification factors included the prognostic factors nodal status (positive/negative), PgR status (positive/negative), and adjuvant chemotherapy (yes/no). Kaplan-Meier estimates of efficacy endpoints were calculated for each treatment arm. All HRs were based on stratified Cox regression using the same stratification factors as the log-rank tests. The cumulative incidence of time to first distant metastasis was calculated accounting for death as competing risk. The Pearson chi-square test or Fisher exact test were used to test for differences in proportions.

RESULTS

Subject Disposition and Demography: The subject disposition is summarized in Figure S1. Of 9779 randomized subjects (1230 in France, 1471 in Germany, 207 in Greece, 184 in Japan, 2753 in the Netherlands, 414 in Belgium, 1275 in the United Kingdom/Ireland, and 2232 in the United States) 13 withdrew consent before treatment, leaving 9766 subjects in the ITT population. Of the subjects included in the ITT population, 273 (2.8%) were deemed ineligible for the following reasons: bilateral tumors (n=23), received neoadjuvant chemotherapy (n=10), distant metastases (n=6), ER negative/PgR negative tumors (n=13), enrolled >10 weeks after surgery/chemotherapy (n=46), history of previous breast cancer (n=27) or other cancer types <5 years before study (n=25), and other/unknown reasons (n=123). Ninety-six subjects (51 tamoxifen, 45 exemestane) did not receive treatment and were excluded from safety analyses but not from primary efficacy analyses. The median and maximum follow-up time for this analysis was 2.75 years; 86% of subjects had 2.75 years of follow-up.

Figure S1. Subject Disposition



Baseline characteristics were similar between the 2 treatment groups (Table S2). The majority of subjects in both treatment groups were ER positive (98% in both groups) and/or PgR positive (74% and 75% in the tamoxifen and exemestane groups, respectively).

Of 4868 subjects randomized to exemestane arm (switch therapy arm), 754 (15.5%) switched early (before completing 2.5 years of tamoxifen treatment), and 1363 (28.0%) switched after completing between 2.5 and 2.75 years of tamoxifen treatment, at which point all subjects were censored for this analysis.

Table S2. Demography and Baseline Characteristics

	Tamoxifen (N=4868)	Exemestane (N=4898)
Mean (SD) age (years)	64 (9)	65 (9)
Age groups, n (%)		
<50 years	160 (3)	171 (3)
50–59 years	1508 (31)	1509 (31)
60–69 years	1895 (39)	1836 (37)
≥70 years	1305 (27)	1382 (28)
Histologic grade, n (%)		
G1 (well)	834 (19)	843 (19)
G2 (moderate)	2362 (53)	2433 (54)
G3–G4 (poor)	1232 (27)	1206 (27)
Gx (unknown)	55 (1)	61 (1)
Missing	385 (8)	355 (7)
Median (range) largest tumor diameter, mm	18 (0–180)	18 (1–110)
Tumor stage, n (%)		
T0 (no evidence of primary tumor)	1 (<1)	1 (<1)
Tis (carcinoma in situ)	2 (<1)	2 (<1)
T1 (≤2 cm)	2848 (59)	2843 (58)
T2 (>2 cm and ≤5 cm)	1763 (36)	1828 (37)
T3 (>5 cm)	174 (4)	161 (3)
T4 (any size)	70 (1)	51 (1)
Tx (not assessable)	8 (<1)	12 (<1)
Missing	2 (<1)	0 (0)
Nodal stage, n (%)		
N0	2555 (52)	2558 (52)
N1–3	2279 (47)	2306 (47)
Not assessed or unknown	34 (1)	34 (1)
ER status, n (%)		
Positive	4768 (98)	4815 (98)
Negative	98 (2)	78 (2)
Not assessed or missing	2 (<1)	5 (<1)
PgR status, n (%)		
Positive	3618 (74)	3681 (75)
Negative	863 (18)	861 (18)
Not assessed or missing	387 (8)	356 (7)
ER+ and/or PgR+, n (%)	4859 (99.8)	4887 (99.8)
Most extensive surgery, n (%)		
Mastectomy	2183 (45)	2148 (44)
Wide local excision	2680 (55)	2744 (56)
None or unknown	5 (<1)	6 (<1)
Months from surgery to HT initiation, n (%)		
<3	2546 (53)	2546 (52)
3–6	1295 (27)	1367 (28)
≥6	976 (20)	939 (19)
Unknown	51 (1)	46 (1)
Received radiotherapy before/during study, n (%)	3314 (69)	3376 (70)
Received prior chemotherapy, n (%)	1743 (36)	1774 (36)

