sNDA 20-726

FDA MEDICAL AND STATISTICAL ODAC REPORT

Drug Name: Femara® Letrozole tablets
Applicant: Novartis
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1. General Information

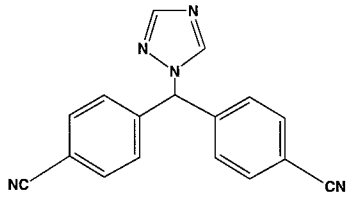
1.1 Pharmacological class

Letrozole is a non-steroidal aromatase inhibitor (inhibitor of estrogen biosynthesis) and an anti-neoplastic agent.

1.2 Description

Letrozole (femara tablets) for oral administration contains 2.5 mg of letrozole. It is chemically described as 4,4'-(1H-1,2,4-Triazol-1-ylmethylene)dibenzonitrile, and its structural formula is

Figure 1 Letrozole - Structural Formula



Letrozole is a white to yellowish crystalline powder, practically odorless, freely soluble in dichloromethane, slightly soluble in ethanol, and practically insoluble in water. It has a molecular weight of 285.31, empirical formula $C_{17}H_{11}N_5$, and a melting range of 184°C-185°C.

Inactive Ingredients. Colloidal silicon dioxide, ferric oxide, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, talc, and titanium dioxide.

1.3 Pharmacokinetics

Letrozole is rapidly and completely absorbed from the gastrointestinal tract and absorption is not affected by food. It is metabolized slowly to an inactive metabolite whose glucuronide conjugate is excreted renally, representing the major clearance pathway. About 90% of radiolabeled letrozole is recovered in urine. Letrozole's terminal elimination half-life is about 2 days and steady-state plasma concentration after daily 2.5 mg dosing is reached in 2-6 weeks. Plasma concentrations at steady-state are 1.5 to 2 times higher than predicted from the concentrations measured after a single dose, indicating a slight non-linearity in the pharmacokinetics of letrozole upon daily administration of 2.5 mg. These steady-state levels are maintained over extended periods, however, and continuous accumulation of letrozole does not occur. Letrozole is weakly protein bound and has a large volume of distribution (approximately 1.9 L/kg).

In the study populations (adults ranging in age from 35 to >80 years), no change in pharmacokinetic parameters was observed with increasing age. Differences in letrozole pharmacokinetics between adult and pediatric populations have not been studied. Differences in letrozole pharmacokinetics due to race have not been studied.

In a study of 347 patients with advanced breast cancer, about half of whom received 2.5 mg Letrozole and half 0.5 mg Letrozole, renal impairment (calculated creatinine clearance: 20-50 mL/min) did not affect steady-state plasma letrozole concentration.

In a study of subjects with varying degrees of non-metastatic hepatic dysfunction (e.g., cirrhosis, Child-Pugh classification A and B), the mean AUC values of the volunteers with moderate hepatic impairment were 37% higher than in normal subjects, but still within the range seen in subjects without impaired function. Patients with severe hepatic impairment (Child-Pugh classification C) have not been studied.

1.4 Drug/Drug Interactions:

A pharmacokinetic interaction study with cimetidine showed no clinically significant effect on letrozole pharmacokinetics. An interaction study with warfarin showed no clinically significant effect of letrozole on warfarin pharmacokinetics.

There is no clinical experience to date on the use of Letrozole in combination with other anti-cancer agents.

1.5 Pharmacodynamics

In postmenopausal patients with advanced breast cancer, daily doses of 0.1 mg to 5 mg Letrozole suppress plasma concentrations of estradiol, estrone, and estrone sulfate by 75%-95% from baseline with maximal suppression achieved within two-three days. Suppression is dose-related, with doses of 0.5 mg and higher giving many values of estrone and estrone sulfate that were below the limit of detection in the assays. Estrogen suppression was maintained throughout treatment in all patients treated at 0.5 mg or higher. Letrozole does not impair adrenal steroidogenesis.

2.0 Regulatory History

On June 17, 1997, Novartis submitted its first-line development plan for Letrozole and the one pivotal Phase III study (025). Food and Drug Administration (FDA) provided comments in a letter dated September 11, 1997, which included an agreement that study 025 “Double-blind, double dummy, randomized, multicenter, 2-arm, Phase III study comparing letrozole 2.5 mg versus tamoxifen 20 mg as first-line therapy in postmenopausal women with advanced breast cancer” would be sufficient for registration if superiority was shown in TTP with consistent results in the other endpoints.

This acceptability of one pivotal study for registration was again confirmed during the End of Phase II meeting on November 23, 1998, and is consistent with FDA’s guidelines entitled “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,” dated May 1998.

In light of the acceptance of the one pivotal study, Novartis proposed that no Integrated Summary of Efficacy (ISE) would be necessary since two small pilot studies in first-line were discontinued for administrative reasons. The two studies, Protocol 012, a calibration study comparing daily oral doses of 0.5 mg letrozole and 2.5 mg letrozole with 30 mg tamoxifen as first-line therapy in postmenopausal patients with advanced breast cancer and Protocol 026 an open-label study of letrozole (2.5 mg p.o. q.d.) versus the combination of letrozole (2.5 mg

p.o. q.d.) + tamoxifen (20 mg p.o. q.d.) as first-line therapy in postmenopausal women with advanced breast cancer were discontinued when 32 and 18 patients, respectively, had been enrolled. The ISE section of the supplemental NDA (sNDA) would contain the same efficacy summary information as provided in the study report for study 025. FDA agreed to this proposal during the pre-sNDA meeting on September 29, 1999.

2.1 Indication

Letrozole is indicated for first-line therapy in postmenopausal women with advanced breast cancer.

2.2 Original Protocol

The original protocol was designed as a 3-arm study comparing 2.5 mg letrozole once daily with 20 mg tamoxifen once daily and with the combination of once daily 2.5 mg letrozole and 20 mg tamoxifen. After preliminary results from a pharmacokinetic study showed that adding tamoxifen to letrozole lowered letrozole blood levels (AUC) by approximately 38% on average, the combination arm was dropped. Those patients assigned combination treatment continued on treatment in blinded conditions according to the design of the original protocol.

2.3 INDs

There is one Novartis IND for Letrozole and this is No. [ ]. This IND is cross-referenced in this supplemental NDA as appropriate.

2.4 NDAs

There is only one pre-existing Novartis NDA for Letrozole, which is No. 20-726. This NDA is cross-referenced in this supplemental NDA as appropriate.

2.5 Protocol Amendments

Amendment 1 (dated 11-Apr-1997)

The original protocol was designed as a 3-arm study comparing 2.5 mg letrozole once daily, 20 mg tamoxifen once daily, and the combination of once daily 2.5 mg letrozole and 20 mg tamoxifen. After preliminary results from a pharmacokinetic study showed that adding tamoxifen to letrozole lowered letrozole blood levels (AUC) by approximately 38% on average, the combination arm was dropped.

The patients who were enrolled in the combination arm were not considered to be receiving a sub-optimal treatment. Patients received the standard effective dose of tamoxifen and a highly active dose of letrozole (estimated exposure of 1.5 - 2.0 mg of letrozole), and it was expected that the combination would have been at least as effective as tamoxifen alone. No negative efficacy or safety effects were expected with the combination arm. Therefore, the patients who had been already enrolled in the 3-arm study continued treatment in blinded conditions according to the design of the original protocol.

Efficacy and safety comparisons are restricted to patients treated with monotherapy. All demographic, efficacy and safety data for patients treated with the combination are listed but no comparisons are made between the combination and either monotherapy treatment

Change of primary objective

The primary objective of this study was to compare the anti-tumor efficacy, as evaluated by the primary variable of objective response rate. The primary objective was changed in Amendment 1 and compares the efficacy, as evaluated by the primary efficacy variable of time to progression.

The change was made in order to comply with new European Guidelines and after consultation with the FDA (Nov 23, 1998 FDA meeting minutes).

The changes summarized in this amendment reflected mainly the following:

- Dropping of the combination arm from the study.
- Change in primary endpoint from "objective response rate" to "time to progression". Objective response rate would be analyzed as a secondary variable. The sample size and statistical sections were adapted accordingly.
- The definition of the core phase was changed: the core phase was now defined as the interval from first patient randomization until 632 patients reached the primary endpoint of progressive disease. The determination of the sample size was based on the primary endpoint, time to progression. The sample size required was 439 patients for each monotherapy treatment arm (878 total). It was estimated that the number of events would be obtained in approximately 3 years from study initiation.
- Allowance of bisphosphonate treatment concomitantly with study drug at randomization in the study.
- No restrictions on previous bisphosphonate treatment.
- Patients with any bone disease, including blastic only or predominantly blastic lesions, were allowed in the protocol.
- Measurements of serum lipid profiles were deleted from the protocol, consequently fasting was no longer required for blood sampling.
- Tumor assessment: a full tumor assessment was required at baseline only.

Amendment 2 (dated 07-Nov-1997)

The original protocol defined eligibility of patients as either metastatic or loco-regional recurrent breast cancer, which was not amenable by surgery or radiotherapy. Patients with locally advanced disease (Stage IIIA, B) were initially excluded from the protocol.

After discussions with investigators, certain Stage IIIB patients were considered eligible for first-line endocrine treatment and would not be candidates for surgical intervention after response to study treatment. Amendment 2 allowed the enrollment of patients with Stage IIIB locally advanced breast cancer. Stage IIIB was defined according to the TNM Staging System of the American Joint Committee on Breast Cancer [10] as either T4, any N, M0 or any T, N3, M0.

