

Both treatment arms were similar in prior treatment. Chemotherapy for advanced disease had been given to 9% of patients assigned letrozole and 11% of patients assigned tamoxifen. Prior adjuvant anti-estrogen treatment had been given to 19% of the patients in the letrozole arm and 18% of the patients in the tamoxifen arm. Duration of adjuvant anti-estrogen treatment, and the duration of the treatment-free interval between the end of adjuvant treatment and study entry were similar in both treatment arms. Details are summarized in Table 10.

Table 10 Prior adjuvant anti-estrogen treatment

Description	letrozole n=456	tamoxifen n=456
Number of patients with prior anti-estrogen treatment	85 (19%)	83 (18%)
Duration of adjuvant anti-estrogen treatment ≥ 2 years	59 (13%)	51 (11%)
Median duration of adjuvant anti-estrogen treatment	2.8 years	2.3 years
Duration of treatment-free interval ≥ 2 years ¹	61 (13%)	66 (15%)
Median duration of treatment-free interval (years) ²	3.1 years	3.4 years
¹ Durations of less than 12 months were protocol violators.		
² Interval between end of adjuvant anti-estrogen treatment and enrollment in current study		
Median duration was estimated by the Kaplan-Meier product-limit method only in patients who had received adjuvant anti-estrogen treatment		

The prior use of adjuvant anti-estrogens differed according to country: generally patients in Canada and USA were more likely to have received adjuvant anti-estrogen treatment than in countries such as China or Russia or India.

9% of letrozole patients and 11% of tamoxifen patients received prior chemotherapy

6.4 Core Treatment Duration

The median duration of core treatment in the letrozole arm was 11 months compared to a median of 6 months in the tamoxifen arm. Table 2-9 indicates that the 2 treatment arms had distinctly different patterns of exposure.

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Table 11 Duration of treatment: exposure classes (ITT population)

Exposure class	Letrozole n=453		Tamoxifen n=454	
No treatment	1	0.2%	1	0.2%
< 1 month	13	2.9%	19	4.2%
≥1 month - < 2 months	19	4.2%	26	5.7%
≥2 months - <3 months	50	11.0%	70	15.4%
≥3 months - <6 months	65	14.4%	106	23.4%
≥6 months - <9 months	41	9.1%	51	11.2%
≥9 months - <12 months	59	13.0%	44	9.7%
≥12 months - <18 months	108	23.8%	70	15.4%
≥18 months - <24 months	67	14.8%	43	9.5%
≥24 months	30	6.6%	24	5.3%
Median duration	11 months		6 months	
Median estimated by Kaplan-Meier product-limit method. Duration of treatment was censored for patients still on core treatment at the cutoff for analysis.				

6.5 Efficacy analyses

6.5.1 Time to progression (TTP)

Letrozole was superior to tamoxifen in TTP, reducing the risk of progression by 30% compared with tamoxifen, and prolonging TTP by over 40% (hazard ratio 0.70, $P=0.0001$). (Table 11, Figure 2). Fewer patients progressed on letrozole (68%) than on tamoxifen (77%) during core treatment.

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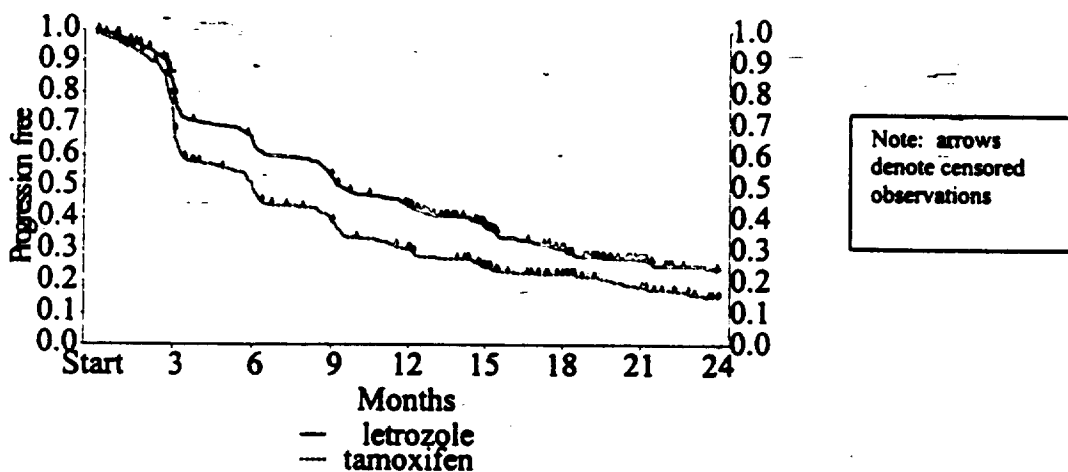
Table 12 Time to progression (TTP)

Analysis	Statistic	letrozole n=453	tamoxifen n=454
	Patients progressed	308 (68%)	350 (77%)
Primary (unadjusted)	Hazard ratio	0.70	
	95% CI	(0.60 to 0.82)	
	P-value	0.0001	
	Median TTP	9.4 months	6.0 months
	95% CI	(8.9 to 11.8 months)	(5.6 to 6.4 months)
	Progression-free rate (PFR) at 6 months	65%	50%
	PFR at 9 months	54%	40%
	PFR at 12 months	44%	30%
Supportive (adjusted)*	Hazard ratio	0.70	
	95% CI	(0.60 to 0.81)	
	P-value	0.0001	

A hazard ratio of less than 1 denotes a lower risk of progression with letrozole; a hazard ratio greater than 1 denotes a lower risk of progression with tamoxifen.

*Adjusted on baseline covariates of prior adjuvant anti-estrogen treatment (yes/no), receptor status (ER+ and/or PgR+ vs unknown and other), and dominant site of disease (soft tissue / bone / visceral).

Figure 2 Time to progression (TTP)



Median TTP was 9.4 months for letrozole and 6.0 months for tamoxifen, with separated 95% CIs (9 months to just under 1 year for letrozole, while for tamoxifen the 95% CI spanned 6 months only – 5.6 to 6.4 months).

The hazard ratio adjusted on the key baseline covariates of receptor status (ER and/or PgR positive / otherwise, coded respectively as 1 or 0), prior adjuvant anti-estrogen treatment (yes / no, coded respectively 1 or 0), and dominant site (soft tissue / bone / visceral; dominant site visceral coded 1 or 0, dominant site bone coded 1 or 0, with soft tissue being 0 on both dummy variables) and 95% CI for the hazard ratio were almost identical as for the unadjusted analysis.

The supportive analyses confirmed that

- Treatment with letrozole significantly decreased the risk of progression (hazard ratio 0.70, $P=0.0001$) and prolonged TTP (median 9 months vs 6 months) compared to tamoxifen.
- The presence of visceral metastases significantly increased the risk of progression (hazard ratio 1.52, $P=0.0001$) compared to soft tissue dominant site.
- Bone dominant site significantly increased the risk of progression (hazard ratio 1.26, $P=0.03$) compared to soft tissue dominant site.
- Neither receptor status nor prior adjuvant treatment with anti-estrogens significantly affected TTP.

The stratified analyses, conducted on each of the key baseline covariates one at a time confirmed that the treatment difference adjusted over the strata for each covariate significantly favored letrozole (Table 12).

The stratified analysis of prior adjuvant anti-estrogen treatment (i.e., no other covariate considered) revealed the superiority of letrozole over tamoxifen in both anti-estrogen naïve patients and patients exposed to anti-estrogens. In naïve patients (almost identical numbers of patients in both treatment arms, 369 for letrozole, 371 for tamoxifen), median TTP was 9.7 months for letrozole and 6 months for tamoxifen. The 95% CIs for the medians were completely separate, with the lower bound for letrozole longer than the higher bound for tamoxifen (9 to 12 months for letrozole, 5.7 to 8.4 months for tamoxifen).

Median TTP was similar in both treatment arms regardless of receptor status, with letrozole being superior to tamoxifen overall.

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Table 13 Stratified analysis on key baseline covariates

Baseline covariate	letrozole		tamoxifen		Logrank P-value
	Events of progression (n)	Median TTP (mos)	Events of progression(n)	Median TTP (mos)	
Prior adjuvant treatment					0.0001
None	250 (369)	9.7	284 (371)	6.0	
Adjuvant treatment	58 (84)	8.8	66 (83)	5.9	
Receptor status					0.0001
ER and/or PgR	199 (294)	9.7	235 (305)	6.0	
Unknown and/or other	109 (159)	9.2	115 (149)	6.0	
Dominant site					0.0001
Soft tissue	68 (113)	12.9	84 (116)	6.4	
Bone	100 (146)	9.7	97 (130)	6.2	
Visceral	140 (194)	8.3	169 (208)	4.7	

Most progressions in both treatment arms were based on objective evidence of progression of disease, detected at 3 months or later. Table 13 provides a breakdown of events counted as progressions.

Table 14 Events of progression: outcome codes

Outcome code	letrozole n=453	tamoxifen n=454
Description of Progression Event	308 (68%)	350 (77%)
PD, objective evidence, after/at visit 3 (3 mo)	234 (52%)	273 (60%)
PD, objective evidence, continued study	63 (14%)	60 (13%)
PD at visit 2 with objective assessment (1 mo)	4 (<1%)	4 (<1%)
Deterioration of general condition due to breast cancer	4 (<1%)	8 (2%)
Death due to breast cancer within 6 weeks of core discontinuation, no documented PD	3 (<1%)	4 (<1%)
Death (AE and symptomatic PD)	0	1 (<1%)

The major reason for censored observations on both treatment arms was patients continuing on core treatment without evidence of progression (Table 14).

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Table 15 Reasons for censoring TTP

Outcome code	letrozole n=453	tamoxifen n=454
Description of Censoring	145 (32%)	104 (23%)
Still on core treatment, no PD	111 (25%)	67 (15%)
Other treatment while responding	0	1 (<1%)
Death due to AE without PD or clinical deterioration	2 (<1%)	5 (1%)
Death due to non -cancer reasons (suicide)	1 (<1%)	0
Death from unknown cause, no evidence of PD or clinical deterioration	3 (<1%)	2 (<1%)
Discontinuation without evidence of PD or clinical deterioration	27 (6%)	28 (6%)
Never received treatment	1 (<1%)	1 (<1%)

6.5.1.1 Exploratory TTP analysis

When other baseline covariates were added, slight changes were observed in the impact on TTP of the key covariates (Table 2-14). Letrozole continued to reduce the risk of progression by about 30% compared with tamoxifen (hazard ratio 0.71, $P=0.0001$). Dominant site viscera continued to increase the risk of progression compared with soft tissue dominant site (hazard ratio 1.49, $P=0.0001$). In the presence of other covariates, bone dominant site had no significant impact on TTP, while a trend was observed for prior adjuvant anti-estrogen treatment (hazard ratio 1.30, $P=0.10$).