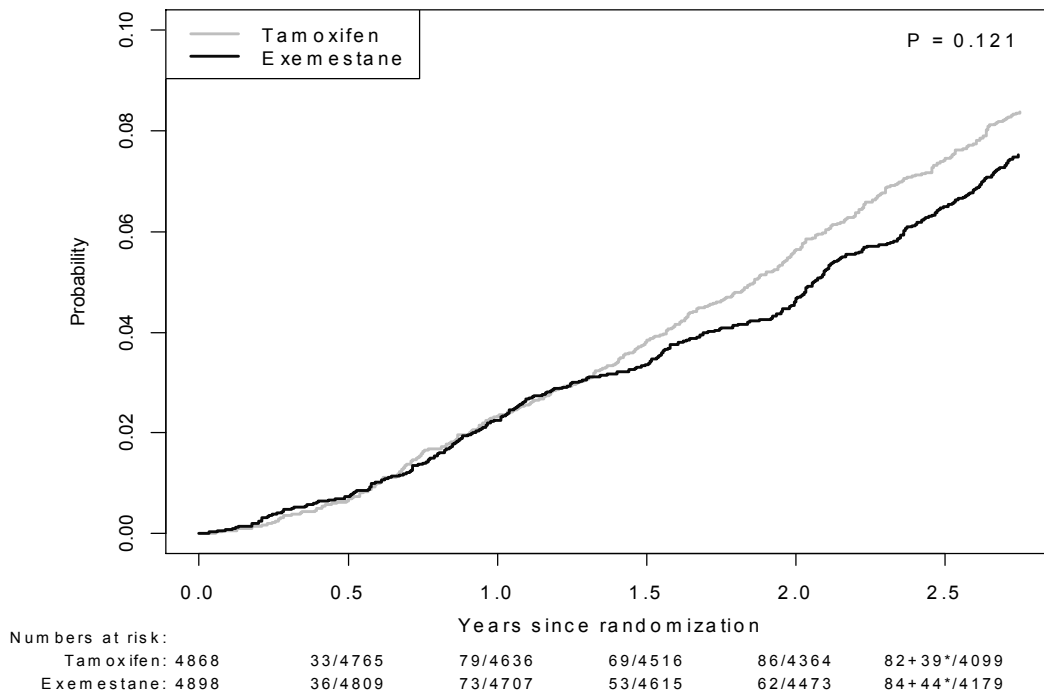
SD=standard deviation, ER=estrogen receptor, PgR=progesterone receptor, HT=hormone therapy

Efficacy Results: A total of 740 DFS events occurred, 352 in exemestane-treated and 388 in tamoxifen-treated subjects. At 2.75 years post-randomization, DFS was 92.5% in the exemestane group and 91.6% in the tamoxifen group, with an exemestane versus tamoxifen HR of 0.89 (95% CI, 0.77-1.03; log-rank $P=0.12$, Figure S2). The HR for DFS on study

drug was 0.83 (95% CI, 0.71–0.97; $P=0.022$, Figure S3). Of the 740 DFS events, 570 were breast cancer related (local recurrence only [including ipsilateral breast cancer], distant metastasis or new primary breast cancer) and 170 were deaths without relapse (intercurrent deaths; 88 exemestane, 82 tamoxifen, Table S3). Events in the exemestane group consisted of local recurrences only (including ipsilateral breast cancer) ($n=42$, 0.9%), distant metastases ($n=201$, 4.1%), and CBC occurrences without distant metastases ($n=21$, 0.4%); events in the tamoxifen group comprised local recurrences only ($n=45$, 0.9%), distant metastases ($n=244$, 5.0%), and CBCs without distant metastases ($n=17$, 0.3%; Table S3). An analysis of DFS by prognostic factors is depicted in Figure S4, showing a homogeneous treatment effect across all subject subgroups.