Amendment 3 (dated 26-Aug-1999)

- The statistical analysis plan was amended as follows:

The definition of the main endpoint time to progression (TTP) was made more explicit and includes those patients who did not have a diagnosis of disease progression at the time of

discontinuation of core treatment, but: 1) had documented evidence of clinical deterioration due to the underlying breast cancer at the time of discontinuation or 2) died within 6 weeks of discontinuation from the core phase due to breast cancer.

The external peer review of tumor imaging of patients was changed to a blinded internal review of all patients' data. This decision was based upon information from the Novartis second-line studies in which external peer review showed no important difference in the overall conclusions when compared to the assessment by investigators.

The "confirmed peer reviewed objective response" was changed to "confirmed overall objective tumor response rate" This confirmation was identified by computer algorithm as a best overall response of CR (complete) or PR (partial) on at least two consecutive occasions at least 4 weeks apart (in practice, visits were 3 months apart). Stable disease (NC, no change) was identified by computer algorithm as lasting at least 24 weeks before being counted as NC. Overall tumor response was reviewed internally against the investigator's reported response. Discrepancies were to be resolved with the investigator.

For sample size calculations for the monotherapy arms, the original protocol envisaged 878 patients being enrolled steadily over 2 years to observe 632 events approximately 12 months after the last patient was enrolled. Accruals were completed in just over 2 years (25 months) with 60% of the patients enrolled in the last 7 months. The sample size was increased from 878 to 900 patients and the observation period was extended from 12 months after the last patient was enrolled to 14 months.

Exploratory analyses as requested by the FDA (Amendment 3) were included in the analysis plan.

The analysis of crossover data (extension phase) was simplified. Amendment 3 mentioned that the analysis will be descriptive only and will be conducted approximately 18 months after analysis of the core treatment data.

- Correlative Science: During the conduct of the study, there was increased interest in analyzing the expression of the HER-2/*neu* (C-*erb*B-2) proto-oncogene and its correlation with tumor response and time to progression. This relationship will be explored by analyzing frozen serum, which remained at the central laboratory after the routine biochemistry analysis had been performed. Frozen serum was available only in a subset of patients.
- The section on safety and tolerability was changed to reflect the new Novartis terminology for "adverse events" and the relationship to study drug is now categorized as either suspected or not suspected. The company no longer requests the outcome of adverse events.

Amendment 4 (dated 09-Jun-2000)

The purpose of this amendment was to implement a formal monitoring scheme for the endpoint of overall survival as recommended by an independent Data Monitoring Committee (DMC). Statistical significance for the endpoint of overall survival will be evaluated using a formal interim monitoring scheme with two interim reviews of mortality, in addition to the final analysis of overall survival at the end of the extension phase of the study. These interim analyses will be reviewed by the DMC.

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.

3.0 Manufacturing Controls

See CMC review by Dr. Chen

4.0 Pharmacology

Letrozole is a synthetic achiral benzydryltriazole derivative. It is an orally active highly selective non-steroidal competitive inhibitor of the aromatase enzyme system competitively binding to the heme of the cytochrome P450 subunit of the enzyme. It significantly lowers serum estrogen (estrone, estradiol an estrone sulfate) concentrations and has no clinically relevant detectable effect on formation of adrenal corticosteroids and aldosterone, or on thyroid function. Letrozole inhibition of the conversion of androgens to estrogens makes it particularly suitable for postmenopausal women whose main source of estrogen is via peripheral aromatization of androgen precursors.

The 2.5 mg letrazole dose was shown to be statistically superior in selected endpoints to both aminoglutethimide and megestrol acetate in two studies for the second-line treatment of metastatic breast cancer (see below). In a third study, Letrozole 2.5 mg was shown to be at least as effective as megestrol acetate. In the context of these 3 large randomized studies, letrozole is the only aromatase inhibitor that has shown superiority over these endocrine therapies.

Letrozole has been tested in Phase I through III clinical trials. As of February 1997, just over 1,200 volunteers/patients had been exposed to letrozole.

4.1 Drug Formulation

4.1.1 Letrozole

Four formulations (F.1, F.2, F.3 and F.4) of Letrozole 2.5 mg tablets were prepared during the development of this product for the Original NDA. The final tablet formulation that was submitted in the Original NDA 20-267 and approved was F.4.

As was the case with clinical trials submitted in the Original NDA, Formulation F.2 has also been used in trials conducted in support of the supplement submitted here. A bioequivalence study (Protocol 010) was previously conducted and the clinical study report submitted in the Original NDA. The BE study showed formulations F.1 and F.2 to be bioequivalent to formulation F.4.

4.1.2 Generic Tamoxifen

An approved European generic tamoxifen formulation (Tamofen®, manufactured by Leiras, OY of Finland) has been used as a comparative agent in the Phase III trials in first-line and adjuvant treatment of breast cancer. These trials compared Letrozole® to Tamofen® 20 mg tablets. The use of this generic tamofen in these studies was discussed with and accepted by FDA (FDA letter dated 25-Jun-96).

A bioequivalence study (Protocol 038) was conducted and a final report provided to the FDA on 12-MAY-99 (Serial No. 215). Novartis subsequently informed the FDA of unfavorable issues surrounding the Contract Research Organization (CRO) [ ],

which was contracted to conduct the bioequivalence study. After negotiations with the FDA, Novartis reached the decision to repeat the bioequivalence study.

A repeat bioequivalence study, Protocol 102, was initiated and follows the same exact outline as the previous study, Protocol 038.

In addition, complete Chemistry, Manufacturing and Controls information for Tamofen®, 20 mg tablets, manufactured by Leiras OY of Finland was submitted to IND [ ] on 14-JAN-00, Serial No. 226. Information pertaining to the manufacturing process, quality and testing of excipients, supplier of drug substance, test methods, packaging, stability, etc. were provided.

See, in addition, pharmacology review by Dr. Brower and biopharmaceutics review by Dr. Kieffer.

5.0 Clinical Background and Pivotal Protocol

5.1 Scientific rationale

Treatment of breast cancer has included efforts to decrease estrogen levels by ovariectomy premenopausally, adrenalectomy postmenopausally, and by use of antiestrogens and progestational agents both pre- and postmenopausally. These interventions lead to decreased tumor mass or delayed progression of tumor growth in some women whose tumor growth depends on estrogen presence.

Tamoxifen is currently the hormonal agent of choice in first-line treatment of patients with advanced breast cancer based on efficacy and toxicity considerations. The present study uses tamoxifen as the standard for evaluating a new aromatase inhibitor for first-line treatment of metastatic breast cancer.

5.2 Prior clinical trials

AR/BC 2 was a phase IIb/III double-blind, randomized, multicenter, multinational clinical trial comparing two doses of letrozole, 0.5 and 2.5 mg orally once daily, with megestrol acetate (Megace) 160 mg by mouth once daily for the treatment of postmenopausal women with estrogen/progesterone receptor positive or unknown advanced breast cancer. Five hundred and fifty-one patients received trial treatment: 188 on 0.5 mg letrozole. 174 on 2.5 mg letrozole, and 189 on megestrol acetate. The treatment groups were well balanced across prognostic factors. Best overall objective tumor response rates (peer reviewed confirmed) for the 0.5 mg letrozole, 2.5 mg letrozole and megestrol acetate treatment groups were 12.8%, 23.6%, and 16.4%, respectively. Treatment comparisons (odds ratios) of these responses revealed a statistically significant difference between the 0.5 and 2.5 mg dose groups in favor of 2.5 mg letrozole. No statistically significant difference was seen between 0.5 mg letrozole and megestrol acetate. A statistically significant difference was observed between 2.5 mg letrozole and megestrol acetate in favor of 2.5 mg letrozole. Duration of response was significantly longer for the 2.5 mg letrozole group than for the megestrol acetate group

although there were no significant differences between 2.5 mg and 0.5 mg letrozole and 0.5 mg letrozole and megestrol acetate.

The incidence of adverse experiences (whether or not drug related) appeared to be similar in the three treatment arms. However, statistically significantly more megestrol acetate patients than either 0.5 mg or 2.5 mg letrozole patients had serious adverse experiences (SAEs): 28.6% vs. 14.9% and 9.8%, respectively, for all SAEs irrespective of trial drug relationship and 12.2% vs. 1.6% and 0%, respectively, for trial -drug-related SAEs.

The incidence of adverse experiences graded as severe or life-threatening (whether or not drug related) was statistically significantly higher in patients receiving megestrol acetate than in patients receiving either letrozole 0.5 mg or letrozole 2.5 mg (39.2% vs. 26.6% vs. 23.5%, respectively).

Cardiovascular SAEs were the most frequently reported events during the core and extension trial. Patients treated with megestrol acetate experienced statistically significantly more SAEs pertaining to the cardiovascular system than patients receiving either dose of letrozole. Irrespective of trial drug relationship, cardiovascular SAEs were observed in 10.1% of patients treated with megestrol acetate and 1.7% and 2.1% of patients receiving 2.5 mg and 0.5 mg of letrozole respectively.

The data of a second phase III trial (P02) that compared the same 2 doses of letrozole with megestrol acetate showed that both doses were at least as active as megestrol acetate with the lower dose showing superiority in time to progression and time to treatment failure when compared to megestrol acetate.

AR/BC 3 was a phase III open, randomized, multicenter, multinational trial comparing letrozole 0.5 mg and 2.5 mg once daily with aminoglutethimide (250 mg b.i.d. with co-administration of hydrocortisone or cortisone acetate) in postmenopausal women with advanced breast cancer who failed anti-estrogens. Five hundred fifty five patients were treated in the trial: 192 on 0.5 mg letrozole, 185 on 2.5 mg letrozole, and 178 on aminoglutethimide. The trial design was open but the tumor responses were verified by an independent blinded external peer review. The treatment groups were balanced across baseline covariates.