The influence on TTP of North American sites compared with European sites was the same (hazard ratio 0.98) but the risk of progression was significantly increased in Rest of the World sites compared with Europe (hazard ratio 1.28, $P=0.01$).

There was a suggested increased risk of progression for patients receiving bisphosphonates compared to those who did not (hazard ratio 1.32, $P=0.06$).

Stratified analyses indicated the superiority of letrozole over tamoxifen on all covariates examined (Table 15).

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Table 16 Stratified analysis of TTP: other baseline covariates of interest

Baseline covariate	letrozole		tamoxifen		Logrank P-value
	Events of progression (n)	Median TTP (mo)	Events of progression (n)	Median TTP (mo)	
Duration of anti-estrogen treatment					0.0001
None - 2 years	270 (395)	9.4	309 (403)	6	
≥2 years	38 (58)	9.5	41 (51)	4.1	
Geographical area					0.0001
Europe	195 (288)	9.9	225 (292)	6.2	
North America	32 (49)	9.7	35 (51)	6	
Rest of World	81 (116)	9	90 (111)	3.5	
Age class					0.0001
< 70 years	215 (301)	8.8	246 (311)	6	
≥70 years	93 (152)	12.2	104 (143)	5.8	

In conclusion, letrozole was significantly superior to tamoxifen in TTP for all baseline covariates examined.

6.5.2 Overall tumor response

Overall objective tumor response (complete response [CR] + partial response [PR]) rate was superior for letrozole (30%) compared with tamoxifen (20%) (odds ratio 1.71, P=0.0006) (Tables 16 and 17).

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Table 17 Overall tumor response

Overall response	letrozole n=453	tamoxifen n=454
Complete response (CR)	34 (8%)	13 (3%)
Partial response (PR)	103 (23%)	79 (17%)
No change / stabilization (NC)	84 (19%)	81 (18%)
Progression of disease (PD)	200 (44%)	250 (55%)
Not evaluable / not assessable (NE/NA)	32 (7%)	31 (7%)
Objective overall response (CR+PR)	137 (30%)	92 (20%)
95% confidence interval	(26 to 35%)	(17 to 24%)
Median duration (months)	23	23
Overall clinical benefit (CR+PR+NC*)	221 (49%)	173 (38%)
95% confidence interval	(44 to 54%)	(34 to 43%)
Median duration (months)	19	19
* NC had to last at least 24 weeks before being counted		

Table 18 Analysis of overall objective tumor response

Analysis	Statistic	letrozole n=453	tamoxifen n=454
Primary (unadjusted)	Odds ratio 95% confidence interval P-value	1.71 (1.26 to 2.31) 0.0006	
Supportive (adjusted) *	Odds ratio 95% confidence interval P-value	1.80 (1.32 to 2.47) 0.0002	
An odds ratio greater than 1 favors letrozole; an odds ratio less than 1 favors tamoxifen. *Adjusted on baseline covariates of prior adjuvant anti-estrogen treatment (yes / no), receptor status (ER+ and / or PgR+ vs unknown or other), and dominant site of disease (soft tissue / bone / visceral).			

The adjusted analysis (adjusted for the key covariates of receptor status, prior adjuvant anti-estrogen treatment and dominant site of disease) was similar to the unadjusted analysis (Table 17).

The supportive analyses indicated that slightly different covariates impact overall response than impact TTP. The analyses may be summarized:

- In the presence of the 3 key covariates, the odds of achieving a CR or PR are significantly higher with letrozole than with tamoxifen (odds ratio 1.80, P=0.0002).
- Prior adjuvant anti-estrogen treatment significantly reduces the odds of achieving a CR or PR compared with anti-estrogen naïve patients (odds ratio 0.64, P=0.04).

- The odds of achieving a CR or PR are significantly reduced in patients with visceral dominant site or bone dominant site compared with soft tissue dominant site (visceral: odds ratio 0.37, P=0.0001; bone: odds ratio 0.29, P=0.0001).
- A trend was observed for a higher odds of achieving an objective tumor response in receptor positive patients than in receptor unknown patients (odds ratio 1.37, P=0.07).

The stratified supportive analyses revealed the superior objective response rate of letrozole over tamoxifen in the key covariates and other covariates of interest (Table 18).

Table 19 Stratified analysis of objective overall tumor response

Baseline covariate	Letrozole		tamoxifen		Cochran Mantel Haenszel P-value
	CR + PR responses (n)	%	CR + PR responses (n)	%	
Prior adjuvant treatment					0.001
None	113 (369)	31	85 (371)	23	
Adjuvant treatment	24 (84)	29	7 (83)	8	
Duration Adjuvant Rx					0.001
None- <2 years	119 (395)	30	89 (403)	22	
≥2 years	18 (58)	31	3 (51)	6	
Geographical area					0.001
Europe	94 (288)	33	65 (292)	22	
North America	13 (49)	27	9 (51)	18	
Rest of World	30 (116)	26	18 (111)	16	
Receptor status					0.001
ER and/or PgR +	92 (294)	31	63 (305)	21	
Unknown and other	45 (159)	28	29 (149)	20	
Dominant site					0.001
Soft tissue	54 (113)	48	40 (116)	35	
Bone	32 (146)	22	18 (130)	14	
Visceral	51 (194)	26	34 (208)	16	
Age class					0.001
< 70 years	79 (301)	26	67 (311)	22	
≥70 years	58 (152)	38	25 (143)	18	

6.5.2.1 Exploratory response rate analysis

Considering all covariates of interest, objective response rate was significantly influenced by:

Treatment, with letrozole increasing the odds (odds ratio 1.79, P=0.0004).

Dominant site, with visceral or bone dominant disease decreasing the odds compared with soft tissue dominant site (visceral: odds ratio 0.38, P=0.0001; bone: odds ratio 0.31, P=0.0001).

Geographical area: there was no difference in response rate in North America compared with Europe, but the odds of achieving an objective tumor response were significantly reduced in Rest of the World sites compared with Europe (odds ratio 0.62, $P=0.02$).

A non-significant trend was seen for prior adjuvant anti-estrogen treatment (odds ratio 0.51, $P=0.09$).

Body mass index possibly had some influence ($P=0.11$) as seen in other studies.

Three other noteworthy results arose in the exploratory stratified analyses. Prior adjuvant anti-estrogen treatment given for 2 years or more appeared to be particularly deleterious for patients in the tamoxifen arm (letrozole 31% response rate, tamoxifen 6%). In patients aged 70 years or more, response rate was 38% for letrozole, 18% for tamoxifen. For both treatment arms, response rate was lower in patients exposed to bisphosphonates (18% for letrozole, 14% for tamoxifen) than in bisphosphonates-naïve patients (32% for letrozole, 21% for tamoxifen).

Time to response was not significantly different between treatments. Median TTR was 3.2 months for both treatment arms.

6.5.3 Overall clinical benefit (CR+PR+NC $\geq$ 24 weeks)

The rate of clinical benefit (objective tumor response or NC lasting at least 24 weeks) was significantly higher for letrozole (49%) than for tamoxifen (38%) (odds ratio 1.55, $P=0.001$).

6.5.4 Duration of tumor response and clinical benefit

Current estimates of duration of response or benefit are unreliable as follow-up time is relatively short. To-date neither duration of objective tumor response nor duration of clinical benefit differed significantly between treatments whether estimated from date of randomization or date of onset of tumor response or benefit. The hazard ratios favored letrozole (0.84 and 0.81 for response and benefit, respectively, calculated from date of randomization, and 0.82 for response, 0.81 for benefit calculated from date of onset).

6.5.5 Time to treatment failure (TTF)

Since both treatments are relatively safe and TTF is closely correlated with TTP, letrozole was significantly superior to tamoxifen in TTF (hazard ratio 0.71, $P=0.0001$). Treatment failure occurred in 75% of patients in the letrozole arm, 85% in the tamoxifen arm. Median TTF was 9.1 months for letrozole, 5.8 months for tamoxifen. The 12-months failure-free rate was 41% for letrozole, 27% for tamoxifen (Table 19).

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Table 20 Analysis of time to treatment failure

Analysis	Statistic	letrozole n=453	tamoxifen n=454
Primary (unadjusted)	Number of treatment failures	341	385
	Hazard ratio	0.71	
	95% confidence interval	(0.61 to 0.82)	
	chi squared P-value	0.0001	
	Median TTF (months)	9.1	5.8
	95% confidence interval (months)	(8.6 – 9.9)	(3.7 – 6.1)
	6 months failure free rate	62%	47%
	9 months failure free rate	51%	36%
	12 months failure free rate	41%	27%

6.5.6 Number of deaths

In the ITT population, 29 (6%) patients died during core treatment with letrozole (or within 6 weeks of discontinuing letrozole), compared with 42 (9%) on tamoxifen. Most deaths were cancer-related (19 of 29 for letrozole, 31 of 42 for tamoxifen). One patient in the tamoxifen arm died after randomization but before starting study treatment. This patient is included in the ITT population, but is not included in the safety population. A total of 7 patients were lost to follow-up (4 for letrozole, 3 for tamoxifen) during core.

After the first interim analysis based on 304 total deaths, the DMC recommended that the extension phase continue as planned and that no change to treatment assignment be introduced. The second interim analysis is planned for 6 months from the first analysis.

6.5.7 Performance status

Karnofsky performance score was remapped to World Health Organization score and presented as baseline grades against worst grade on treatment. In the letrozole arm, deterioration in grade occurred in 27% (121 of 442) patients (11 patients had only a baseline assessment), compared with 32% (143 of 447) of tamoxifen patients (6 patients had only a baseline assessment, 1 had no baseline assessment).

6.5.8 Patients with metastatic disease

When patients with stage IIA, IIB, IIIA or IIIB breast cancer were excluded (i.e., leaving only patients with metastatic breast cancer), the results were almost identical to the results of the whole study. For example, the hazard ratio for TTP in the ITT population was 0.70, 95% CI 0.60 to 0.82, $P=0.0001$; in patients with metastatic disease, the hazard ratio was 0.69, 95% CI 0.59 to 0.81, $P=0.0001$.