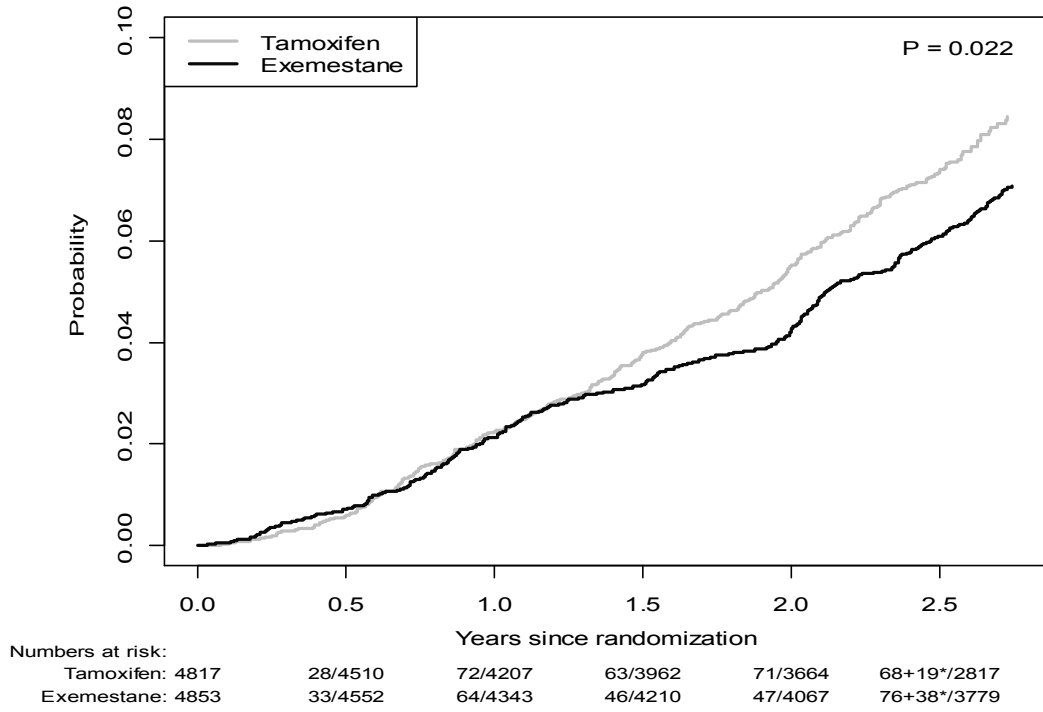
At 2.75 years of follow-up, RFS was numerically, but not significantly, improved with exemestane compared to tamoxifen (HR, 0.85; 95% CI, 0.72–1.00; $P=0.056$; Figure S5). Time to first distant metastasis significantly favored exemestane-treated subjects (HR, 0.81; 95% CI, 0.67–0.98; $P=0.028$; Figure S6). Neither overall survival (HR, 1.04; 95% CI, 0.85–1.28; $P=0.71$) nor time to CBC (HR, 1.30; 95% CI, 0.72–2.36; $P=0.39$) differed significantly between groups; however, the total numbers of CBCs ($n=38$) and deaths ($n=358$) were low. There were 174 deaths in subjects randomized to tamoxifen, and 184 in those randomized to exemestane; causes of death are shown in Table S4. Incidences of new primary nonbreast cancers were: colorectal cancer (24 in exemestane arm vs 14 in tamoxifen arm), lung cancer (11 vs 9), endometrial cancer (7 vs 12), and other primary cancer types (66 vs 54).

Figure S2. Probability of Disease Free Survival before 2.75 years for the ITT Population



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Figure S3. Probability of Disease Free Survival (on Study Drug)



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Figure S4. Disease Free Survival at 2.75 years for Subject Subgroups by Prognostic Factor