Best overall objective response rates (confirmed and peer reviewed) were 16.7%, 17.8% and 11.2 % for 0.5 mg letrozole, 2.5 mg letrozole and aminoglutethimide, respectively. Treatment comparisons revealed no statistically significant differences between the three treatment groups. The median duration of objective response, although not statistically significant, was much longer for 2.5 mg letrozole (23.2 months) and 0.5 mg letrozole (20.6 months), than for aminoglutethimide (14.0 months). Both the 0.5 and 2.5 ing dose of letrozole were statistically significantly superior to aminoglutethimide in time to progression (TTP) and time to treatment failure (TTF). Letrozole (2.5 mg) was furthermore better tolerated than aminoglutethimide with fewer patients reporting skin rash (3.8% vs 12.9 %) or somnolence (4.3% vs 9.0%). fewer patients with drug-related AEs (32.4% vs 44.9%) or drug-related SAEs (0% vs 2.8%).

There was a statistically significant difference in overall survival between letrozole 2.5 mg and aminoglutethimide in favor of letrozole. The overall survival of the 2.5 mg letrozole arm was also statistically significantly longer than for the 0.5 mg letrozole arm, supporting the dose response effect of letrozole documented earlier in trial AR/BC 2.

The results of this study are consistent with previous data indicating that 2.5 mg once daily is the optimal dose for treatment of advanced breast cancer in postmenopausal patients after anti-estrogens.

In the context of these 3 large randomized trials, letrozole is the only aromatase inhibitor that has shown superiority over the 2 endocrine therapies, megestrol acetate and aminoglutethimide. The high anti-tumor activity, selectivity and safety of letrozole 2.5 mg in treatment of postmenopausal women with advanced breast cancer suggested that letrozole might be beneficial as first-line treatment of advanced breast cancer.

5.3 Pivotal Trial Protocol

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

5.3.1 Trial objectives

5.3.1.1 Primary:

To compare time to progression (TTP) between the two treatment arms (2.5 mg letrozole once daily and 20 mg tamoxifen once daily).

5.3.1.2 Secondary:

a. To compare the tolerability and toxicity of the two treatment arms.
b. To determine the survival time in each of the two treatment arms.
c. To summarize time to progression, objective response rate, and time to treatment failure for the second-line therapy using the subset of patients in the cross-over treatment period.

5.3.2 Core/extension phase and core/cross-over treatment:

5.3.2.1 Core/extension phase

The **core phase,** estimated to be 3 years, is defined as the interval from first patient first visit until 632 patients have reached the primary endpoint of progressive disease. The patient enrollment period is estimated at 2 years. The primary analysis is planned at the end of the core phase (e.g. after 632 patients have progressive disease). Patients whose response was first observed at the end of the core phase should have a confirmatory assessment. Such patients will be included in the core analysis.

The **extension phase** is defined as the period of the trial from the end of the core phase until 18 months thereafter, or sooner if all patients discontinued second-line trial treatment earlier for any reason. The total duration of core and extension phase is estimated to be 4.5 years. The extension analysis is planned at the end of the extension phase.

5.3.2.2 Core/crossover treatment

The **core (1st-line) treatment period** of a patient is defined as the time at which first-line therapy with trial drug was initiated until the start of second-line therapy, e.g. after progression on first-line treatment.

Patients who have been on core treatment with trial drug 1 and who **discontinue** core treatment due to an (S)AE should either be crossed over to trial drug 2 immediately or per protocol e.g. at progression of disease. This decision will be left to the discretion of the investigator. Patients being crossed over at progression should receive no further treatment with anticancer agents until documentation of disease progression. Note that patients who do not discontinue the trial due to an (S)AE will remain on the same trial treatment until disease progression.

The **cross-over (2nd-line) treatment period** of a patient is defined as the time at which a patient was switched to cross-over therapy until further progression of disease or until any other reason for discontinuation, whichever comes first.

Patients diagnosed with progression on letrozole and who are in the opinion of the investigator still suitable for endocrine therapy will receive tamoxifen (cross-over therapy). Patients diagnosed with progression on tamoxifen and who are in the opinion of the investigator still suitable for endocrine therapy will receive letrozole (cross-over therapy).

Patients with progressive disease within the first 3 months of first-line therapy should not be crossed over to second-line therapy and should be treated further at the investigator's discretion. Such a patient will not remain in the protocol but will be followed up for survival. However, if a patient is crossed over then the patient will remain on trial.

Patients with complete or partial response, or with disease stabilization on either trial drug should remain on the same trial drug until progression of disease.

Patients will be followed for overall survival until 90% of enrolled patients have died.

5.3.3 Blinding

Drugs will be supplied double blind using the double dummy technique. The investigators and Novartis personnel involved in conducting and monitoring the trial will be blinded to trial drug codes except in the case of an emergency.

Medication for letrozole patients will include two bottles containing medication for 3 months, i.e.: One bottle with letrozole tablets and one bottle with tamoxifen placebo tablets. Medication for tamoxifen patients will include two bottles containing medication for 3 months, i.e..: One bottle with tamoxifen tablets and one bottle with letrozole placebo tablets.

Letrozole and letrozole-placebo tablets will be of identical appearance. Tamoxifen and tamoxifen-placebo will be of identical appearance. On each treatment day, the patient should take two tablets in the morning with a large glass of water.

5.3.3.1 Breaking treatment codes

Upon request from an investigator, drug codes will be unblinded in cases of emergency when the trial treatment must be known.

The investigator will for each individual patient receive a blinded code break card which contains details of drug treatment that is covered by scratch-off labels. In the event of an emergency, the scratch-off label can be removed to provide identification of the treatment given. The scratch-off labels should not be removed for any other reason.

If the investigator feels a code-break is required, the local Novartis Monitor or Medical advisor should first be consulted unless the delay would endanger the patient. If a code-break occurs the investigator will record the reason for the code-break and the date of opening in the remark section of the Case Report Form (CRF). The patient will then be withdrawn from the trial unless the investigator considers the patient might still benefit from treatment, in which case trial treatment can be continued. The investigator will communicate the code breaking event to the local monitor within I working day. Patients for whom an emergency code break was made will be counted in the analysis as treatment failures, regardless of the reason for the code break.

For Non-emergency code breaking the following policy is to be used when a code break is requested for a patient who has been withdrawn from the trial in any situation and in the case where cross-over therapy with study medication is not considered. A code break should not be requested in the case a patient is on cross-over therapy as such a patient will have received both letrozole and tarnoxifen treatment.

1. The investigator must first consult the local Novartis monitor. The investigator must provide a written justification why she/he is considering to withdraw the patient from the study. The justification must be given in English.

2. The local Novartis monitor will telefax this justification together with a copy of the completed termination sheet and a completed form requesting a code break to the Letrozole Clinical Trial Manager Basle (Dr. A.Verbeek)

3. If the clinical team in Basle feels a code break is justified for ethical reasons, they will sign the form requesting a code break and inform the Drug Safety Unit officer in the Novartis affiliated country or any other appointed person who will then provide the randomization code for that patient.

4. The Drug Safety Unit officer or the deputy in the Novartis affiliate who is not involved with the project will then directly contact the investigator (by telephone or by telefax) to transmit the information requested. This procedure will minimize the number of people with knowledge of the patient's treatment.

5. The investigator should be instructed to keep the information transmitted strictly confidential

6. The local monitor and the International Clinical Statistician (Mrs. H.A. Chaudri) will receive a written confirmation from the Drug Safety responsible person in the Novartis affiliate that treatment information was transmitted to the investigator without divulging the actual treatment concerned.

The information that a non-emergency code break occurred (together with relevant details) will be kept on the database for this trial. The file of non-emergency code breaks will be updated regularly, and the Letrozole Clinical Team in Basle will receive monthly status reports of the code breaks (without treatment information, coded or decoded).

5.3.4 Evaluations

Evaluations are scheduled at baseline (prior to trial treatment), after 1 month (optional)**,** 3 months, 6 months and every 3 months thereafter until the patient is withdrawn from the trial.

Tumor evaluations will be performed every 3 months or earlier in case of progression. If a patient is switched to cross-over therapy between the prefixed evaluation times, tumor evaluations need then be done every three months after the start of cross-over therapy. Visits starting at the cross-over treatment will be numbered 51, 52, etc.

The trial is designed to unblind the sponsor but not the investigator at the end of the core phase. The investigators and patients will remain blinded and continue the trial under double--blind conditions. The core (inferential) analysis will be performed on the core phase data; this analysis does not constitute an interim analysis.

5.3.5 Inclusion criteria

1. Compliant postmenopausal women with with Stage IIIB locally advanced disease, metastatic breast cancer or with loco-regional recurrence not amenable to treatment by surgery or radiotherapy.

   Postmenopausal status will be defined by any of the following criteria:

   -no spontaneous menses for at least 5 years.
   -spontaneous menses within the past 5 years but amenorrheic for at least 12 months and LH, FSH values according to the definition of postmenopausal normal range of the laboratory involved.
   -bilateral oophorectomy.
   -radiation castration and amenorrheic for at least 3 months.

2. Age $\geq$ 18 years

3. Histological or cytological evidence of breast cancer.

4. Patients whose tumors are either estrogen-receptor (ER) and/or progesterone-receptor (PgR) positive (according to the definition of the laboratory involved) or with both unknown. Patients will be regarded as ER or PgR positive if any assay (biochemical or immunohistochemical) of primary or secondary tumor tissue is positive. Patients will be regarded as receptor unknown if no assay is known to be available.