6.5.9 Patients with locally advanced disease

Results were similar for each treatment arm as for the whole study in the small subset of patients with locally advanced disease (stage IIIA or IIIB), although differences between

treatments were not statistically significant because of the low power (29 patients on letrozole, 33 on tamoxifen).

6.5.10 Summary of efficacy findings

Letrozole demonstrated superiority to tamoxifen in key efficacy endpoints necessary for a hormonal treatment to be deemed clinically meaningful for first-line treatment of postmenopausal patients with advanced breast cancer. The total median follow-up is approximately 18 months. These efficacy endpoints include the primary endpoint TTP, and the secondary endpoints of TTF, ORR and rate of clinical benefit. Letrozole was superior to tamoxifen in TTP (hazard ratio 0.70, 95% CI 0.60 to 0.82, $P = 0.0001$). Median TTP was 9.4 months for letrozole and 6.0 months for tamoxifen. At the time of the analyses, 68% of the letrozole patients as compared to 77% of the tamoxifen patients had disease progression. These results show that the risk of progression was 30% less and TTP was more than 40% longer for letrozole than for tamoxifen. Similar results were seen for TTF as both therapies are equally well tolerated.

Letrozole was superior to tamoxifen in overall objective tumor response (30% vs 20%, odds ratio 1.71, 95% CI 1.26 to 2.31, $P = 0.0006$). Letrozole was also superior to tamoxifen in rate of clinical benefit (49% vs 38%, respectively, odds ratio 1.55, 95% CI 1.19 to 2.01, $P = 0.001$). The duration of response and duration of clinical benefit were not significantly different.

The endpoints TTP and ORR were examined by supportive analyses adjusted for key baseline covariates including prior anti-estrogen treatment, receptor status and dominant site of disease. These adjusted comparisons yielded similar results as the unadjusted comparison and demonstrated superior results for letrozole across the various subgroups.

With review of the data, some aspects need comment. The response rate for tamoxifen (20%) seen in this study is lower than reported in the literature where response rates have ranged for 30 – 45% [1-4] despite the fact that the TTP of tamoxifen compares favorably with past experience. Recently, comparable rates for tamoxifen have been reported in the completed first-line anastrozole studies [5].

Approximately one third of the patients randomized to this study had unknown receptor status. The response rates for patients with unknown receptor status (28% letrozole, 20% tamoxifen) were remarkably similar to those of the receptor positive patients (31% letrozole, 20% tamoxifen) indicating that the majority of these unknown receptor status postmenopausal patients are most likely receptor positive as would be expected [8].

Another aspect which needs comment is that approximately 20% of this patient population received prior adjuvant anti-estrogen treatment. It is anticipated that world-wide in the future a much larger proportion of patients will relapse after adjuvant anti-estrogens making them less responsive to a second course of tamoxifen in the advanced disease setting. In this current study in patients who had prior adjuvant anti-estrogen treatment, the response rate was 29% for letrozole and 8% for tamoxifen. This difference provides further evidence that letrozole offers a significant therapeutic advantage as first-line treatment in this patient population with advanced breast cancer.

6.6 Supportive studies

Two small pilot studies in first-line treatment of patients with advanced breast cancer (012 and 026) were discontinued for administrative reasons when 32 and 18 patients, respectively, had been enrolled. Given the small size of these 2 studies, no ISE was prepared.

6.7 Safety analysis

6.7.1 Overview

Three first-line studies evaluating letrozole in postmenopausal women with advanced, metastatic breast cancer are listed in Table 20.

Table 21 Summary of key studies used for safety evaluation

Study No.	Type of Control	No. of patients in the safety population	Population
025	Tamoxifen	932*	Postmenopausal, advanced breast cancer
012	Tamoxifen	32	Postmenopausal, advanced breast cancer
026	Tamoxifen	18	Postmenopausal, advanced breast cancer
* In study 025, 939 patients were enrolled, but the safety population only included 932 patients who were GCP compliant and had received at least one dose of study medication.			

The safety data from a study (024) will also be presented. This was a double-blind, randomized, parallel-group study comparing the efficacy and safety of 4 months pre-operative treatment with letrozole (2.5 mg once daily [o.d.]) or tamoxifen (20 mg o.d.) in postmenopausal women with primary untreated advanced breast cancer. Adverse event and SAE data are available for 327 patients (157 in the letrozole group and 170 in the tamoxifen group). Ongoing studies, study in and a recently completed study in provided. These studies include:

The cutoff date for adverse event data for this ISS is March 8, 2000 and the cutoff date for serious adverse event data is February 29, 2000.

6.7.2 Overall drug exposure

In each of the 3 first-line studies, the median duration of exposure was longer in the letrozole group than in the tamoxifen or combination treatment groups. In study 025, the median duration was 11 months for letrozole 2.5 mg and 6 months for tamoxifen 20 mg. In study 026, the median duration was 15 months for letrozole 2.5 mg and 3 months for letrozole 2.5 mg/tamoxifen 20 mg. In study 012, the median duration was also 15 months for letrozole (0.5 mg or 2.5 mg) and 3 months for tamoxifen 30 mg.

There were 486 patients exposed to letrozole monotherapy (letrozole 2.5 mg for 476 patients, 0.5 mg for 10 patients), 465 patients exposed to tamoxifen monotherapy (20 mg for 455 patients, 30 mg for 10 patients) and 31 patients exposed to the combination of letrozole 2.5 mg and tamoxifen 20 mg.

In the 3 first-line studies, there were 222 patients who received letrozole monotherapy for more than 12 months, 141 patients who received tamoxifen monotherapy for more than 12 months, and 6 patients who received combination therapy for more than 12 months.

6.7.3 Overall adverse events (study 025)

Adverse events were collected during the core phase of treatment, and SAEs were collected during the core phase of treatment and 6 weeks after administration of last dose of study medication. Most patients experienced at least one adverse event during the core phase of this study. The nature and frequency of adverse events were similar for both letrozole and tamoxifen. The 5 most common adverse events in both monotherapy groups were bone pain, hot flushes, back pain, nausea, and arthralgia. The adverse events reported in this study were similar to those previously reported for letrozole and tamoxifen. The overall incidence of adverse events is summarized by primary system organ class and by preferred term in Tables 5-1 and 5-2, respectively.

The dictionary used for coding adverse events was the World Health Organization-based MedDRA.

6.7.4 Most frequently affected body systems

Adverse events that occurred in at least 5% of any treatment group, regardless of study drug relationship, are summarized by primary system organ class in Table 22. The most frequently affected system organ class for both monotherapy groups was the musculoskeletal, connective tissue and bone disorder class.

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Table 22 Number of patients with adverse events, regardless of study drug relationship, in most frequently affected primary system organ classes ($\geq 5\%$ in any group): 025

	Letrozole	Tamoxifen	Combination
	n (%)	n (%)	n (%)
Patients studied			
Total no. of patients studied	455	455	22
Total no. of patients with an AE	408 (90)	394 (87)	17 (77)
MedDRA primary system organ class			
Musculoskeletal, connective tissue & bone disorders	233 (51)	225 (50)	6 (27)
General disorders & administration site conditions	160 (35)	157 (35)	3 (14)
Gastrointestinal disorders	152 (33)	152 (33)	8 (36)
Respiratory, thoracic & mediastinal disorders	125 (28)	116 (26)	5 (23)
Vascular disorders	125 (28)	112 (25)	5 (23)
Infections & infestations	104 (23)	89 (20)	5 (23)
Nervous system disorders	104 (23)	92 (20)	4 (18)
Skin & subcutaneous disorders	87 (19)	74 (16)	8 (36)
Metabolism & nutrition disorders	53 (12)	62 (14)	5 (23)
Reproductive system & breast disorders	53 (12)	59 (13)	5 (23)
Cardiac disorders	49 (11)	48 (11)	3 (14)
Psychiatric disorders	41 (9)	37 (8)	0
Surgical & medical procedures	38 (8)	33 (7)	1 (5)
Investigations	37 (8)	36 (8)	2 (9)
Renal & urinary disorders	24 (5)	9 (2)	1 (5)
Neoplasms benign & malignant	22 (5)	20 (4)	3 (14)

6.7.5 Frequency of adverse events

Adverse events reported for this study were similar to those previously reported for letrozole and tamoxifen. The most common adverse events were bone pain, hot flushes, back pain, nausea, arthralgia, dyspnea, cough and fatigue (Table 23). Thromboembolic events, regardless of relationship to the study medication, were reported for 6 patients (1%) in the letrozole group and 11 patients (2%) in the tamoxifen group. Pulmonary embolus, regardless of relationship to the study medication, was reported in 2 patients (one in each monotherapy arm). Thromboembolic events included thrombophlebitis superficial, venous thrombosis NOS limb, phlebitis NOS, thrombosis NOS, venous thrombosis NOS and venous thrombosis deep limb.

Most adverse events were mild to moderate in severity (88% and 84% in the letrozole and tamoxifen groups, respectively). Few cases of discontinuation of study drug due to adverse events were reported (3% and 2% in the letrozole and tamoxifen groups, respectively).

Table 23 Number of patients with most frequent adverse events regardless of study drug relationship ($\geq 5\%$ in any group): 025

	Letrozole n (%)	Tamoxifen n (%)	Combination n (%)
Patients studied			
Total no. of patients studied	455	455	22
Total no. of patients with an AE	408 (90)	394 (87)	17 (77)
MedDRA preferred term			
Bone pain	89 (20)	83 (18)	2 (9)
Hot flushes (NOS)	81 (18)	70 (15)	3 (14)
Back pain	77 (17)	79 (17)	2 (9)
Nausea	66 (15)	72 (16)	5 (23)
Arthralgia	63 (14)	58 (13)	2 (9)
Dyspnea (NOS)	62 (14)	66 (15)	2 (9)
Cough	49 (11)	47 (10)	3 (14)
Fatigue	48 (11)	51 (11)	2 (9)
Constipation	41 (9)	40 (9)	1 (5)
Pain in limb	38 (8)	32 (7)	3 (14)
Chest pain NEC	34 (8)	35 (8)	1 (5)
Headache NOS	34 (8)	30 (7)	0
Diarrhea NOS	33 (7)	18 (4)	1 (5)
Post-mastectomy lymphoedema syndrome	30 (7)	29 (6)	1 (5)
Vomiting NOS	30 (7)	33 (7)	0
Insomnia NEC	26 (6)	18 (4)	0
Weight decreased	25 (6)	20 (4)	1 (5)
Alopecia (i.e., hair thinning)	24 (5)	18 (4)	3 (14)
Breast pain	24 (5)	25 (6)	3 (14)
Hypertension NOS	24 (5)	18 (4)	1 (5)
Influenza	24 (5)	17 (4)	4 (18)
Weakness	24 (5)	15 (3)	1 (5)
Edema lower limb	23 (5)	23 (5)	2 (9)
Pain NOS	22 (5)	27 (6)	0
Abdominal pain NOS	19 (4)	22 (5)	2 (9)
Appetite decreased NOS	19 (4)	27 (6)	1 (5)
Note: In addition, urinary tract infection NOS, abdominal pain upper, abdominal pain lower, anorexia and lower respiratory tract infection NOS were also reported for 5% of patients in the combination therapy group, but <5% of patients in the letrozole and tamoxifen groups.			