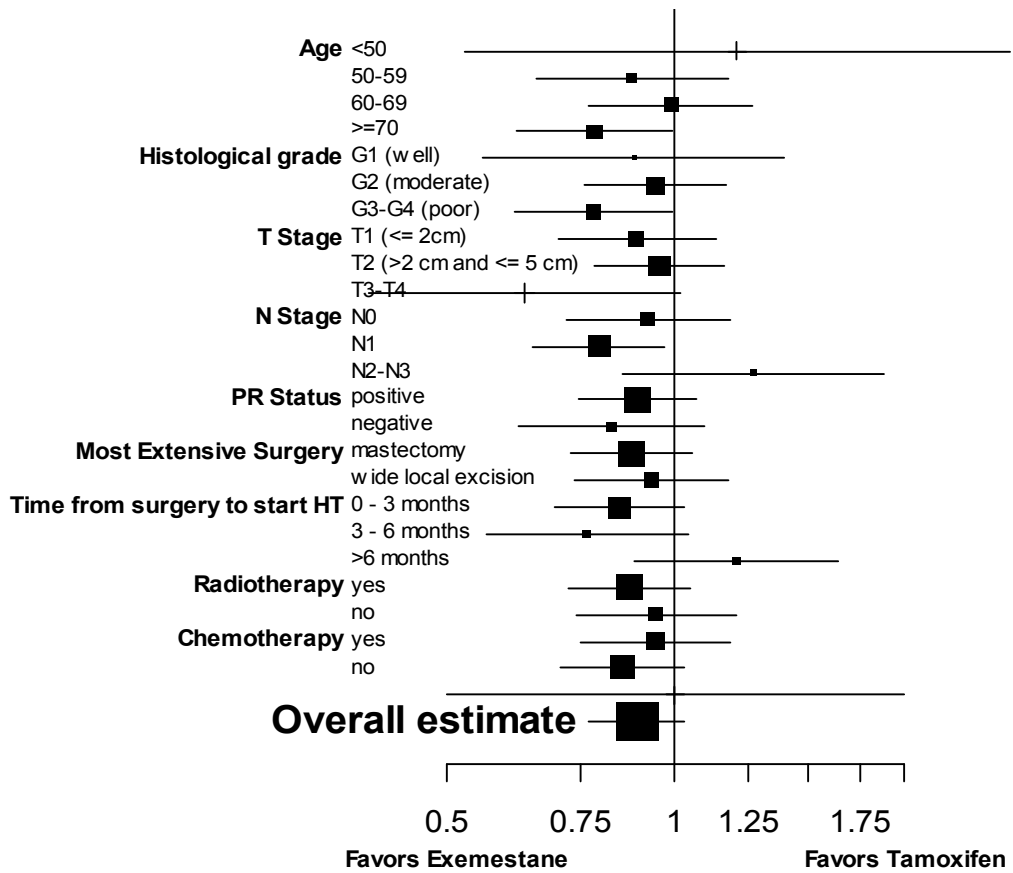


Table S3. Disease Free Survival Events by Treatment Group

Event (n,%)	Tamoxifen (n=4868)	Exemestane (n=4898)	Total (N=9766)
Total DFS events	388 (8.0)	352 (7.2)	740 (7.6)
Local recurrence only ^a	45 (0.9)	42 (0.9)	87 (0.9)
Distant metastases	244 (5.0)	201 (4.1)	445 (4.6)
Contralateral breast cancer ^b	17 (0.3)	21 (0.4)	38 (0.4)
Intercurrent deaths	82 (1.7)	88 (1.8)	170 (1.7)

DFS=disease free survival

^a Includes ipsilateral breast cancer, except for local recurrence with additional distant metastases.

^b Excluding distant metastases

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Figure S5. Probability of Recurrence-Free Survival