5. Patients must have measurable or evaluable disease except for patients with bone disease only who are always eligible even in case of blastic lesions only.

6. Patients previously treated for metastatic disease (one regimen of chemotherapy), should present with objective evidence of progression; i.e. appearance of new lesions or existing lesions becoming larger (> 25% in measurable lesions) or worse (in case of evaluable lesions) within three months prior to trial entry.

7. Karnofsky performance rating of at least 50% (corresponds to WHO grade 0-2).

8. Written informed consent.

5.3.6 Exclusion criteria

1. Patients with CNS metastases, bilateral diffuse lymphangitic carcinomasis of the lung (> 50% of lung involvement), evidence of metastases estimated as more than a third of the liver as defined by sonogram and/or CT scan.

2. Inflammatory breast cancer (histologically proven).

3. Other concurrent or previous malignant diseases except for contralateral breast carcinoma, cone biopsied in-situ carcinoma of the cervix uteri or adequately treated basal or squamous cell carcinoma of the skin.

4. Patients with uncontrolled cardiac disease (including unstable angina) and/or uncontrolled diabetes mellitus.

5. Known hypersensitivity to any of the constituents of the trial drug.

6. Laboratory values: Serum calcium $\geq$ 11 .6 mg/dL (or $\geq$ 2.75 mmol/L).

7. History of noncompliance to medical regimens and patients who are considered unreliable.

8. Patients with tumors which are both estrogen and progesterone receptor negative, or estrogen receptor negative and progesterone receptor unknown or estrogen receptor unknown and progesterone receptor negative. ER negative status e.g. <10 fmol/mg cytosol protein or negative by immuno-histochemical tests or according to the standards of the laboratory.

9. Adrenalectomy or hypophysectomy.

10. Patients who are known HIV positive (no specific tests are required for confirmation of eligibility).

11. Previous treatments:

Patients who have received any of the following treatments should NOT be enrolled in the trial.

a. Radiotherapy to the sole area of cancer being evaluated. (However, if cancer progression is documented within a radiation site three or more months after the completion of radiation therapy, the patient is eligible for enrollment.).

b. Prior systemic endocrine treatment for metastatic disease, locally advanced disease or locoregional recurrence not curable by surgery or radiotherapy.

c. More than one systemic anti-tumor chemotherapy regimen for recurrent or advanced breast cancer.

d. Patients who have received neo-adjuvant/adjuvant anti-estrogen therapy and recurred while on neo-adjuvant/adjuvant therapy or recurred within 12 months of completing their neo-adjuvant/adjuvant anti-estrogen therapy.

e. Patients who have received neo-adjuvant/adjuvant endocrine therapy other than antiestrogens.

f. Systemic investigational drugs within the past 30 days or topical investigational drugs within the past 7 days

Allowed previous treatments:

a. Previous bisphosphonate treatment is allowed. Patients presenting with bone metastasis only and who progress in bone while on bisphosphonate therapy should stop bisphosphonate therapy prior to or at randomization in the trial. Patients presenting with other than bone metastasis only may continue treatment with bisphosphonates if needed.

b. Patients may have received corticosteroids, immunotherapy/biological response modifiers (e.g. Interferon) as part of their adjuvant treatment or one allowed chemotherapy regimen for advanced disease.

c. Patients who relapsed on hormone replacement therapy and still show evidence of progression $\geq$ 2 months following discontinuation of hormone replacement therapy.

d. Patients may have had neo-adjuvant/adjuvant chemotherapy.

5.3.7 Stratification

No stratification, other than by country, is foreseen for the randomization.

5.3.8 Concomitant treatments

Patients must be instructed not to take any additional medications (including over- the-counter products) during the trial without prior consultation with the investigator. If concomitant therapy must be added or changed, the reason and name of the drug should be recorded on the Concomitant Medication page of the Case Report Form.

5.3.8.1 Concomitant treatments NOT allowed

1. Anti-cancer treatments such as chemotherapy, immunotherapy/biological response modifiers (BRMs) or endocrine therapy (including steroids).

2. Radiotherapy to the sole site of disease is not allowed. Note: Radiotherapy to a limited area (e.g. for painful disease) other than the sole site of measurable and evaluable disease is allowed. If radiotherapy for the sole site is required, the patient will be considered to have progression of disease and wiH be taken off study.

3. Prolonged systemic corticosteroid treatment, except for topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g.

intra-articular). Note: Short duration (< 2 weeks) of systemic corticosteroids is allowed (e.g. Chronic Obstructive Pulmonary disease).

4. Chronic concomitant bisphosphonate therapy after randomization or > 2 courses of concomitant intravenous bisphosphonate therapy for the treatment of hypercalcernia. Note: iv treatment course = pamidronate 60 - 90 mg iv or edidronate 7.5 mg/kg iv x 3 or clodronate 1500 mg iv or 300 mg iv daily for 5 days.

5. Patients should not receive bisphosphonate treatment for prevention of bone metastases at any time, i.e. neither at randomization nor during the trial.

6. Any investigational drugs.

5.3.8.2 Concomitant treatments Allowed in the trial

1. Patients may receive concomitant bisphosphonate treatment in addition to trial drug at randomization in the trial for the treatment of bone metastasis.

2. Patients may receive concomitant bisphosphonate treatment at start of the cross-over therapy when progression in bone is documented.

5.3.9 Trial Procedures

Table 1 Trial Procedures

Double-blind Rx: Core and cross-over treatment: letrozole or tamoxifen	Core and cross-over treatment						
Visit[a] Trial month	1 0	2 1	3 3	4 6	5 9	$6 $12	Term Visit
Informed Consent (to be done before Visit 1)	X						
Personal data, medical history, concomitant diseases, check of inclusion/exclusion criteria	X						
Physical Examination Including Weight	X	X	X	X	X	X	X
Previous / Current Medications Adverse Experiences	X	X X	X X	X X	X X	X X	X X
Performance Status	X	X	X	X	X	X	X
ECG , if indicated	X						
Chest X-ray for Safety	X						
TUMOR ASSESSMENT -Chest X-rays or CT Scan -Abdominal CT Scan or Liver Ultrasound -Bone Scan with X-ray of Suspicious Areas or CT scan or Skeletal Surveyed -Measure Superficial or Palpable Lesions **OVERALL TUMOR RESPONSE**	X		X X	X X	X X	X X	X X
LABORATORY TEST -Hematology -Blood Chemistry	X		X	X	X	X	X

- In case a patient is switched to cross-over treatment, the numbering of the cross-over visits will start at 51 and continue with 52, 53, etc. Three-monthly evaluations will then continue from visit 51 onwards according to the same procedures as described for the core treatment.
- Visit 2 is optional
- Follow-up of patients who discontinue the trial will be done at least every 6 months to collect survival data until 90% of the patients have died.
- An ECG should be performed at baseline and at any time thereafter if warranted by signs and symptoms.
- Chest X-rays include anteroposterior (AP) and one lateral view and should be performed at any time if warranted by signs and symptoms.
- Skeletal Survey includes anteroposterior (AP) and lateral views of skull, total spine (AP and lateral), clavicle, ribs, pelvis and long bones.
- Areas positive at baseline should be evaluated at every subsequent visit and at termination.
- All tumor evaluations should be done within 14 days prior to the scheduled visit.

- Scans and X-rays that were negative at baseline do not have to be repeated unless warranted by signs or symptoms.
- Termination evaluations should be done when the patient discontinues at any point during the trial. Follow up of patients who discontinue the trial will be done at least every 6 months to collect survival data until the end of the extension phase

5.3.10 Satistical methodology

5.3.10.1 Sample size determination

The annual tamoxifen hazard rate is assumed to be 0.9. To ensure that there is 80% power to detect a hazard ratio between tamoxifen and letrozole of 1.25 with a significance level of 5% (two-sided), we require a sample size of 395 patients per treatment arm (790 patients total). This sample size will give us approximately 632 total events at approximately 3 years from first patient first visit (FPFV). Assuming a 10% loss to follow-up, we require a sample size of 439 patients per treatment arm (878 patients total). Patients who were enrolled in the study on letrozole alone or tamoxifen alone before the amendment will be included in the total patient accrual. Patients who were enrolled in the study on combination treatment before the amendment will not be included in the 878 patient total.

With the sample size calculated for time to progression, we will also be able to detect a 10% difference in the secondary variable first-line confirmed peer-reviewed overall objective response rate. A confirmed objective response is a complete response or partial response (CR + PR) confirmed by a second evaluation at least 4 weeks later, and verified by peer review. If there is a discrepancy between the peer review assessment, the central radiologist's assessment, and the investigator's assessment, the peer review assessment will be considered final.

Tamoxifen response rates for this patient population have been reported to be between 30 and 35%. To ensure that there is sufficient power to detect a 10% difference, the tamoxifen response rate is assumed to be 35%. In order to demonstrate a 10% statistically significant difference between the treatment groups with a significance level of 5% (two-sided) and a power of 80%, 395 patients per treatment group are needed.

Assuming that 10% of patients will be lost to follow-up for tumor response, 439 patients per treatment group (878 patients total) should be enrolled in order to obtain 395 patients per treatment group (790 patients total).

5.3.10.2 Efficacy variables

1. Time to Progression

Time to progression is calculated as the time from randomization to progression of disease, discontinuation for unsatisfactory therapy effect, death due to cancer or unknown cause. Data from patients who discontinued for other reasons and patients who are receiving first-line

therapy without a documented peer-reviewed PD at the time of analysis will be considered censored observations. A patient who crossed over to second-line therapy without a documented peer-reviewed PD will have her time to progression censored at the day prior to administration of the second-line therapy medication. Patients who die without tumor staging or tumor assessments before three months will be considered as having progressive disease (PD) regardless of the reason for discontinuation. A patient whose best response during the trial was not assessable/not evaluable (NA/NE) and who did not die will be included in the analysis (denominator). 'Progression' must be verified by peer review.