6.7.6 Suspected drug related adverse events

Study drug relationship for each adverse event was determined by the investigator and recorded in the case report form (CRF) as being: not related, unlikely, possible, probable, or highly probable, as defined in the study protocol. Adverse events with a study drug relationship of "not related" or "unlikely" were considered "not related." Adverse events with a study drug relationship of "possible," "probable," "highly probable," or with a missing relationship, are considered to have a suspected relationship.

Adverse events that were suspected to be related to study drug were reported with similar frequency (38% letrozole and 37% tamoxifen), and were similar in nature in both monotherapy groups. Suspected study drug related adverse events occurring in at least 3% of patients in any treatment group are summarized in Table 24.

Table 24 Adverse events; most frequently affected organ system ($\geq 3\%$ in any group):
025

	Letrozole n (%)	Tamoxifen n (%)	Combination n (%)
Patients studied			
Total no. of patients studied	455	455	22
Total no. of patients with an AE	173 (38)	167 (37)	11 (50)
MedDRA primary system organ class			
Preferred term			
Vascular disorders	87 (19)	81 (18)	5 (23)
Hot flushes NOS	74 (16)	61 (13)	3 (14)
Gastrointestinal disorders	53 (12)	48 (11)	6 (27)
Nausea	28 (6)	29 (6)	3 (14)
Skin & subcutaneous tissue disorders	46 (10)	40 (9)	5 (23)
Alopecia (i.e., hair thinning)	23 (5)	14 (3)	3 (14)
Sweating increased	9 (2)	12 (3)	0
General disorders & administration site conditions	23 (5)	23 (5)	2 (9)
Nervous system disorders	23 (5)	21 (5)	0
Metabolism & nutrition disorders	14 (3)	26 (6)	1 (5)
Reproductive system & breast disorders	13 (3)	15 (3)	3 (14)
In addition, hypertension NOS, hyperemia, dry mouth, abdominal pain, abdominal distension, abdominal pain lower, abdominal pain upper, pruritus NOS, dry skin, night sweats, fatigue, influenza like illness, anorexia, vaginal discharge, vulvovaginal dryness, breast pain, perineal pain female, edema lower limb, cardiac disorders (total), respiratory, thoracic and mediastinal disorders (total), lung infiltration NOS, blood and lymphatic system disorders (total) and neutropenia were also reported for 3% of patients in the combination therapy group (n = 22), but <3% of patients in the letrozole and tamoxifen groups			

6.7.7 Discontinuations due to adverse events

The frequency of discontinuations from the study due to adverse events was similar for both monotherapy groups. Adverse events leading to premature discontinuation are summarized by system organ class in Table 25.

Table 25 Patients discontinued for adverse events: 025

	Letrozole n (%)	Tamoxifen n (%)	Combination n (%)
Patients studied			
Total no. of patients studied	455	455	22
Total no. of patients discontinuing due to an AE	19 (4.2)	31 (6.8)	1 (4.5)
MedDRA primary system organ class			
Cardiac disorders	1 (0.2)	2 (0.4)	0
Gastrointestinal disorders	4 (0.9)	4 (0.9)	0
General disorders & administration site conditions	2 (0.4)	2 (0.4)	0
Hepato-biliary disorders	0	1 (0.2)	0
Injury & poisoning	1 (0.2)	0	0
Investigations	0	1 (0.2)	0
Metabolism & nutrition disorders	1 (0.2)	1 (0.2)	0
Musculoskeletal, connective tissue & bone disorders	3 (0.7)	6 (1.3)	0
Neoplasms benign and malignant	2 (0.4)	4 (0.9)	0
Nervous system disorders	0	7 (1.5)	0
Psychiatric disorders	0	2 (0.4)	0
Reproductive system & breast disorders	2 (0.4)	0	0
Respiratory, thoracic & mediastinal disorders	4 (0.9)	3 (0.7)	1 (4.5)
Skin & subcutaneous tissue disorders	0	2 (0.4)	0
Vascular disorders	5 (1.1)	6 (1.3)	0

6.7.8 Deaths and other serious adverse events (study 025)

The number of patients who died, experienced other serious or clinically significant adverse events or discontinued prematurely due to adverse events are summarized in Table 26.

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Table 26 Deaths and other serious or clinically significant adverse events (025)

	Letrozole n (%)	Tamoxifen n (%)	Combination n (%)
Total no. of patients studied	455	455	22
No. of patients who died	29 (6)	41 (9)	2 (9)
No. of patients with SAEs	101 (22)	106 (23)	4 (18)
No. discontinued due to AEs	19 (4)	31 (7)	1 (5)

6.7.8.1 Deaths

During the core phase of the study, there were 72 patient deaths in the safety population. There were 29 patient deaths in the letrozole group, 41 deaths in the tamoxifen group and 2 deaths in the combination treatment group. Most of the deaths were cancer related. There were 17 patient deaths considered not cancer related and 4 deaths of unknown cause. Patient deaths, considered not cancer related or of unknown cause, are listed in Table 27.

There were 3 deaths in the letrozole treatment arm that may have been due to a vascular event. Patient F/15/7159 had a history of diabetes and thrombophlebitis and the cause of death was a pulmonary embolism and myocardial infarction. There were 2 other patients with pulmonary embolism being suspected as the cause of death. The cause of death for patient USA/1456/7853 was not clear. The investigator felt that there was inadequate data to evaluate the patient's death, but thought the cause could have been cardiac arrhythmia or a pulmonary embolism. The cause of death for patient ZA/S004/2766 was also not clear, but the investigator suspected it could be due to a pulmonary embolism. These deaths were judged by the investigator not to be study-drug related.

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Table 27 Deaths during core phase or within 6 weeks of discontinuation of core therapy that were not cancer related or were of unknown cause: 025

Country/Center/Patient	Age of patient	Days to death	Cause of death
Letrozole treatment group:			
AUS / 0006 / 06089	70	113	coronary occlusion
D / 0002 / 07005	59	652	suicide
F / 0005 / 07213	66	141	hepatic cirrhosis
F / 0015 / 07159	77	3	ischemia and possible pulmonary embolism
I / 0010 / 06272	77	611	sudden death (cause unknown)
IND / 0003 / 06921	58	104	massive myocardial infarction
RA / 0019 / 06357	65	25	septic shock
USA / 1449 / 07885	81	670	cardiac arrest
USA / 1456 / 07853	65	393	unknown (possible pulmonary embolism)
ZA / 5004 / 02766	61	348	possible pulmonary embolus
Tamoxifen treatment group:			
CDN / 0006 / 06164	59	196	pneumonia
DK / 0008 / 00019	57	1056	apoplexia cerebri
E / 0008 / 06585	79	32	angor*
I / 0019 / 06709	58	10	coma (cause unknown)
NL / 0001 / 06331	69	30	cause unknown
PL / 0001 / 06881	80	210	bronchial asthma
RUS / 0004 / 02721	58	68	cerebral circulatory disturbance
RUS / 0005 / 06504	62	92	cardiopulmonary insufficiency
U / 0011 / 06350	85	24	not cancer related
USA / 1397 / 08029	76	51	not cancer related
ZA / 2012 / 08427	71	262	not cancer related

6.7.8.2 Serious adverse events

SAEs were similar in nature and frequency, and were reported for 101/455 patients (22%) in the letrozole group, 106/455 patients (23%) in the tamoxifen group and 4/22 patients (18%) in the combination treatment group.

One additional SAE (hospitalization due to deterioration and superficial thrombophlebitis) was reported for Patient DK/1/7439 (letrozole group) after the cutoff date for the ISS.

SAEs considered related to study drug were reported for 11/455 patients (2%) in the letrozole group and 15/455 patients (3%) in the tamoxifen group. There were no SAEs related to study drug reported in the combination therapy group. The frequency of related SAEs was low, and many were reported for only one patient each.

The most frequently reported related SAEs were thromboembolic events, reported for 3 patients (1%) in the letrozole group and 7 patients (2%) in the tamoxifen group. In addition,

SAEs of pulmonary embolism were reported in 2 patients on tamoxifen, which were judged by the investigators as possibly study-drug related.

6.7.9 Adverse events in supportive populations (studies 026 and 012)

In study 026 (18 patients, 9 letrozole 2.5 mg, 9 letrozole 2.5 mg/tamoxifen 20 mg), all patients experienced adverse events. The most common adverse event in both groups was bone pain. No unusual adverse effects were noted.

In study 026, one patient in the letrozole 2.5 mg group discontinued from the study due to adverse events (anorexia and weight loss). One patient in the letrozole 2.5 mg/tamoxifen 20 mg group died during the study due to cardio-respiratory arrest and pulmonary edema NOS.

In study 026, none of the patients in the letrozole 2.5 mg group died. Two patients in the letrozole 2.5 mg/tamoxifen 20 mg group died. One patient (M0761K/016) died due to cardio-respiratory arrest and pulmonary edema NOS that was not considered treatment-related by the investigator. In addition, one patient (M0766E/009) discontinued from the study for unsatisfactory therapeutic effect, and died within 42 days of administration of last dose of study drug due to her breast cancer.