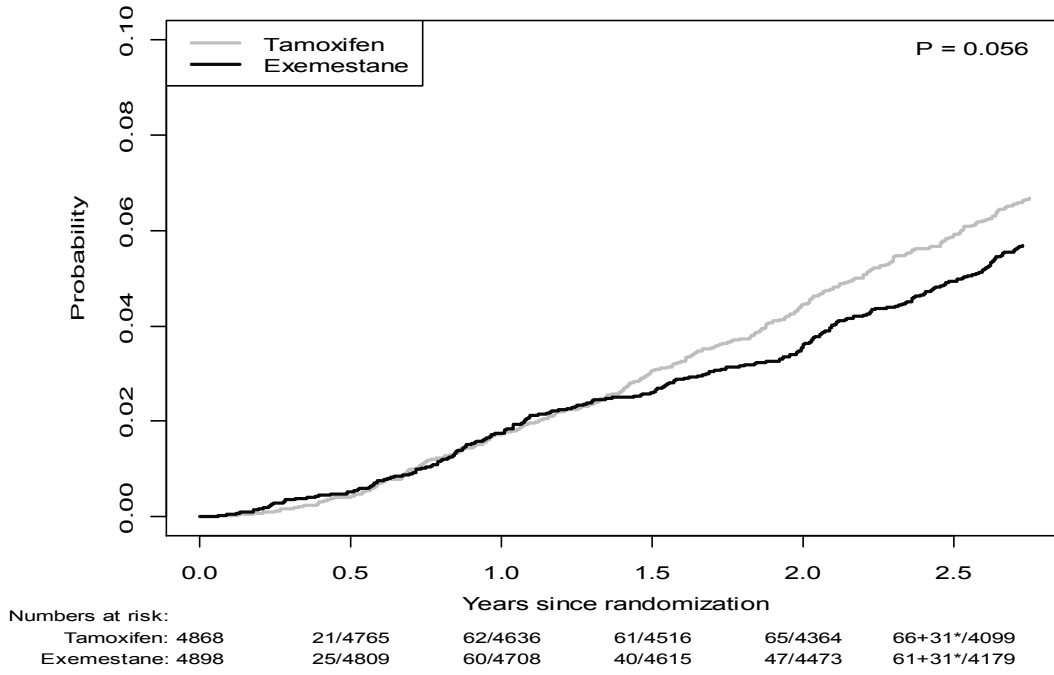
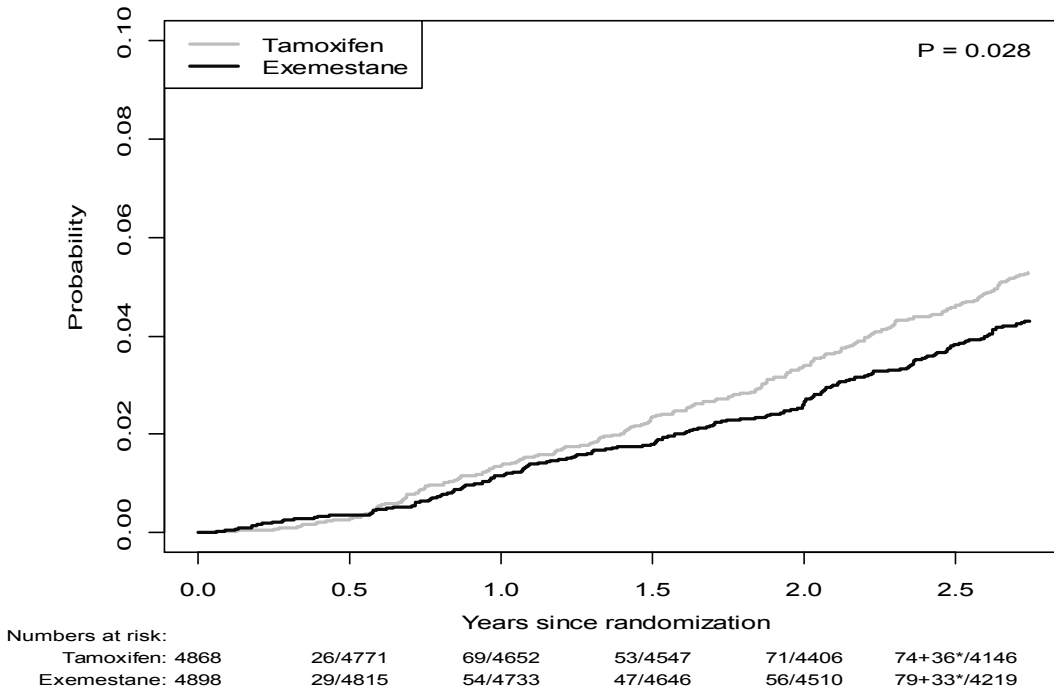


Figure S6. Time to First Distant Metastasis



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Safety Results: Causes of death are summarized in Table S4. There were 174 deaths in the tamoxifen arm and 184 deaths in the exemestane arm (3.57% and 3.76% of subjects, respectively). Eighteen subjects in the exemestane group and 11 subjects in the tamoxifen group were recorded as having cardiac deaths without recurrence of breast cancer. These differences were not significant.

Table S4. Causes of Death by Treatment Group

Event (n, %)	Tamoxifen (n=4868)	Exemestane (n=4898)	Total (N=9766)
Deaths	174 (100.0)	184 (100.0)	358 (100.0)
Breast cancer ^a	94 (54.0)	100 (54.3)	194 (54.2)
Second malignancy	22 (12.6)	25 (13.6)	47 (13.1)
Cardiac related	11 (6.3)	18 (9.8)	31 (8.7)
Thromboembolism	3 (1.7)	4 (2.2)	7 (2.0)
Pulmonary related	6 (3.4)	5 (2.7)	11 (3.1)
Cerebral related	9 (5.2)	7 (3.8)	16 (4.5)
Vascular related	3 (1.7)	2 (1.1)	5 (1.4)
Other	14 (8.0)	12 (6.5)	26 (7.3)
Unknown reason	12 (6.9)	11 (6.0)	23 (6.4)

^aSix breast cancer subjects were ineligible as had distant metastases at randomization; in total 94 and 100 breast cancer deaths occurred in the tamoxifen and exemestane treatment groups, respectively; 92 and 96 of the deaths occurred after relapse and were breast cancer related deaths.