2. Response Rate

Tumor evaluations (used to determine peer review confirmed objective response rate) are planned to be collected pre-randomization, and every 3 months until discontinuation from the trial. The peer review confirmed overall objective response rate will include all patients assessed by peer review as having a confirmed partial or complete response during the core phase of the trial. Only tumor response data from first-line treatment will be used. Responses occurring on second-line therapy (cross-over) will not be considered as response in the primary analysis. Patients who die without tumor staging or tumor assessments before three months will be considered as having progressive disease (PD) regardless of the reason for discontinuation. By protocol design, patients who have stable disease or are responding to first-line therapy will not be crossed to second-line therapy. Patients whose response (to first trial treatment) was first observed at 12 months should have a confirmatory assessment and will be included in the analysis. A patient whose tumor assessment is not assessable/ not evaluable (NANE) by peer review will be included in the analysis (denominator).

3. Duration of Response

Duration of Response includes all patients who had a confirmed overall response, verified by peer review while on first-line treatment during the core phase of the trial. Duration of response is calculated as the time from randomization to progression of disease, discontinuation for unsatisfactory therapy effect, death due to cancer or unknown cause. Data from patients who discontinued for other reasons and patients who are receiving first-line therapy without a peer-reviewed documented PD when the core phase ends, will be considered censored observations. A patient who crossed over to second-line therapy without a peer review documented PD will have her duration of response censored at the day prior to administration of the second-line therapy medication.

4. Duration of “clinical benefit”

CR + PR + NC $6 months

5. Time to Treatment Failure

Time to treatment failure is calculated as the time from randomization to progression of disease, discontinuation for unsatisfactory therapy effect, death, discontinuation due to underlying disease or to trial treatment. Data from patients who discontinued for other reasons

and patients who are receiving first-line therapy without a peer-reviewed documented PD at the time of analysis will be considered censored observations. Data from a patient who crossed over to second-line therapy will be considered an event at the last day prior to administration of the second-line therapy medication. Patients who die without tumor staging or tumor assessments before three months will be considered as having progressive disease (PD), regardless of the reason for discontinuation. A patient whose best response during the trial was not assessable/not evaluable (NANE) and who did not die will be included in the analysis (denominator). 'Progression' must be upheld by peer review.

6. Time to Response

Time to Response is calculated as the time from randomization to date of first documented confirmed overall response (CR or PR), verified by peer review. In cases who achieved a CR on at least two occasions after one or more assessments of PR, the earliest documentation of PR will define the end-date.

7. Karnofsky Performance Status

Karnofsky Performance Status (WHO) at the primary analysis and the extension analysis will be summarized by treatment group and category over time. The following summary information will be provided for each trial treatment: a) baseline performance status tabulated against the best perfon-nance status, and b) baseline performance status tabulated against the worst performance status.

5.3.10.3 Data sets analyzed

All patients in the amended protocol who have a baseline tumor assessment, documented evidence of advanced disease, and at least one dose of trial medication will be included in the analysis of the primary and secondary variables. This dataset will be designated as Intent-to--Treat (ITT) patients. The patients assigned monotherapy before Amendment I will be included in this dataset for the primary analysis. However, the patients assigned combination therapy (before Amendment 1) will be included in the safety analysis only. The efficacy data of the combination therapy will be tabulated separately from the monotherapy efficacy data,

5.3.10.4 Statistical methodology

The data will be analyzed by Novartis. The protocol does not envisage data analyses carried out independently by the investigator: if performed, they should be submitted to Novartis before publication or presentation.

The data from each center are intended to be pooled with data from other centers conducted under this protocol so that an adequate number of patients will be available for analysis. No interim analysis is planned. However, the accrual rate and number of events will be checked once before the end of accrual to determine if the sample size assumptions should be altered.

Two separate main analyses are planned. The first analysis, which is considered primary, is to include the information of the first-line data at the end of the core phase. The available second-line therapy data will not be summarized in the core report. The second analysis is planned for the end of the extension phase of the trial and the extension report will include an update of the first-line therapy data and a summary of the second-line therapy results. No interim analyses are planned.

Two main analyses of the survival information are planned. The first is at the end of the core phase. The patients will be analyzed according to their original treatment randomization regardless of the current treatment being received. The second analysis is planned for the end of the extension phase of the trial and the patients will be assigned to their original randomization regardless of the current treatment being received.

5.3.10.5 Sensitivity analyses

In addition to the main analyses outlined above, sensitivity analyses will be performed using the same basic models as for the main analyses. The sensitivity analyses will consider as events the data for patients lost to follow-up or who do not present for examination within a specified window of the scheduled visit. Details of the windows will be provided in a separate document. Depending on the timing of loss to follow-up or apparent loss to follow-up (missing data), as well as on the type of information missing, the observation may be considered as a progression of disease, a treatment failure, or a death, or as all of these events.

The sensitivity analyses are exploratory. The purpose of conducting these additional analyses is to determine whether there is any effect on the estimates of treatment differences if loss to follow-up is considered an event.

5.3.10.6 Baseline Covariates (Prognostic Factors)

Several baseline covariates (prognostic factors) have been identified as predictive of at least one response outcome. Three key covariates, adjuvant therapy (hormonal therapy, chemotherapy, none), dominant site (two indicator variables: bone yes/no and visceral yes/no), and bisphosphonate use (none, predominantly oral or intravenous) will be incorporated into the statistical analyses. Other baseline covariates of interest which will not be used for adjusting treatment comparisons but for which response will be tabulated are:

Body mass index

Age class

Number of anatomical sites involved (extent of disease)

Disease-free interval

Receptor status

Previous chemotherapy for advanced disease

Performance Status

5.3.10.7 Analysis of First-line Therapy Data

Time to progression, duration of response, time to treatment failure, survival for the primary analysis and the extension analysis of first-line therapy data will be summarized using the Kaplan-Meier product-limit method with time being the number of days from randomization to event. The Cox proportional hazards regression model will be used to 1) compare the treatment groups, and 2) compare the treatment groups with predictive baseline covariates (adjuvant therapy, dominant site, and bisphosphonate use) in the model. (For duration of response and duration of "clinical benefit", treatment comparisons will be unadjusted, because of confounding with response). The Cox model adjusted for predictive baseline covariates will be considered the primary analysis method. Two-sided 95% confidence intervals of the median for each treatment and the risk ratio of each comparison will be presented. In addition, an exploratory analysis with all predefined baseline covariates (body mass index, age class, number of anatomical sites involved, disease-free interval, receptor status, previous chemotherapy for advanced disease, performance status) will be performed using stepwise selection model building.

The confirmed peer reviewed objective response rate in the core phase, and peer reviewed tumor response data for complete first-line therapy data will be tabulated according to response category and treatment arm, and by baseline covariate, response category, and treatment group. Logistic regression (adjusted for predictive baseline covariates. adjuvant therapy, dominant site of disease, and bisphosphonate use) will form the primary analysis. The tamoxifen treatment arm will be the reference arm. An unadjusted analysis, and 95% confidence interval for each odds ratio will be provided. Ninety-five percent confidence intervals for tumor response of each treatment arm will be presented. In addition, an exploratory analysis with all predefined baseline covariates (body mass index, age class, number of anatomical, sites involved, disease-free interval, receptor status, previous chemotherapy for advanced disease, performance status) will be performed using stepwise selection model building.

For the analysis of time to death (e.g. overall survival), patients will be assigned to their original randomization group regardless of the alternative therapies patients may have received. This analysis will be performed as long as the number of events (deaths) is adequate in each treatment group.

Time to response will be summarized by treatment group.

Karnofsky Performance Status (WHO) at the primary analysis and the extension analysis will be summarized by treatment group and category over time. The following summary information will be provided for each trial treatment: a) baseline performance status tabulated

against the best perfon-nance status, and b) baseline performance status tabulated against the worst performance status.

5.3.10.8 Analysis of Second-line Therapy Data

Significance testing will not be performed with the second-line therapy data due to the non-randomized nature of this subset of patients. Only confidence intervals will be reported where appropriate.

Time to progression, duration of response, duration of clinical benefit, and time to treatment failure for the analysis of second-line therapy data will be summarized using the KaplanMeier product-limit method with time being the number of days from start of second-line therapy to the event. Two-sided 95% confidence intervals of the median for each treatment will be presented. Median time to progression will be tabulated according to response category and treatment group, and by predictive baseline covariates (adjuvant therapy, dominant site, and bisphosphonate use), response category, and treatment group.

The confirmed peer reviewed objective response rate of the second-line therapy data will be tabulated according to response category and treatment group, and by predictive baseline covariates (adjuvant therapy, dominant site, and bisphosphonate use), response category, and treatment group. Ninety-five percent confidence intervals for objective response rate of each treatment arm will be presented. The baseline tumor assessment used for determination of response will be the last assessment performed prior to receiving second-line therapy.

In addition, if the exploratory analysis from the first-line data of the predefined baseline covariates (body mass index, age, class, number of anatomical sites involved, disease-free interval, receptor status, previous chemotherapy for advanced disease, performance status) show any additional predictive covariates, a summary of these covariates by treatment group will be included.

Time to response will be summarized by treatment group.

Karnofsky Performance Status (WHO) will be summarized by treatment group and category over time. The following summary information will be provided for each trial treatment: a) baseline performance status tabulated against the best performance status, and b) baseline performance status tabulated against the worst performance status. The baseline Kamofsky Performance Status is the last performance status recorded prior to administration of second-line therapy.