In study 012, the total number of patients studied was 22 letrozole 0.5 or 2.5 mg and 10 Tamoxifen 30 mg. The total no. of patients with an AE was 14 (63.6%) and 9 (90.0%), respectively. Musculoskeletal and gastrointestinal disorders occurred most frequently in both treatment groups. All suspected treatment-related adverse events were reported in one or less patients in each treatment group. None of the patients treated with letrozole 0.5 mg experienced SAEs. Two patients treated with letrozole 2.5 mg and one patient treated with tamoxifen 30 mg experienced SAEs. Patient 4/153/1075 in the tamoxifen group discontinued from the study for this SAE. Two of these patients recovered. Patient 4/152/1074 remained unchanged for 12 months following onset of this SAE. None of these SAEs was considered treatment related by the investigators. One patient in the tamoxifen group discontinued from the study due to hypercalcemia

6.7.10 Deaths and other serious adverse events from ongoing trials

6.7.10.1

6.7.10.2

6.7.11 Summary of adverse event findings

The adverse event profile of letrozole was consistent across all 3 studies. In the large study (025), most patients experienced at least one adverse event, and the nature and frequency of adverse events were similar for both letrozole and tamoxifen. The most common adverse events in both treatment groups were bone pain, hot flushes, back pain and nausea. Most adverse events were mild to moderate in severity, and many were related to the patients' underlying breast cancer. The frequency and nature of SAEs were similar for both treatment groups, and only a small percentage of patients discontinued from the studies due to adverse events. The frequency of deaths was also low, and most were considered cancer related. Similar data were reported in the 2 smaller studies (012 and 026). In addition, SAE data from approximately 3200 patients in 4 ongoing or recently completed studies showed a similar safety profile to that reported in these 3 studies. In summary, the adverse events reported in these clinical studies were similar to those previously reported for letrozole and tamoxifen.

6.7.12 Laboratory data Study 025

The clinical laboratory evaluations performed during the study were:

- Hematology: hemoglobin, and hematocrit.
- Blood chemistry: creatinine, SGOT (AST), SGPT (ALT), alkaline phosphatase, GGT, total bilirubin and total calcium.

Hemoglobin was measured at baseline and during the core phase of study 025. Decreases in hemoglobin were mostly grade 1/2 in severity, and occurred with similar frequency in both treatment groups.

Serum chemistry was analyzed at baseline and during the core phase of the study. Shift tables of best baseline CTC grade against worst CTC grade during the study for, bilirubin, SGOT, SGPT, alkaline phosphatase, GGT, total calcium and serum creatinine showed no difference between the treatment groups.

The most common CTC grade 3/4 laboratory abnormality at baseline, or at any time during the core phase of the study, was elevated GGT. The number of patients with elevated GGT was similar for both treatment groups, and was not considered to be clinically relevant in this population of patients with advanced breast cancer. The nature and frequency of laboratory abnormalities were similar for both treatment groups, and there were no clinically meaningful trends observed.

6.7.13 Laboratory data (studies 026 and 012)

6.7.13.1 Study 026

Hematology and blood chemistry variables were assessed at each study visit. Changes from baseline in laboratory variables were similar for both treatment groups, except for platelet count, where 4 patients in the letrozole group had increases more than 25% from baseline values. One patient in the letrozole 2.5 mg/tamoxifen 20 mg group experienced a laboratory adverse event (hypokalemia).

6.7.13.2 Study 012

Hematology and blood chemistry variables were assessed at each study visit. Changes from baseline in laboratory variables were similar for all treatment groups. Fifty percent of patients in the letrozole 2.5 mg and tamoxifen 30 mg groups and 70% of patients in the letrozole 0.5 mg group had at least one abnormal post-baseline laboratory value. The majority of these events were mild in severity (CTC grade 1). Only 2 patients had clinically significant laboratory abnormalities (one letrozole patient had a CTC grade 4 increase in total bilirubin and one tamoxifen patient had a CTC grade 3 increase in GGT).

Two patients in the letrozole group reported adverse events associated with abnormal blood chemistry values (mild non-insulin diabetes mellitus and mild elevations in triiodothyronine and thyroxine levels), that were not considered treatment related. One patient in the tamoxifen group experienced hypercalcemia and discontinued from the study.

6.7.14 Summary of findings from laboratory data

Overall, the nature and frequency of laboratory abnormalities were similar for the letrozole and tamoxifen treatment groups, and there were no clinically meaningful trends observed. Most laboratory abnormalities were mild or moderate in severity. The most common grade 3 or 4 laboratory abnormality was elevated GGT. The frequency of patients with elevated GGT was similar for both treatment groups, and was not considered to be clinically relevant in this population of patients with advanced breast cancer.

6.7.15 Other supportive studies (study P024)

Study 024 was a double-blind, randomized, parallel-group, Phase IIb/III study comparing the efficacy and safety of letrozole (2.5 mg qd) or tamoxifen (20 mg qd) as pre-operative therapy for 4 months in postmenopausal women with primary untreated breast cancer. The frequency of adverse events was the same for both groups (Tables 28 and 29).

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Table 28 Summary of most frequent adverse events (5% in either group) by body system and preferred term irrespective of relationship to study treatment: 024

	Letrozole 2.5 mg n (%)	Tamoxifen 20 mg n (%)
Patients studied		
Total no. of patients studied	157	170
Total no. with an AE	89 (56.7)	97 (57.1)
Total no. with medication discontinued due to an AE	1 (0.6)	3 (1.8)
COSTART body system — IMN preferred term		
Body as a whole	27 (17.2)	31 (18.2)
Fatigue	7 (4.5)	9 (5.3)
Cardiovascular system	12 (7.6)	10 (5.9)
Digestive system	23 (14.6)	28 (16.5)
Nausea	10 (6.4)	13 (7.6)
Infections & infestations	5 (3.2)	12 (7.1)
Infection viral	4 (2.5)	11 (6.5)
Musculoskeletal disorders	18 (11.5)	15 (8.8)
Nervous system	28 (17.8)	20 (11.8)
Headache	12 (7.6)	8 (4.7)
Respiratory system	9 (5.7)	10 (5.9)
Skin and appendages	44 (28.0)	55 (32.4)
Hot flushes	32 (20.4)	43 (25.3)
Special senses	8 (5.1)	5 (2.9)
Urogenital & reproductive system	15 (9.6)	18 (10.6)

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Table 29 Summary of adverse events suspected of being related to study treatment ($\geq 2\%$ in either group): 024

	Letrozole 2.5 mg n (%)	Tamoxifen 20 mg n (%)
Patients studied		
Total no. of patients studied	157	170
Total no. of patients with at least one AE suspected of being related to study treatment	59 (37.6)	58 (34.1)
Total no. of patients with medication discontinued due to an AE suspected of being related to study treatment	1 (0.6)	1 (0.6)
IMN preferred term		
Hot flushes	32 (20.4)	40 (23.5)
Nausea	7 (4.5)	9 (5.3)
Fatigue	4 (2.5)	4 (2.4)
Headache	4 (2.5)	1 (0.6)
Asthenia	3 (1.9)	5 (2.9)
Sweating increased	3 (1.9)	5 (2.9)
Weight increase	3 (1.9)	4 (2.4)
Leukorrhea	0	6 (3.5)

6.7.15.1 Discontinuations due to adverse events

Four patients discontinued study medication because of adverse events (one patient in the letrozole group for a pulmonary embolism and 3 patients in the tamoxifen group for hepatitis C, erythema multiforme and cholestasis).

6.7.15.2 Deaths and other serious adverse events

No death was reported during the study or within 6 weeks of any patient receiving the last dose of study medication.

One patient in each treatment group experienced thromboembolic events. No other SAEs occurred more than once in either treatment group. The frequency of SAEs was similar in both treatment groups. Two SAEs suspected of being related to study medication were reported (one patient in the letrozole group was discontinued for pulmonary embolism and one patient in the tamoxifen group discontinued for erythema multiforme. The most frequent SAEs are summarized in Table 30.

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Table 30 Summary of all serious adverse events irrespective of relationship to study treatment (from SAERs): 024

	Letrozole 2.5 mg	Tamoxifen 20 mg
Patients studied		
Total no. of patients studied	157	170
Total no. (%) of patients with a SAE*	10 (6%)	8 (5%)
MedDRA preferred term		
Angina pectoris	1	0
Atrial tachycardia	1	0
Edema NOS	0	1
Gastric ulcer	0	1
Gastritis NOS	1	0
Umbilical hernia NOS	1	0
Pain NOS	0	1
Fistula NOS	1	0
Pyrexia	0	1
Weakness	1	0
Cholestasis	0	1
Cellulitis	1	0
Hepatitis C	0	1
Infection NOS	0	1
Fracture NOS	1	0
Dizziness (excl vertigo)	1	0
Syncope	1	0
Cystalgia	0	1
Mastitis	0	1
Erythema multiforme	0	1
Pulmonary embolism	1	0
Thromboembolic events	1	1
* Patients could have experienced more than one SAE.		

6.7.16 Safety data from other sources

6.7.16.1 Marketing experience

Serious adverse drug reactions reported to Novartis from July 16, 1999 to February 23, 2000 were retrieved from the Novartis Council for International Organizations of Medical Science standardized listing of adverse drug reactions (On-line System for the Collection of Adverse Reaction Reports [OSCAR]) database. There were 10 reports of SAEs from the commercial use of Letrozole (2.5 mg) during this time period. There was no trend observed; in fact, only one occurrence of each drug reaction was reported. These SAEs were similar in nature to those reported for the studies summarized in this ISS, and no deaths were reported. Based on

the number of prescriptions sold during this time period, the number of patients who received commercial treatment with Letrozole is estimated to be approximately [REDACTED] SAEs are summarized in Table 31.

Table 31 Serious adverse events reported during commercial use

Country	Age	Reaction description
AUS	55	polyarthrititis
NL	69	abnormal liver function tests
IND	58	myocardial infarction
F	61	pericarditis, pleural effusion, hypereosinophilia
USA	50	arterial thrombosis
CDN	83	varicose veins, swollen abdomen
E	81	respiratory insufficiency
D	57	hemolytic anemia
F	unknown	thrombopenia
D	40	hepatic neoplasm

6.7.17 Adverse event summary

The safety of Letrozole, at the recommended daily dose of 2.5 mg, compared with tamoxifen has been assessed in one large study (025) with 932 patients and 2 smaller supportive studies (012 and 026) with 50 patients.

In the large study, the median duration of exposure was longer with letrozole (11 months) compared with tamoxifen (6 months). In the smaller studies, the median duration of exposure was also longer with letrozole (15 months) compared with tamoxifen (3 months). Across these 3 studies, 222 patients (46%) were treated with letrozole for more than 12 months compared with 141 patients (30%) treated with tamoxifen. Based on these data, it was apparent that long-term treatment with letrozole was generally well tolerated in this patient population.