AEs were reported for 4817 (98.95%) subjects in the tamoxifen treatment group and 4853 (99.49%) subjects in the exemestane group. SAEs are summarized by Medical Dictionary for Regulatory Affairs (MedDRA [Version 12]) system organ class (SOC) in Table S5. The frequency of any SAE was low (<0.5%). Of the subjects evaluable for safety, the most common SAEs (by MedDRA preferred term) for the tamoxifen group were pulmonary embolism (tamoxifen vs. exemestane, 16/4817 subjects, 0.33% vs. 9/4853 subjects, 0.19%), cerebrovascular accident (14/4817 subjects, 0.29% vs. 12/4853 subjects, 0.25%), deep vein thrombosis (13/4817 subjects, 0.27% vs. 2/4853 subjects, 0.04%) and pneumonia (13/4817 subjects, 0.27% vs. 12/4853 subjects, 0.25%), and the most common SAEs for the exemestane group were infection (11/4817 subjects, 0.23% vs. 14/4853 subjects, 0.29%), fracture (8/4817 subjects, 0.17% vs. 13/4853 subjects, 0.27%), and myocardial infarction (8/4817 subjects, 0.17% vs. 13/4853 subjects, 0.27%).

Table S5. Serious Adverse Events

MedDRA ^a System Organ Class Term	Tamoxifen (n=4817)		Exemestane (n=4853)	
	N	%	N	%
Infections and infestations	88	1.8	77	1.6
Reproductive system and breast disorders	71	1.5	25	0.5
Vascular disorders	68	1.4	35	0.7
General disorders and administration site conditions	67	1.4	44	0.9
Gastrointestinal disorders	57	1.2	55	1.1
Respiratory, thoracic and mediastinal disorders	57	1.2	47	1.0
Nervous system disorders	59	1.2	76	1.6
Cardiac disorders	40	0.8	80	1.6
Injury, poisoning and procedural complications	44	0.9	58	1.2
Musculoskeletal and connective tissue disorders	44	0.9	79	1.6
Surgical and medical procedures	27	0.6	20	0.4
Hepatobiliary disorders	23	0.5	19	0.4
Neoplasms benign, malignant and unspecified (including cysts and polyps)	20	0.4	26	0.5
Skin and subcutaneous tissue disorders	19	0.4	14	0.3
Psychiatric disorders	12	0.2	14	0.3
Preferred term not specified	12	0.2	12	0.2
Renal and urinary disorders	11	0.2	11	0.2
Metabolism and nutrition disorders	9	0.2	10	0.2
Eye disorders	8	0.2	12	0.2
Endocrine disorders	7	0.1	5	0.1
Blood and lymphatic system disorders	6	0.1	13	0.3
Ear and labyrinth disorders	6	0.1	2	0.0
Congenital, familial and genetic disorders	3	0.1	2	0.0
Immune system disorders	0	0.0	3	0.1
Investigations	1	0.0	7	0.1

N = number of subject reporting a serious adverse event, MedDRA = Medical Dictionary for Regulatory Affairs

^aMedDRA Version 12

Treatment was discontinued before 2.75 years in more tamoxifen-treated subjects (1434 [29.5%]) than exemestane-treated subjects (926 [18.9%]). Reasons for discontinuation, as reported on the CRFs, were as follows: AEs (n=554 [11.4%] tamoxifen vs 411 [8.4%] exemestane; treatment refusal (179 [3.7%] vs 84 [1.7%]), disease recurrence (242 [5.0%] vs 195 [4.0%]), new primary tumor (19 [0.4%] vs 20 [0.4%]), protocol deviation (52 [1.1%] vs 17 [0.3%]), intercurrent illness and/or significant personal events not associated with treatment (20 [0.4%] vs 6 [0.1%]), death (60 [1.2%] vs 75 [1.5%]), switch-related reasons (146 [3.0%] vs 0), and other/unknown reasons (162 [3.3%] vs 118 [2.4%]). Thus, 1113 subjects (22.9%) randomized to tamoxifen and 636 (13.0%) randomized to exemestane discontinued for reasons other than disease recurrence, new primary tumor, or death.

All causality AEs are summarized by MedDRA Preferred Term in Table S6, respectively. In both groups, the most frequently affected organ systems were vascular disorders and musculoskeletal and connective tissue disorders. The most frequently occurring AEs for the tamoxifen group were hot flush, fatigue, arthralgia, pain and nausea; and for the exemestane group, the most frequently occurring AEs were hot flush, arthralgia, fatigue, pain and insomnia.