5.3.10.9 Overall survival

Time to death (overall survival) will be summarized using the Kaplan-Meier product-limit method with time being the number of days from randomization to event. The Cox proportional hazards regression model will be used to 1) compare the treatment groups, and 2) compare the treatment groups with predictive baseline covariates (adjuvant therapy, dominant

site, and bisphosphonate use) in the model. The Cox model adjusted for predictive baseline covariates will be considered the primary analysis method. Two-sided 95% confidence intervals of the median for each treatment and the risk ratio of each comparison will be presented.

For the analysis of time to death (survival), patients will be assigned to their original randomization group regardless of the alternative therapies patients may have received. This analysis will be performed as long as the number of events (deaths) is adequate in each treatment group.

The primary analysis of overall survival will take place at the end of the extension phase. Updated survival analyses should take place annually until at least 90% of enrolled patients have died.

5.3.11 Safety and tolerability

The safety and tolerability of the treatments will be assessed based on the frequency and severity of clinical and laboratory adverse experiences compared to the tamoxifen treatment group. For the summary of adverse experiences, physical examinations, and laboratory parameters, all patients who have a baseline measurement (Visit 1), received at least one day of trial treatment, and have at least one post-baseline measurement will be included in the presentation (intent-to-treat patients). For safety and tolerability data, a "post-baseline measurement" is defined as the report of any examination or visit subsequent to baseline.

5.3.11.1 Methodology

Summaries of adverse experiences, physical examination, and laboratory parameters will be provided for all data in the trial, using a standardized system of nomenclature. Adverse experiences will be summarized by COSTART body system, and, within each body system, by preferred term, defined by the dictionary in current use at the time of analysis.

If appropriate, the relative proportions of patients in each treatment arm with adverse experiences of key body systems (digestive system, cardiovascular system) or key preferred terms (hot flushes, nausea, musculoskeletal pain, vaginal discharge) will be compared using chi-squared tests or Fisher's exact test.

Laboratory data will be graded using the NCI-CTC scale. Cross-tabulations by treatment arm will be presented of baseline CTC grade and worst (highest or lowest as appropriate) CTC grade observed during the trial for hemoglobin, liver function tests, renal function tests as defined.

Body weight, and key laboratory data will be presented graphically over time.

More detailed safety and tolerability analyses will be specified in the analysis plan.

5.3.12 Definition of the tumor measurement and response

5.3.12.1 Tumor measurements

All measurements should be recorded in metric notations (centimeters and tenths of centimeters) using a ruler or calipers.

Four categories of tumor are defined:

(a) Measurable, bidimensional - bidimensional measurable lesions are those for which two designated perpendicular diameters may be measured either by palpation (with calipers or ruler) or on radiologic (X-ray, CT scan, ultrasound, NMR) assessment (by ruler). The surface area of the lesion is approximated by multiplying its longest diameter with its greatest perpendicular diameter. For multiple lesions the tumor size is equal to the sum of the products of the diameters of all lesions.

(b) Measurable, unidimensional - malignant disease measurable by palpation (with calipers or ruler) or radiologic assessment (by ruler) in only one dimension. The size of the lesion is recorded as that single largest dimension. For multiple lesions, the tumor size is equal to the sum of the single dimensions of all the lesions. Examples are:

- Abdominal mass

- Mediastinal and hilar masses (not bidimensionally measurable by CT scan) - these are considered unidimensionally measurable only when a pre involvement chest X-ray is available. The tumor size is determined by subtracting the normal mediastinal or hilar width from the width containing malignant disease.

- Hepatomegaly due to tumor involvement without measurable discrete lesion on CT scan or ultrasound - the tumor size is determined as the sum of three linear measurements to the liver edge: from the xiphoid notch and the costal margins 10 cm bilateral from the xiphoid notch.

(3) Non-measurable, evaluable - malignant disease which is not measurable by ruler or caliper, but its progress is readily evaluable by physical or radiologic evaluation. Response or increasing disease can only be estimated. Examples include:

- diffuse pelvic or abdominal masses
- confluent multinodular or lymphangitic lung metastases
- ill-defined skin metastases
- mixed lytic and blastic bone metastases in which the lytic portion of the lesion is $\geq$ 50% of the lesion size

- mediastinal and hilar masses not bidimensionally measurable on CT scan for which no pre involvement chest X-ray is available
- mixed lytic and blastic bone metastases in which the lytic portion of the lesion is $\geq$ 50% of the lesion size

(d) Non measurable, non-evaluable - i) pleural effusion, ii) ascites, iii) blastic or mixed blastic and lytic bone lesion (< 50% lytic), iv) biologic markers or serum chemistry (e.g. alkaline phosphatase, serum calcium).

To be considered measurable, a baseline lesion must have a minimum diameter to compensate for measurement error: 1cm for soft tissue lesions, 1 cm for lung lesions including pleural lesions measured by CT scan, 3 cm for liver lesions measured by ultrasound or 2 cm for liver lesions measured by CT scan.

All measurable lesions with diameter(s) which decrease to < 0.5 cm will continue to be recorded as having a diameter of 0.5 cm until the lesion is completely resolved or until the diameter increases to > 0.5 cm. When the diameter increases to > 0.5 cm, the actual measured diameter will again be recorded. When the lesion is completely resolved record as 0.0 x 0.0 cm.

5.3.12.2 Evaluation of Tumor Response

a) **Complete response (CR)***:* disappearance of all known disease determined by two observations not less than four weeks apart.

b) ***Partial response (PR)****:*

Measurable lesions:

In the case of bidimensional lesions (e.g. pulmonary nodules surrounded by lung tissue on X-ray, cutaneous/subcutaneous metastases or peripheral lymph node metastases): decrease by 50% or more in the sum of the products of the two largest diameters of each individual lesion determined by two observations not less than four weeks apart.

In the case of unidimensional lesions (e.g. mediastinal enlargement, lung metastases not surrounded by lung tissue, intra-abdominal mass): decrease by 50% or more in the largest linear tumor measurement determined by two observations of the lesions not less than four weeks apart. In situations such as infiltration of the breast, liver involvement and mediastinal enlargement, objective regression is a 50% or greater decrease in that measurement which is regarded as being in excess of that usual for the site under consideration.

Liver metastases (not UICC) may be accepted as a measurable lesion, if the liver ultrasound or CT scan contains at least one well defined measurable defect, clearly attributable to metastases, with a diameter respectively > 3 cm in for ultrasound measurements or > 2 cm for the CT scan determinations.

Evaluable but non-measurable lesions:

(e.g. pulmonary infiltration, skin infiltration)

Serial evidence of appreciable change documented by radiography or photography must be obtained and be available for subsequent reviews.

Estimated decrease in tumor size of 50% or more for at least four weeks.

It is not necessary for every lesion to have regressed to qualify as partial response, but in all cases no lesions should increase in size and no new lesions should appear.

Non measurable, non-evaluable disease:

Hypercalcemia associated with tumor flare should not be interpreted as progressive disease; however persistent hypercalcemia which requires more than two I.V. treatment courses with bisphosphonates should be considered as progression in bone.

A new pleural effusion appearing on trial and proven to be malignant indicates disease progression.

c) **No change (NC):**

Stable disease or reduction of the measurable or evaluable lesions by less than 50%, or increase by less than 25% in the size of one or more lesions without new lesions appearing, for at least 4 weeks.

If non-measurable but evaluable lesions represent the bulk of disease and these clearly do not respond, even though measurable lesions have improved, the response must be considered as "no change" and not as "partial response".

d) **Progressive disease (PD):**

25% or more increase in the size of one or more measurable lesions, or estimated increase of 25% or more in existent non-measurable disease, or appearance of new lesions.

A new pleural effusion appearing on trial and proven to be malignant indicates disease progression.

5.3.12.3 Evaluation of bone metastases

Objective response

a) Complete Response (CR): complete disappearance of lesions on X-ray.

b) Partial response (PR): Partial decrease in size of lytic lesions or recalcification of lytic lesions.

2.2 No change (NC)

Because of the slow response of bone lesions, the designation "no change" should not be applied until at least eight weeks have passed from start of therapy.

2.3 Progressive disease (PD)

Increase in size of existing lesions or appearance of new lesions. Occurrence of bone compression or fracture and its healing should not be used as the sole indicator for evaluation of therapy.

Blastic (sclerotic) lesions and mixed blastic/lytic lesions (<50% lytic) will be monitored by X-rays and/or CT scan but will not be evaluated for response. However, a worsening of these pre-existing lesions will be considered as progression in bone.

Note: Occurrence of bone compression or fracture and its healing should not be used as the sole indicator for evaluation of therapy.

Hypercalcemia associated with tumor flare should not be interpreted as progressive disease however persistent hypercalcemia which requires more than two IV treatment courses with bisphosphonates should be considered as progression of disease.

5.3.12.4 Overall response

1. If both measurable and non-measurable/evaluable disease are present in a given patient, the result of each should be recorded separately. Overall assessment of response involves all parameters: measurable and non-measurable/evaluable. Non measurable/non-evaluable disease should be assessed for progression.

2. Progression in any site, or the appearance of a new lesion, indicates disease progression despite objective responses in other sites.

3. In case of measurable lesions, the poorest response designation shall prevail in the overall assessment of response.

4. If in the responses by organ site there are equal or greater numbers of complete plus partial responses than of "No Change" designation, then the overall response will be partial.