The adverse event profile of letrozole was consistent across all 3 studies. In study 025, most patients experienced at least one adverse event, and the nature and frequency of adverse events were similar for both letrozole and tamoxifen. The most common adverse events in both treatment groups were bone pain, hot flushes, back pain and nausea. Most adverse events were mild to moderate in severity, and many were related to the patients' underlying breast cancer. The frequency and nature of SAEs were similar for both treatment groups, and only a small percentage of patients discontinued from the studies due to adverse events. The frequency of deaths was also low, and most were considered cancer related. Similar data were reported in the 2 smaller studies (012 and 026). In addition, SAE data from approximately [REDACTED]

[REDACTED] showed a [REDACTED]
In summary, the adverse events reported in these clinical studies were similar to those previously reported for letrozole and tamoxifen.

Overall, the nature and frequency of laboratory abnormalities were similar for the letrozole and tamoxifen groups, and no clinically meaningful trends were observed. Most laboratory abnormalities were mild or moderate in severity. The most common CTC grade 3/4 laboratory abnormality was elevated GGT. The frequency of patients with elevated GGT was low, similar for both treatment groups, and not considered to be clinically relevant in this population of patients with advanced breast cancer.

7. Study results per FDA

7.1 Patient characteristics

Table 32 describes the characteristics of patients enrolled in study 025.

Table 32 Patient characteristics

Characteristic	Letrozole (n=456)	Tamoxifen (n=456)
Median Age (range)	65 (31-96)	64 (31-93)
<50 (no. of pts)	26	34
>70 (no. of pts)	139	134
Median BMI (range)	25.9 (14.6-44.5)	25.5 (15.6-52.7)
>30 (no. of pts)	85	78
ER+ and/or PR+	296 (65%)	308 (68%)
ER and PR unknown	160 (35%)	148 (32%)
Prior adjuvant therapy	171 (38%)	183 (40%)
Chemotherapy only	74	90
Hormonal therapy only	68	59
Both	29	34
Prior antiestrogens	86 (19%)	83 (18%)
Prior advanced disease chemo	27 (6%)	25 (6%)
Duration of antiestrogen Rx		
<2 years	26	32
≥2 years	60	61
Dominant disease site		
Soft tissue	120 (26%)	124 (27%)
Bone	153 (34%)	136 (30%)
Visceral	183 (40%)	196 (43%)
Liver	61	55
Performance status		
100	114 (25%)	121 (27%)
90	141 (31%)	146 (32%)
80	120 (26%)	111 (24%)
70	53 (12%)	40 (9%)
<70	30 (6%)	39 (8%)

Based on the above data the two patient treatment populations appear to be comparable with no significant difference in the various prognostic factors. It should be noted that the sponsor recorded prior advanced disease chemotherapy in 9% of letrozole and 11% of tamoxifen treated patients. The reason for the discrepancy is uncertain but the arms were balanced in either case.

7.2 Efficacy results

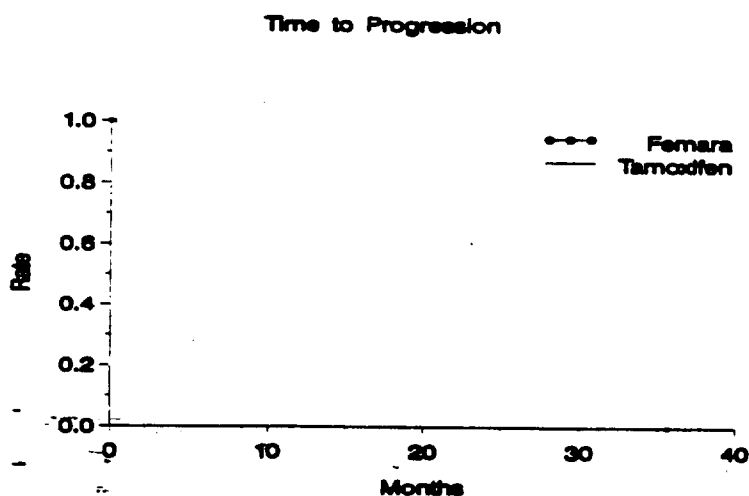
7.2.1 Time to progression

Table 33 and Figure 3 provide time to progression data based on FDA evaluation. Time to progression significantly favored letrozole treatment.

Table 33 Time to progression

	Median TTP (mo)	95% C.I.	P value (L-R)	HR (95% C.I.)
Letrozole	9.87	(9.11-12.20)	0.0001	0.713 ((0.61-0.84))
Tamoxifen	6.15	(5.79-8.45)		

Figure 3 Time to Progression - FDA



7.2.2 Response rate and response duration

Overall treatment response rates, response rates by dominant site and response rates by hormone receptor status are summarized in Table 34.

Table 34 Response rate per FDA

	Letrozole		Tamoxifen		p
	Number	Percent	Number	Percent	
Response Rate					
CR	39/456	9	14/456	3	
PR	108/456	24	84/456	18	
Total	147/456	32	98/456	21	0.0003*
Response rate by Dominant Site					
Liver	8/61	13	6/55	11	0.7
Other visceral	46/122	38	29/141	21	0.003
Bone	36/153	24	20/137	15	0.10
Soft tissue	57/120	48	43/123	35	0.051
Response rate by receptor status					
ER+ or PR+ or both	97/295	33	67/306	22	0.0025
ER and PR unknown	50/161	31	31/150	21	0.04

* Odds Ratio 1.74, 95% C.I. (1.291, 2.34) or 0.58 (0.4274, 0.7748)

Several comments should be made regarding observed response rates. First it is obvious that response rates to letrozole are superior to tamoxifen response rates. One possible explanation for this is that the tamoxifen response rates are artificially low. Textbooks frequently report tamoxifen response rates of 30-50%, or higher, in the first line advanced disease/metastatic disease setting. To determine the accuracy of these response rates the metastatic breast cancer literature was reviewed for first-line hormone or combined hormone therapy/chemotherapy randomized trials conducted in post-menopausal women with advanced-metastatic disease in which tamoxifen alone was one of the treatment arms. Table 35 presents that data.

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Table 35 First-line Tamoxifen therapy of postmenopausal women with advanced/metastatic breast cancer - literature

Author	# Pts	Tamoxifen dose/day	Predominant Metastases ST/B/V* (%)	Evaluation frequency (mo)	Response rate (%)
Muss 1998	67	20	15/48/37	q3	31
Gill 1993	58	40	15/30/55	q3	26
Powles 1982	62	20	--	q1	31
Mouridsen 1979	65	30	51/20/29	q1-3	39
Mouridsen 1980	46	30	35/28/37	q1-3	44
Rose 1986	98	30	47/18/35	q1-2	46
Hoogstraten 1984	95	20	--	q1-1.5	46
Ingle 1986	49	20	22/33/45	q1-2	43
Gertch	64	20	18/42/40	q1 x 3, then q3	30
Morgan 1985	48	20	31/46/23	q1-2	36
Ettinger 1986	103	20	47/35/18	q1.5	42
Ingle 1981	69	20	23/22/55	q1-2	33
Muss 1994	84	20	8/48/44	q1-3	17
Gale 1994	108	20	--	--	27
Australian 1986	113	40	8/35/57	q3	22
Present study	456	20	27/30/43	q3	21

* Predominant disease site - Visceral/bone/soft tissue

Response is defined as a specified amount of tumor shrinkage that persists for at least 1 month. In comparing response rates in the above table it appears that they are higher when follow-up intervals are shorter. This is the expected result since the longer the interval of follow-up the more likely that a tumor will increase in size within the interval. In the present study since the follow-up interval was 3 months study tumor measurement data was reviewed a second time to find patients who met response criteria at one visit but who had progressed or not been evaluated at the next scheduled visit. It was hypothesized that if these individuals had been evaluated sooner than three months after their response a percent would have been classified as responders rather than as non-responders. Table 36 presents these results. As indicated 25 tamoxifen treated patients and 31 letrozole treated patients met PR or CR criteria on one visit. None of these patients were either responders on a follow-up visit or had a follow-up visit. Since a total of 24 patients (14T, 10L) progressed solely on physical examination findings and since 10 (1T, 9L) did not have a 3 month follow-up it is conceivable

that if patients were seen at monthly rather than 3 monthly intervals that many of these 34 individuals might have been classified as responders.

Based on the above considerations it does not appear that the observed tamoxifen response rates are inordinately low. This supports the conclusion that letrozole is superior to tamoxifen with regard to response rates.

Table 36 Responders based on a single visit

Rx	Met response criteria on 1 visit (Number of Pts)	F/U exam not done	Diagnostic test documenting progression			
			P.E.	Chest x-ray	Bone X-ray	CT scan
Tam	25	1	14	3	6	1
Let	31	9	10	6	4	2

Another issue is whether letrozole, or any hormone therapy is appropriate for individuals with liver metastases. As indicated in Table 34 patients with liver metastases have lower response rates than patients with other visceral disease, bone predominant or soft tissue predominant disease. However, whereas liver responses with tamoxifen therapy were relatively short-lasting (3, 3, 6, 6, 6, 20 months) responses with letrozole therapy were longer lasting (3, 6, 11, 11, 12, 12, 12, 15 months). Because response of hepatic metastases to chemotherapy is also expected to be lower than response rates at other sites this data supports the use of hormonal therapy for all metastatic disease sites.

Response Duration

Table 37 indicates median response duration. Response durations were comparable for both letrozole and tamoxifen treatment.

Table 37 Response duration

Treatment	# of responders	Median response duration (mo)	95% C.I.	p
Letrozole	147	11.5	10.2-12.1	0.94
Tamoxifen	98	10.3	9.0-12.1	

7.2.3 Improvement in Performance Status

An analysis was performed to determine whether letrozole and/or tamoxifen treatment improved performance status. Because there is no information on the reproducibility of performance status measurement from investigator to investigator nor on how much performance status has to improve to be clinically important the following analysis must be considered to be exploratory. As performed, performance status was considered to be improved if there was at least a 10% increase, over baseline, on at least two consecutive visits. Results are summarized in Table 38. Overall, 110 of 344 letrozole treated patients (32%) improved their performance status during treatment as compared to 65 of 336 (19%) of tamoxifen treated patients. This difference was statistically significant $p=0.0002$.