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Table S6. All Causality Adverse Events Reported in ≥2% of Subjects

Number (%) of subjects	Tamoxifen (n=4817)				Exemestane (n=4853)			
	Any		Grade ≥3 ^b		Any		Grade ≥3 ^a	
	N	%	N	%	N	%	N	%
Hot flush	1429	29.7	52	1.1	1272	26.2	24	0.5
Fatigue	669	13.9	21	0.4	686	14.1	19	0.4
Arthralgia	447	9.3	31	0.6	875	18.0	77	1.6
Pain	431	8.9	33	0.7	473	9.7	24	0.5
Nausea	361	7.5	16	0.3	338	7.0	8	0.2
Insomnia	351	7.3	20	0.4	466	9.6	30	0.6
Depression	317	6.6	23	0.5	302	6.2	19	0.4
Vaginal discharge	302	6.3	6	0.1	105	2.2	1	0.0
Weight increased	275	5.7	4	0.1	221	4.6	11	0.2
Myalgia	264	5.5	10	0.2	314	6.5	22	0.4
Headache	246	5.1	10	0.2	296	6.1	13	0.3
Oedema	235	4.9	4	0.1	256	5.3	8	0.2
Vulvovaginal dryness	229	4.7	9	0.2	270	5.6	18	0.4
Constipation	205	4.3	3	0.1	168	3.5	3	0.1
Dizziness	204	4.2	10	0.2	187	3.8	13	0.3
Infection	186	3.9	21	0.4	147	3.0	18	0.4
Dyspnoea	184	3.8	26	0.5	171	3.5	33	0.7
Muscle spasms	183	3.8	5	0.1	94	1.9	3	0.1
Flushing	177	3.7	14	0.3	112	2.3	1	0.0
Cough	174	3.6	3	0.1	163	3.4	3	0.1
Alopecia	170	3.5	1	0.0	234	4.8	1	0.0
Libido decreased	160	3.3	6	0.1	188	3.9	7	0.1
Rash	158	3.3	5	0.1	176	3.6	8	0.2
Lymphoedema	156	3.2	2	0.0	156	3.2	0	0.0
Diarrhea	153	3.2	11	0.2	234	4.8	17	0.3
Vaginal hemorrhage	153	3.2	0	0.0	78	1.6	0	0.0
Bone pain	150	3.1	8	0.2	182	3.7	21	0.4
Back pain	148	3.1	9	0.2	139	2.9	9	0.2
Hyperhidrosis	146	3.0	4	0.1	78	1.6	2	0.0
Amnesia	135	2.8	5	0.1	170	3.5	5	0.1
Anxiety	134	2.8	3	0.1	132	2.7	9	0.2
Mood altered	126	2.6	10	0.2	137	2.8	8	0.2
Pruritus	117	2.4	4	0.1	114	2.3	6	0.1
Oedema peripheral	117	2.4	3	0.1	103	2.1	2	0.0
Asthenia	108	2.2	8	0.2	133	2.7	6	0.1
Abdominal pain	105	2.2	8	0.2	95	1.9	9	0.2
Osteoporosis	104	2.2	2	0.1	228	4.7	11	0.2
Hypertension	104	2.2	23	0.5	163	3.4	43	0.9
Dyspepsia	95	2.0	5	0.1	113	2.3	2	0.0
Neuropathy peripheral	84	1.7	0	0.0	158	3.3	2	0.0
Arthritis	83	1.7	12	0.3	147	3.0	20	0.4
Musculoskeletal pain	53	1.1	2	0.0	99	2.0	5	0.1

MedDRA = Medical Dictionary for Regulatory Affairs, ^aMedDRA Version 12

^bGrade ≥3 = severe, threatening and fatal.

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Table S7 shows those AEs for which the incidences in the 2 groups differed by $\geq 1\%$, for which the between-group difference was significant at the 1% level, or for which the incidence in either group was $\geq 10\%$.

Treatment with exemestane was associated with significantly higher incidences of arthralgia, carpal tunnel syndrome, diarrhea, and hypercholesterolemia and osteoporosis, but significantly fewer occurrences of hot flush, vaginal hemorrhage, vaginal discharge, or thrombosis. Of note, there were no significant differences in fracture rates between the 2 groups. Similar results were observed when the reported AEs were coded using NCI CTC (Version 2.0) categories rather than the MedDRA preferred terms.