   Note: "No Change" in non-measurable lesions will not detract from a partial response in measurable lesions but will reduce a complete response in measurable lesions to partial response overall. However, if non-measurable evaluable lesions represent the bulk of

disease and these do not clearly respond even though measurable lesions have improved, the result must be concluded as "No change" and not as "Partial Response"

5. A malignant pleural effusion present at baseline must resolve completely for an overall complete response to be achieved.

5.3.12.5 Duration of response

Complete Response (CR): The period of CR should last from the date the CR is first recorded until the date when progressive disease is first noted.

Partial Response (PR): In patients who only achieve partial response, only the period of overall response should be recorded.

Overall Response (OR): The period of overall response lasts from the first day of treatment until the date of the first observation of progressive disease.

5.3.12.6 Determination of Overall Tumor Response

Table 2 Response Determination

Measurable Disease Response	Nonmeasurable Evaluable Disease Response	Nonmeasurable Nonevaluable Disease Response	Overall Tumor Response
CR	CR	CR	CR
PR	CR	CR	PR
CR	PR	CR	PR
CR	CR	Not CR, but no new lesion	PR
CR,PR	NC bulk of disease*	CR or not CR, but no new lesion	NC
NC	CR, PR bulk of disease*	CR or not CR, but no new lesion	PR
CR,PR	NC	CR or not CR, but no new lesion	PR
NC	CR,PR	CR or not CR, but no new lesion	NC
CR, PR bulk of disease*	NC	CR or not CR, but no new lesion	PR
NC bulk of disease*	CR,PR	CR or not CR, but no new lesion	NC
CR,PR,NC	PD	CR or not CR, but no new lesion	PD
PD	CR,PR,NC	CR or not CR, but no new lesion	PD

*Bulk of disease is defined as number of lesions not individual lesion size.

5.4 Investigators

Table 3 Investigators

Investigator	Study	Center #	City	Country
Abdi, Dr. Ehtesham	025	6	Bendigo Vic 3550	Australia
Adachi, Isamu	NJ05		Tokyo 104-0045	Japan
Abenhardt, Dr. med. Wolfgang	025	2	D-80335 München 2	Germany
Aiginger, Prof. Dr. Paul	025	1	A-1130 Wien	Austria
Aigotti, Ronald E., M.D.	026	0787	South Bend, IN 46617	US
Albertsson, Dr. Maria, läk	025	4	S–21401 Malmö	Sweden
Alden, Dr. M.	025 026	1389 0822	Sellersville, PA 18960	US
Allgood, Dr. J.	025 026	1390 0860	Escondido, CA 92025	US
Andersen, Dr. Erik	025	11	Dk-8800 Viborg	Denmark
Andersen, Dr. Jørn	025	10	Dk-8000 Arhus C.	Denmark
Andrade, Dr. Jurandyr	024	4	14048-900 Ribeirão Preto, SP	Brazil
Andrelsch, Prof. W.	024	12	40625 Duesseldorf	Germany
Aoyama, Dr. Hideaki	NJ05		Nagoya, Aichi 460-0001	Japan
Apffelstaedt, Dr. J.	025 024	2012 003	Zaf-2005 Cape Town	South Africa
Arvantinos, Dr. Gerassimos	025	3	New Kifissia – Athens	Greece
Asaga, Dr. Taro	NJ05		Yokohama, Kanagawa 241-0815	Japan
Asbury, Dr. R.	025	1406	Rochester, NY 14623	US
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Ayabe, Dr. Hiroyoshi	NJ05		Nagasaki 852-8102	Japan
Ayed, Prof. Ben	024	007	Bab Saadoun, Tunis	Tunisia
Badolato, Dr. C.	025 026	1516 1069	Melbourne, FL 32901	US
Bajetta, Prof. Emilio	012	001	Milan	Italy
Balbiani, Dr. Luis	024 025	014 001	1405 Capital Federal	Argentina
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Bapsy, Dr. P. P.	025	2	Bangalore-560 029	India
Barnes, Dr. Lester F.	025 026	1392 0832	Fort Smith, AR 72901	US
Barni, Dr. Sandro	012	2	I-20052 Monza Mi	Italy
Barsoum, Prof. Mohsen	024	003	Cairo	Egypt

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Bastús, Dr. Roma	025	002	E-08221 Terrassa (Barcelona)	Spain
Beauduin, Dr. Marc	025	002	B-7100 Haine St Paul	Belgium
Becquart, Dr. Dominique	024 025	004 003	B-2020 Antwerpen	Belgium
Belda, Joaquin Llixiona	024	002	46009 Valencia	Spain
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Ben Ahmed, Prof. Slim	024	009	4000 Sousse	Tunisia
Ben-Baruch, Dr. Noa	025	003	Rehovot, 76100	Israel
Bernstein, Dr. Joel	025 026	1393 0862	La Jolla, CA 92307	US
Berry, Dr. William	026	0836	Raleigh, NC 27607	US
Bertram, Dr. K.	025	1459	Tacoma, WA 98431	US
Bezwoda, Prof. W.	024	002	Johannesburg	South Africa
Biermann, Dr. William A.	026	0837	Philadelphia, PA 19107	US
Bitran, Dr. J.	025 026	1396 0791	Park Ridge, IL 60068	US
Blachly, Dr. Ronald	025	1397	Jonesboro, AR 72401	US
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Blanco, Dr. Guillermo	025	001	Fin-90221 Oulu	Finland
Blayney, Dr. D.	025 026	1398 0785	Pomona, CA 91767	US
Boni, Dr. Corrado	025	007	I–42100 Reggio Emilia	Italy
Bordelon, Dr. Jill	026	0838	Ruston, LA 71270	US
Borrego, Manuel Ruiz	024	006	41013 Sevilla	Spain
Braems, Dr. Sabine	025	005	B-8310 Brugge	Belgium
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Brenner, Dr. Joseph	025	006	Holon, 58100	Israel
Brotherton, Dr. T.	025 026	1400 0747	Danville, VA 24541-4155	US
Brown, Dr. R.	025 026	1401 0804	Sarasota, FL 34239	US
Buzdar, Dr. Aman U.	024	020	Houston, TX 77030	US
Buzzi, Dr. Franco	025	020	I–5100 Terni	Italy
Caggiano, Dr. V.	025 026	1402 0847	Sacramento, CA 95816	US
Cagnolati, Dra Silvia	025	003	Arg-(1097)-La Plata	Argentina
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Castagnari, Dr. Aldo	025	004	Arg-(1824) Lanus	Argentina
Castillo, Dra. C.	025	5	Arg-3400 Corrientes	Argentina
Cernaianu, Dr. Aurel	026	0810	Staten Island, NY 10305	US
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Chollet, Prof. Philippe	024 025	003 002	63011 Clermont Cedex 1	France
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Coppola, Dr. Frederico	025 024	006 012	Buenos Aires	Argentina
Costello, Dr. Shaun	025	009	Dunedin New Zealand	Australia
Couture, Dr. Félix	025	005	Québec, Québec G1R 2J6	Canada
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De Angelis, Dr. Rodolfo Lucero	024 025	007 007	Arg-Mendoza 5500	Argentina
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Toi, Dr. Masakazu	NJ05		Bunkyo-ku, Tokyo 113-0021	Japan
Torello, Dr. Helena	025	021	Arg-1680 Munro	Argentina

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Tsutsui, Dr. Shinichi	NJ05		Fukuoka 811-1347	Japan
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van Veelen, Dr. H.	025	012	Nl-8934 Ad Leeuwarden	Netherlands
Vanstraelen, Dr. Dany	025	010	B-3500 Hasselt	Belgium
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Weissman, Dr. Charles	026	0767	Latham, NY 12110	US
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Yunus, Dr. F.	025 026	1464 0852	Memphis, TN 38104-3499	US
Zarba, Dr. Juan Jose	025	026	Arg- 7000 Tucuman	Argentina
Zielinski, Prof. Dr. Christoph	025	004	A-1090 Wien	Austria
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6.0 Study Results per Sponsor

6.1 Analysis populations

All efficacy analyses, inferential or exploratory, were based on the intent-to-treat population, defined as 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 (see below).

In early 2000, one site (center 7, Netherlands) which had randomized and treated 5 patients (2 assigned letrozole, 2 tamoxifen, and 1 combination), was found to have committed serious GCP violations in another Novartis sponsored study. Novartis decided to exclude these 5 patients from all analyses, and all tabulations (including demographic characteristics), but to list all data fully for these patients. No firm evidence of GCP violation was found in Protocol 025 when Novartis audited the site. The main analyses of time to progression and overall objective tumor response were repeated including the 4 patients assigned monotherapy from this center, without impact.

Patients assigned combination treatment were included in the safety population, defined as all patients who were randomly assigned study treatment, and who took at least one dose of study medication, excluding patients at the one GCP non-compliant center.

One patient, RA/15/6373, received the alternative treatment (letrozole) instead of the randomized treatment (tamoxifen). She remained on the treatment dispensed, until she progressed 4 weeks after entering the study. At progression, this patient entered the follow-up for overall survival. The patient died from progressive disease approximately 6 weeks later. She was counted in the analysis as an event on letrozole.

6.2 Patient disposition

From 26-Nov-1996 through 07-Jan-1999, a total of 939 patients were randomized. For the original 3-arm study 73 patients were randomly assigned one of three treatments. For the 2-arm study (protocol Amendment 1) 866 patients were randomly allocated monotherapy

treatment. In total there were 458 patients assigned 2.5 mg letrozole, 458 patients were assigned 20 mg tamoxifen and 23 patients were assigned combination treatment.

Patients were randomized from 29 participating countries to the monotherapy arms: 589 (64%) patients in Europe (293 on letrozole and 296 on tamoxifen), 100 (11%) patients in North America (49 on letrozole and 51 on tamoxifen) and 227 (25%) in the Rest of the World (116 on letrozole and 111 on tamoxifen).