Table 38 Improvement in performance status

Initial P.S.	Letrozole					Tamoxifen				
	Increase P.S. (2+ consecutive determinations)					Increase P.S. (2+ consecutive determinations)				
	# Pts	+10	+20	+30	Total (%)	# Pts	+10	+20	+30	Total (%)
90	141	38	—	—	38 (27)	146	19	—	—	19 (13)
80	120	24	8	—	32 (27)	111	16	7	—	23 (21)
70	53	13	8	3	24 (45)	40	9	3	0	12 (30)
60	25	3	8	2	13 (52)	29	2	2	4	8 (28)
50	5	2	0	1	3 (60)	10	2	1	0	3 (30)
Total	344				110 (32)*	336				65 (19)*

* $\chi^2 = 14.9$ $p=0.0002$

7.3 Safety

Duration of time on therapy for patients receiving letrozole or tamoxifen is summarized in Table 39. Letrozole patients remained on core treatment longer than did tamoxifen patients. The median duration of letrozole treatment was approximately 13 months versus approximately 8 months for tamoxifen treatment.

Table 39 Duration of core treatment

Time on treatment (mo)	Letrozole (458 pts)	Tamoxifen (458 pts)
1-3	445	442
4-6	334	287
7-9	290	205
10-12	241	160
13-15	184	124
16-18	119	81
19-21	76	51
22-24	39	34
25-27	22	18
28-30	15	8

The sponsor has adequately summarized adverse events associated with letrozole and tamoxifen in Section 6.7 of this report. The following discussion will compare letrozole and tamoxifen as regards known serious tamoxifen adverse effects.

Serious adverse effects known to be associated with tamoxifen treatment for up to 5 years include thromboembolic events, endometrial cancer, and possible ocular toxicity (retinopathy,

cataracts). Other adverse events of lesser severity include hot flashes, atrophic vaginitis, and suppression of peripheral blood counts. Potential beneficial effects of tamoxifen include reduction in risk of developing contralateral breast cancer, increase in bone mineral density, and improvement in serum lipoproteins with resultant decrease in cardiovascular deaths.

Table 40 documents a comparison of letrozole and tamoxifen with regard to the aforementioned adverse effects. In this table all adverse events were counted irrespective of whether they were, or were not, attributed to protocol treatment.

Table 40 Serious adverse events

Toxicity	Letrozole (455 pts)	Tamoxifen (455 pts)
Peripheral thromboembolic events	8 (2%)	11 (2%)
Cardiovascular events	7 (2%)	4 (1%)
Cerebrovascular events	5 (1%)	6 (2%)
Fractures	21 (5%)	18 (4%)
Endometrial cancer	0 (0%)	1 (0.2%)
Ocular toxicity	7 (2%)	5 (1%)
Hot flashes	82 (18%)	72 (16%)
Vaginal discomfort	12 (3%)	9 (2%)
Decreased WBC's or platelets	3 (0.7%)	0 (0%)

Peripheral thromboembolic events included venous thrombosis, thrombophlebitis, portal vein thrombosis and pulmonary embolism. Cardiovascular events included angina, myocardial infarction, myocardial ischemia, and coronary heart disease. Cerebrovascular events included transient ischemic attacks, thrombotic or hemorrhagic strokes and development of hemiparesis. Regarding fractures 21 femora treated patients had a total of 26 fractures compared to 20 fractures in 18 tamoxifen treated patients. As is evident from the above table and from the sponsor's adverse events summary both letrozole and tamoxifen manifest a similar toxicity spectrum.

The number of patients with cardiovascular, cerebrovascular and peripheral vascular adverse events listed in Table 40 are in the same ballpark as corresponding sponsor data but differ somewhat because the terms that the sponsor used to classify patients as having events is not entirely comparable to the terms that the FDA reviewer used. A comparison of sponsor and FDA reviewer accepted terms for fractures and cardiovascular/ cerebrovascular events is indicated in Tables 41 and 42.

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Table 41 Terms for Fracture

Term	Sponsor Included	FDA Included
Fractures		
Femoral neck fracture	X	X
Femur fracture NOS		
Fracture NOS		
Fractured pelvis NOS		
Fractured sacrum		
Hip fracture		
Humerus fracture		
Pubic rami fracture		
Radius fracture		
Rib fracture		
Spinal fracture NOS		
Patella fracture		
Foot fracture		
Forearm fracture		
Tibia fracture		
Wrist fracture		
Pathological fracture		
Costal pain	X	No
Spinal cord compression	X	No
Fall (broken ribs, back compression fracture, broken pelvis after fall)	X	X
Myelopathy NEC	X	No
Hip arthroplasty	X	No

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Table 42 Terms for Cardiovascular and Cerebral arterial events

Term	Sponsor Included	FDA Included
Chest Pain		
Thoracic pain (chest pain NEC) not tumor related	X	No
Angina (Pain NOS)	X	X
Chest pain aggravated	X	No
Cardiovascular		
Angina pectoris	X	X
Cardiac arrest	X	No
Cardiac failure NOS	X	No
Cardiac failure congestive	X	No
Coronary artery disease (NOS)	X	X
Coronary artery occlusion	X	X
Left ventricular failure	X	No
Myocardial infarction	X	X
Myocardial ischaemia	X	X
Cerebrovascular		
Cerebrovascular accident NOS	X	X
Cerebrovascular disorder NOS	X	X
Hemorrhagic stroke	X	X
Cerebral infarction	X	X
Transient ischemic attack	X	X
Vascular disorder NOS	X	X
Dysarthria	X	X
Hemiparesis	X	X
Peripheral motor neuropathy	X	No
Peripheral neuropathy NEC	X	No

7.3.1 Adverse events as a function of age

The sponsor and the FDA performed an analysis of safety data by age using the following age groupings: ≤ 55 , >55 to <70 , and ≥ 70 . Within each age group, and for each treatment, adverse events were comparable in both analyses.

7.3.2 Adverse events by ethnicity

The trial population was 86% Caucasian, 3% Black and 11% Oriental/other. The small number of non-Caucasian patients limits an analysis of adverse events by ethnicity.

7.3.3 Discontinuation of therapy prior to progression

Therapy was discontinued prematurely in 11 letrozole treated patients and 18 tamoxifen treated patients. Reasons for treatment discontinuation are presented in Table 43. As is evident from the table safety was not the cause for premature discontinuation, in most instances. Pain, especially bone pain was the most frequent reason for terminating treatment prior to objective progression.

Table 43 Premature therapy discontinuation

Principal Cause	Letrozole (11 pts)	Tamoxifen (18 pts)
Bone pain	6	9
Thrombosis (venous or arterial)	3	4
Heart failure	0	1
Respiratory failure	0	1
Weight loss	1	0
New primary	0	1
Somnolence	0	1
Unknown	1	1

8.0 References

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9.0 Financial Disclosure

Standard procedures were followed to collect financial disclosure information i.e. FDA forms 3454 and 3455, as appropriate. If no initial reply follow-up letters X 2 were sent at 4-week intervals. At study close out and/or as part of retrospective collection investigators were told to update the sponsor if any change occurred during a 1-year period from the date of the last patient visit at their site.

Methods to minimize bias included:

- Independent data monitoring via sponsor or CRO
- Multiple investigators
- Double-blind, double-dummy design

Only a single investigator, _____ Georgetown University, indicated that _____ had received grants and income from the sponsor. Georgetown University accrued 3 patients to the study.

Forty-three USA institutions participated in study. _____ Principal investigators at 5 of these institutions failed to file the appropriate forms and one or more co-investigators at 20 institutions failed to file forms. The total number of patients enrolled at the institutions lacking forms was 39.

The experience in Austria, Canada, France, Great Britain, Greece, Germany, India, Portugal, Netherlands, Poland, Russia, Sweden, Tunisia, and United Kingdom is comparable. No

information was provided for the single site in China that had the second largest study accrual (49 patients).

Based on the above there does not seem to be significant financial disclosure problems.

10.0 Study Synopsis

Title of study: Double-blind, double dummy, randomized, multicenter, 2-arm, Phase III trial comparing letrozole 2.5 mg versus tamoxifen 20 mg as first-line therapy in postmenopausal women with advanced breast cancer.

PI's: Dr H Müridsen, Dr M Gershanovich, Prof Y Sun,

Study center(s): A total of 939 patients were randomized in 201 sites in 29 countries

Study period: First randomization: 26-Nov-1996. Cutoff date for primary analysis of core treatment phase: 08-Mar-2000

Objectives:

Primary: To compare efficacy, as evaluated by time to progression (TTP).

Secondary: To compare the tolerability and toxicity of the two treatment arms, to determine the overall survival time in each of the two treatment arms, to evaluate objective response rate (CR + PR), overall clinical benefit rate (CR + PR + NC $\geq$ 24 weeks), duration of response and clinical benefit, and time to treatment failure (TTF) between the two treatment arms (2.5 mg letrozole once daily and 20 mg tamoxifen once daily) during the core phase of the study and to evaluate time to treatment failure for the second-line treatment using the subset of patients in the crossover treatment period.

Methodology: The study was randomized and double-blind, double dummy with a parallel arm design for the core phase of the study. The core phase was defined as the interval between the date of the first patient randomization (dispensed study medication) until the cutoff date for the primary analysis (core treatment). On progression of disease or any other reason leading to discontinuation of core treatment, patients could be switched to the alternative treatment, still under double-blind conditions, provided that they remained suitable for endocrine anti-cancer treatment. The extension phase is defined as the interval between cutoff date for the primary analysis (core treatment) until approximately 18 months afterwards (the time when the majority of patients on crossover treatment would have progressed). All patients are followed for survival after discontinuation of study treatment(s) until the cutoff date for analysis of the extension phase (expected to be no later than the end of 2001).

Number of patients: In the original protocol, there were 3 treatment arms: letrozole 2.5 mg, tamoxifen 20 mg, and letrozole 2.5 mg in combination with tamoxifen 20 mg. It was planned to enroll a minimum of 1,371 patients; 457 patients in each treatment arm. Amendment 1 eliminated the combination treatment arm due to potential pharmacokinetic interactions between tamoxifen and letrozole. Patients assigned combination treatment continued on study

as per protocol, but enrollment to the combination treatment arm was stopped. The study was redesigned with a new randomization schema for a 2-arm study.

From 26-Nov-1996 through 07-Jan-1999, a total of 939 patients were randomized, ^{including} including 23 patients who had been assigned combination treatment. Five patients from one site were excluded from the primary safety and efficacy analyses due to GCP non-compliance at that site. The safety population includes all patients, who were randomly assigned study treatment and took at least one dose of study medication, excluding patients at one GCP non-compliant center. Patients assigned combination treatment were included in the safety population.