Table S7. Adverse Events (MedDRA Terms) with $\geq 10\%$ Frequency, with $\geq 1\%$ Treatment Difference, or with a Between-Group Difference level with P-Value ≤ 0.1

MedDRA ^a preferred term	Tamoxifen (n=4817)		Exemestane (n=4853)		P-value	Total (n=9690)	
	n	%	n	%		n	%
Hot flush	1429	29.7	1272	26.2	0.000	2701	27.9
Fatigue	669	13.9	686	14.1	0.729	1355	14.0
Arthralgia	447	9.3	875	18.0	0.000	1322	13.7
Insomnia	351	7.3	466	9.6	0.000	817	8.4
Weight increased	275	5.7	221	4.6	0.012	496	5.1
Vaginal discharge	302	6.3	105	2.2	0.000	407	4.2
Alopecia	170	3.5	234	4.8	0.002	404	4.2
Diarrhea	153	3.2	234	4.8	0.000	387	4.0
Osteoporosis	104	2.2	228	4.7	0.000	332	3.4
Flushing	177	3.7	112	2.3	0.000	289	3.0
Muscle spasms	183	3.8	94	1.9	0.000	277	2.9
Hypertension	104	2.2	163	3.4	0.000	267	2.8
Neuropathy peripheral	84	1.7	158	3.3	0.000	242	2.5
Vaginal hemorrhage	153	3.2	78	1.6	0.000	231	2.4
Arthritis	83	1.7	147	3.0	0.000	230	2.4
Hyperhidrosis	146	3.0	78	1.6	0.000	224	2.3
Musculoskeletal pain	53	1.1	99	2.0	0.000	152	1.6
Hypercholesterolemia	40	0.8	94	1.9	0.000	134	1.4
Sleep disorder	42	0.9	83	1.7	0.000	125	1.3
Vaginal infection	90	1.9	30	0.6	0.000	120	1.2
Carpal tunnel syndrome	17	0.4	72	1.5	0.000	89	0.9
Paraesthesia	21	0.4	56	1.2	0.000	77	0.8
Musculoskeletal stiffness	17	0.4	45	0.9	0.001	62	0.6
Arthropathy	19	0.4	41	0.8	0.007	60	0.6
Nail disorder	39	0.8	18	0.4	0.007	57	0.6
Joint stiffness	11	0.2	42	0.9	0.000	53	0.5
Endometrial hyperplasia	49	1.0	1	0.0	0.000	50	0.5
Thrombosis	37	0.8	9	0.2	0.000	46	0.5
Phlebitis	32	0.7	11	0.2	0.002	43	0.4
Tendonitis	11	0.2	32	0.7	0.002	43	0.4
Blood alkaline phosphatase increased	6	0.1	33	0.7	0.000	39	0.4
Genital discharge	31	0.6	7	0.1	0.000	38	0.4
Hypercalcemia	5	0.1	26	0.5	0.000	31	0.3
Endometrial disorder	27	0.6	2	0.0	0.000	29	0.3
Uterine polyp	25	0.5	4	0.1	0.000	29	0.3
Vulvovaginal pruritus	24	0.5	5	0.1	0.001	29	0.3

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Table S7. Adverse Events (MedDRA Terms) with $\geq 10\%$ Frequency, with $\geq 1\%$ Treatment Difference, or with a Between-Group Difference level with P-Value ≤ 0.1

MedDRA ^a preferred term	Tamoxifen (n=4817)		Exemestane (n=4853)		P-value	Total (n=9690)	
	n	%	n	%		n	%
Vulvovaginal mycotic infection	18	0.4	4	0.1	0.005	22	0.2
Endometrial hypertrophy	20	0.4	0	0.0	0.000	20	0.2
Colitis	2	0.0	16	0.3	0.002	18	0.2
Hypoalbuminemia	14	0.3	2	0.0	0.006	16	0.2
Cervical polyp	12	0.2	1	0.0	0.005	13	0.1
Vulvovaginal candidiasis	11	0.2	1	0.0	0.009	12	0.1
Blood cholesterol increased	0	0.0	8	0.2	0.008	8	0.1
Trigger finger	0	0.0	8	0.2	0.008	8	0.1
Endometrial atrophy	7	0.1	0	0.0	0.008	7	0.1

MedDRA = Medical Dictionary for Regulatory Affairs

^aMedDRA Version 12

CONCLUSIONS: The two treatment groups were not significantly different in the primary endpoint of DFS in the ITT population. The findings of this study are summarized below:

- The overall event rate in both groups at 2.75 years was 570 breast cancer events among 9766 subjects in the ITT population.
- Exemestane was associated with improvement in:
 - DFS (HR: 0.89; P=0.12), ITT.
 - DFS on study (HR: 0.83; P=0.022).
 - RFS (HR: 0.85; P=0.056).
 - Time to distant metastases (HR: 0.81; P=0.028).
- High rates of early discontinuation of tamoxifen, and timing of the switch to exemestane; both may have affected outcome (DFS).
- No unexpected safety issues with exemestane relative to tamoxifen were observed.