The ITT efficacy population consists of all patients, who were randomly assigned study treatment with monotherapy and had advanced breast cancer at study entry, excluding patients at the one GCP non-compliant center. The ITT population includes 2 patients (1 on each treatment arm) who never took any dose of study medication. A total of 907 patients are included in the ITT efficacy population (453 assigned letrozole, 454 assigned tamoxifen). The safety population comprises 932 patients (455 assigned letrozole, 455 assigned tamoxifen, and 22 assigned the combination).

Indication and main criteria for inclusion: Postmenopausal patients with histological or cytological evidence of breast cancer presenting with locally advanced or loco-regionally recurrent disease not amenable to treatment by surgery or by radiotherapy, or with metastatic disease were eligible for study. Patients had not been previously treated with endocrine anti-cancer agents for their advanced disease. Patients could have received adjuvant anti-estrogen treatment provided that they had both a treatment-free interval and disease-free interval of at least 12 months between end of adjuvant treatment and entry into Protocol 25. No more than one regimen of chemotherapy in the advanced disease setting was allowed. Patients had to be estrogen-receptor and/or progesterone-receptor positive or with both receptors unknown, with measurable or evaluable disease, and a Karnofsky performance status of at least 50%. Amendment 1 allowed patients with blastic bone lesions only to be enrolled.

Drugs:

Investigational drug: Letrozole 2.5 mg (or matching letrozole placebo) was supplied as 6 mm diameter, film-coated tablets. The tablets were supplied in bottles of 100, sufficient for 3 months (once daily oral dose to be taken in the morning). Letrozole and its placebo were of identical outward appearance and taste.

Reference treatment: Generic tamoxifen was supplied as Tamofen" (Leiras, Finland), 20 mg active substance (or matching tamoxifen placebo), tablets in bottles of 100 (once daily oral dose to be taken in the morning). Tamoxifen and its placebo were of identical outward appearance and taste.

Duration of treatment: The randomized treatment was administered until disease progression, or until other reasons (e.g. adverse event) led to discontinuation. If the patient remained suitable for endocrine anti-cancer therapy, treatment could be switched to the alternative, still under double-blind conditions.

Results per FDA:

Efficacy: The letrozole and tamoxifen monotherapy treatment arms were well balanced with respect to baseline demographic characteristics, extent of disease and prior therapy. Letrozole was superior to tamoxifen in prolonging time to progression, Median TTP letrozole 9.9 months 95% CI (9.1-12.2) versus tamoxifen 6.2 months 95% CI (5.8-8.5), $p=0.0001$, HR 0.713 95% CI (0.61-0.84) and in objective response rate 32% versus 21%, $p=0.0003$, odds ratio 1.74 95% CI (1.29,2.34) Letrozole response rates were superior to tamoxifen in women with hormone receptor positive cancer cells and in women with unknown receptor status. There were no significant differences between treatments in duration of overall tumor response. In an exploratory analysis 110 of 344 letrozole treated patients (32%) improved their performance status ($\geq 10\%$ Karnofsky scale for ≥ 2 consecutive visits) during treatment as compared to 65 of 336 (19%) tamoxifen treated patients ($p=0.0002$).

Safety: Adverse events (AEs) irrespective of relationship to study treatment were reported for 90% of patients in the letrozole arm and 87% of patients in the tamoxifen arm. AEs reported by more than 10% of patients for letrozole and tamoxifen respectively, were bone pain (20%, 18%), back pain (17%, 17%), nausea (15%, 16%), dyspnea (14%, 14%), arthralgia (14%, 13%), cough (11 %, 10%) and fatigue (11 %, 11 %). Serious adverse events are noted in the following table:

Toxicity	Letrozole (455 pts)	Tamoxifen (455 pts)
Peripheral thromboembolic events	8 (2%)	11 (2%)
Cardiovascular events	7 (2%)	4 (1%)
Cerebrovascular events	5 (1%)	6 (2%)
Fractures	21 (5%)	18 (4%)
Endometrial cancer	0 (0%)	1 (0.2%)
Ocular toxicity	7 (2%)	5 (1%)
Hot flashes	82 (18%)	72 (16%)
Vaginal discomfort	12 (3%)	9 (2%)
Decreased WBC's or platelets	3 (0.7%)	0 (0%)

Peripheral thromboembolic events included venous thrombosis, thrombophlebitis, portal vein thrombosis and pulmonary embolism. Cardiovascular events included angina, myocardial infarction, myocardial ischemia, and coronary heart disease. Cerebrovascular events included transient ischemic attacks, thrombotic or hemorrhagic strokes and development of hemiparesis. Regarding fractures 21 letrozole treated patients had a total of 26 fractures compared to 20 fractures in 18 tamoxifen treated patients. As is evident from the above table both letrozole and tamoxifen manifest a similar toxicity spectrum.

Conclusions: Letrozole is superior to tamoxifen for the first-line treatment of advanced breast cancer, as manifested by significantly longer time to progression and significantly higher overall objective tumor response rate. Letrozole was equally well tolerated as tamoxifen.

11.0 120-Day Safety Update

The sponsor is requested not to submit the 120 day update as there already exists sufficient letrozole safety data.

12.0 ODAC

sNDA 20-726 was submitted to the December 13, 2000 ODAC meeting. The background information provided to ODAC and the FDA questions regarding this submission are indicated below:

12.1 Background

At the June 1999 meeting the Committee indicated that for approval of new cytotoxic drugs for initial treatment of metastatic breast cancer a favorable effect on survival in randomized controlled trials is required. The Committee indicated that a favorable effect on time to tumor progression (TTP) is not adequate for approval. An impressive improvement of TTP in the range of 4-6 months would be adequate for accelerated approval. A better tumor response rate is not adequate for approval.

The rationale is that most cytotoxic drugs have significant toxicity. TTP and tumor response rate are not shown to be surrogates for survival. Usually only a minority of patients have a tumor response and most of these are partial responses. TTP effects are usually modest. In the absence of a favorable effect on survival it is not clear that a better TTP or tumor response rate is sufficient to overcome the drug toxicity.

In contrast the FDA has accepted a favorable effect on tumor response or TTP in randomized controlled trials as adequate for approval of hormonal drugs for initial treatment of metastatic breast cancer. Demonstration of statistical superiority or non-inferiority of survival is not required, but updated survival data are required at the time of approval. If survival is trending strongly against the new hormonal drug, a decision on approval will be delayed until more mature survival data are available. Mature survival data are not usually available when Marketing Applications for hormonal drugs are initially submitted to the FDA.

The rationale is that hormonal drugs have modest toxicity relative to cytotoxic drugs. A favorable effect on tumor response rate or TTP comes at a lesser cost in toxicity than with cytotoxic drugs.

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12.2 Questions to ODAC

1. Does the Committee agree with the FDA's criteria for approval of hormonal drugs for initial treatment of advanced metastatic breast cancer?

Yes 13 No 0 Abstain 0

2. Does the single study comparing Femara with Tamoxifen show that Femara is effective for initial hormonal treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown advanced metastatic breast cancer?

Yes 13 No 0 Abstain 0

3. In view of the efficacy is the safety of Femara adequate?

Yes 13 No 0 Abstain 0

4. Is the Femara SNDA approvable?

Yes 13 No 0 Abstain 0

13.0 Labeling

The division has revised the sponsor's label and has forwarded the revisions to the sponsor for incorporation into the final label.

14.0 Recommendation

Full approval with labeling revisions.

/S/
Martin H. Cohen, M.D.
Medical Reviewer
December 22, 2000

/S/
John R. Johnson, M.D.
Medical Team Leader
12-21-00

/S/
Ning Li, Ph.D.
Statistical Reviewer

/S/
Gang Chen, Ph.D.
Statistical Team Leader

Staten

MEDICAL OFFICER REVIEW OF A PROTOCOL AMENDMENT # 3

.D:

DRUG: Femara (letrozole tabs)

SPONSOR: Novartis

P.I. Margaret Dugan, M.D.

M.O. Martin H. Cohen, M.D.

DATE RECEIVED: September 7, 1999

SEP 13 1999

This amendment proposes 7 protocol modifications. All are satisfactory except for the definition of Time to Progression (TTP).

The sponsor's definition of TTP is:

- appearance of a new lesion, or increment ≥ 25 % of measurable lesion or progression in evaluable or unmeasurable, non-evaluable disease
- termination of core therapy with documented evidence of clinical deterioration due to breast cancer at the time of discontinuation
- death due to breast cancer or death of unknown cause while on study drug (core) or within 6 weeks of discontinuation. For death due to unknown cause, there must be documented evidence of clinical deterioration due to breast cancer.

Time to progression is right-censored if any of the following conditions apply at cutoff for analysis:

- Receiving trial treatment without evidence of progression
- Deaths from non-cancer causes
- Deaths of unknown cause without evidence of clinical deterioration due to breast cancer
- Discontinuation of core therapy (or crossover to the alternative therapy) without evidence of clinical deterioration due to breast cancer prior to discontinuation and no death due to breast cancer in the 6 weeks following discontinuation.

The end-date for TTP analysis will be the earliest date of documented progression of disease (visit date). In the absence of a clear diagnosis of progression, the end-date for TTP will be the date of the last clinical visit or previous tumor assessment (visit date) if the tumor assessment at the last clinical visit is incomplete. The exception to this would be in the case of death or termination without tumor assessment, then the date of death or date of last contact respectively will be used. For cases where there is documented clinical deterioration of

general condition due to breast cancer, or death of unknown cause with documented clinical deterioration due to breast cancer the date of the earliest visit at which the deterioration is documented will be taken.

FDA Interpretation

The problem with the above definition is that progression can be based on "clinical deterioration". Clinical deterioration is not defined. Further, it is difficult to imagine how clinical deterioration due to cancer could occur in the absence of objective evidence of disease progression. Also, in the FDA experience, cancer related clinical deterioration does not occur acutely so that investigators who suspect disease progression should have sufficient time to document that progression.

The FDA believes that in the absence of documented tumor progression patients who leave the study for any reason should be censored on the date of their last complete evaluation for progressive disease.

ISI

Martin H. Cohen, M.D.
September 13, 1999

ISI

John R. Johnson, M.D.
September 13, 1999

Division File
A. Staten

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