Patient disposition for all randomized patients is summarized in **Table 4**. When patients discontinued core treatment, they could be offered the alternative treatment (if assigned monotherapy) providing they remained suitable for endocrine anti-cancer treatment; if not, patients entered the follow-up for overall survival (terminated study during core). At the time of this analysis, a similar percentage of patients in both monotherapy arms received crossover treatment. In the letrozole arm, 24% of patients compared with 15% in the tamoxifen arm remain on core treatment without evidence of progression.

Table 4 Patient disposition for all randomized patients in the core phase

	letrozole 2.5 mg	**Tamoxifen 20 mg**
Total patients randomized	**458 (100%)**	**458 (100%)**
No. patients still on core, no PD	111 (24%)	67 (15%)
Patients who did not discontinue at the cut-off date of the analysis, but PD was documented by the investigator	7 (2%)	5 (1%)
No. patients entering crossover[1]	200 (44%)	197 (43%)
No. who terminated study during core[2]	140 (31%)	189 (41%)
[1]There were 5 patients (3 letrozole, 2 tamoxifen) who were switched to crossover at the analysis cutoff date (core discontinuation CRF pages); however, the crossover visit data (visit 51 CRF) page had not been received. [2] Discontinued core treatment but did not enter crossover (terminated study treatment).		

The reasons for core treatment discontinuation are summarized in Table 2-2. The main reason was disease progression (65% of patients in the letrozole arm, 74% of patients in the tamoxifen arm). The frequency of discontinuation due to an adverse event or death was low, and similar in both monotherapy arms.

Table 2-2. Reasons for patient discontinuation for all randomized and GCP compliant patients

	letrozole 2.5 mg	Tamoxifen 20 mg
Total no. patients	**456 (100%)**	**456 (100%)**
No. who discontinued core treatment	338 (74%)	384 (84%)
- death	11 (2%)	11 (2%)
- for AEs	10 (2%)	15 (3%)
- protocol violations	13 (3%)	4 (1%)
- progression[1]	296 (65%)	338 (74%)
- other	8 (2%)	16 (4%)
[1]The five patients (two in each monotherapy arm and 1 in combination arm) from the one GCP non-compliant center discontinued for progression and are not included in this table.		

6.2.1 Groupings for analysis

The analysis populations are described in **Table 5**. The ITT population excluded 9 patients, 5 who were randomly assigned study treatment (3 letrozole, 2 tamoxifen,) but were subsequently found not to have active breast cancer at study entry, and 4 from the one GCP non-compliant center. The safety population excluded 7 patients, 5 from the one GCP non-compliant center and 2 who never received study medication. Patients assigned combination treatment were included in the safety population.

Table 5 Number of patients in analysis populations by treatment

Description	letrozole 2.5mg	tamoxifen 20mg	combination	Total
Randomized	458	458	23	939
GCP compliance questionable	2	2	1	5
Randomized and GCP compliant	456	456	22	934
Never treated	1	1	0	2
Safety population	455	455	22	932
No active breast cancer	3	2	1	6
ITT population	453	454	0*	907
*Comparisons were made only between the 2 monotherapy arms. All efficacy (and other) data are listed for all patients who received combination therapy.				

6.3 Baseline demographic and background characteristics

A summary of demographic data is provided in **Table 6**. Approximately one-third of all patients were 70 years of age or older (34% letrozole, 31% tamoxifen). All but 3 patients (tamoxifen arm) were postmenopausal as defined in the protocol. Additionally, one patient on tamoxifen

had follicle stimulating hormone and luteinizing hormone levels not in the postmenopausal range, but the patient's baseline estradiol level indicated that she was postmenopausal.

Table 6 Demographic summary by treatment arm

		letrozole n=456	**tamoxifen n=456**
Age (years)	Median	65.0	64.0
	Minimum – Maximum	31 – 96	31 – 93
Body mass index	N	441	442
	Median	26.1	25.9
	Minimum – Maximum	14.6 – 44.5	15.6 – 52.7
Race	White/Caucasian	388 (85%)	395 (87%)
	Black	12 (3%)	13 (3%)
	Oriental	28 (6%)	25 (6%)
	Other	28 (6%)	23 (5%)

Relevant medical history and concomitant medical conditions medical conditions were similar for the two major treatment arms. A summary is provided in **Table 7**.

Table 7 Relevant medical history or concomitant medical conditions (³ 10%)

Description	Letrozole n=456	Tamoxifen n=456
Relevant medical history / concomitant medical condition	380 (83%)	372 (82%)
- Vascular disorders	175 (38%)	150 (33%)
- Surgical and medical procedures	162 (36%)	170 (37%)
- Musculoskeletal, connective tissue and bone disorders	88 (19%)	85 (19%)
- Cardiac disorders	80 (18%)	69 (15%)
- Metabolic and nutrition disorders	68 (15%)	71 (16%)
- Gastrointestinal disorders	63 (14%)	51 (11%)
- Respiratory, thoracic disorders	62 (14%)	44 (10%)
- Infections and infestations	48 (11%)	53 (12%)
- Nervous system disorders	57 (13%)	50 (11%)
- Neoplasms benign and malignant (including cysts and polyps)	42 (9%)	58 (13%)
- Psychiatric disorders	46 (10%)	42 (9%)

Extent of disease at baseline is summarized in **Table 8**. As indicated the 2 treatment arms were comparable as regards disease free interval and dominant disease sites.

Table 8 Extent of cancer at baseline

	letrozole n=456	tamoxifen n=456
Disease free interval		
< 1 month	145 (32%)	146 (32%)
≥ 1 month - < 24 months	58 (13%)	63 (14%)
≥ 24 months	253 (56%)	246 (54%)
Dominant site of disease:		
Soft tissue only	113 (25%)	116 (25%)
Bone	146 (32%)	130 (29%)
Bone only	69 (15%)	72 (16%)
Bone and soft tissue	77 (17%)	58 (13%)
Visceral	195 (43%)	208 (46%)
Visceral only	53 (12%)	61 (13%)
Visceral and bone	44 (10%)	44 (10%)
Visceral and soft tissue	41 (9%)	51 (11%)
Visceral and bone and soft tissue	57 (13%)	52 (11%)
Dominant site missing*	2 (<1%)	2 (<1%)
*Dominant site missing in 4 patients without active advanced breast cancer. Dominant site: Soft tissue prevails if only soft tissue sites are involved; bone prevails if bone or bone and soft tissue sites are involved; visceral prevails if any visceral metastasis is present, regardless of the involvement of soft tissue or bone sites.		

The most common histologic diagnosis was infiltrating ductal carcinoma (59% letrozole, 57% tamoxifen).

There were 62 patients (29 letrozole, 33 tamoxifen) who entered the study with locally advanced (Stage IIIA/IIIB) disease. Except for these patients, and 4 patients (2 letrozole, 2 tamoxifen) who entered the study with Stage IIA/B disease, the remaining patients had metastatic disease at study entry.

A summary of hormone-receptor status is provided in **Table 9**. Baseline tumor receptor status was similar for both treatment arms.

Table 9 Baseline overall receptor status

	Letrozole n=456	tamoxifen n=456
ER+ or PgR+	120 (26%)	120 (26%)
ER+ and PgR+	175 (38%)	187 (41%)
Both unknown	158 (35%)	149 (33%)
Other	3 (1%)	0

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 receivved 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.

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)

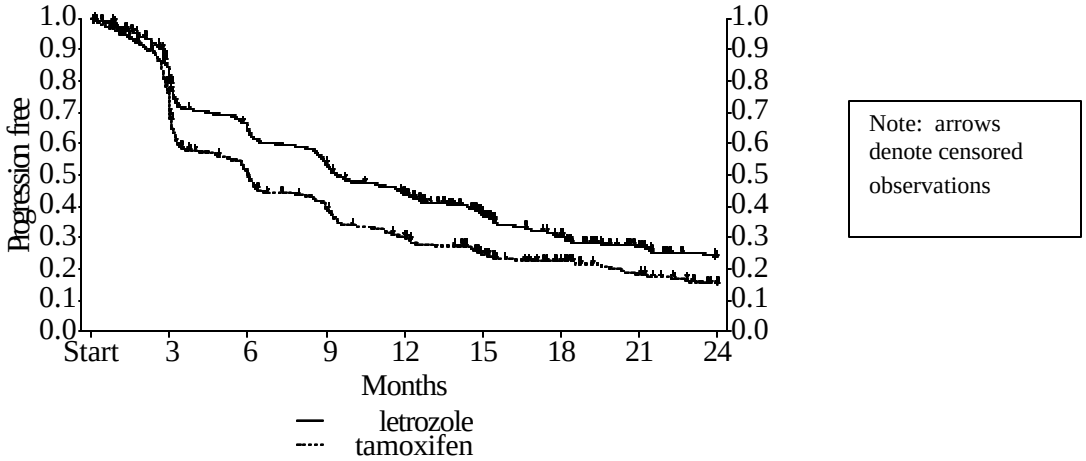
Letrozole was superior to tamoxifen in TTP, reducing the risk of progression by 30% compared with tamoxifen, and prolonging TTP by over 40% (hazard ratio 0.70, P=0.0001). **(Table 11, Figure 2)**. Fewer patients progressed on letrozole (68%) than on tamoxifen (77%) during core treatment.

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.

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 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)**.

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)**.

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)**.

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) 95% confidence interval Median duration (months)	137 (30%) (26 to 35%) 23	92 (20%) (17 to 24%) 23
Overall clinical benefit (CR+PR+NC*) 95% confidence interval Median duration (months)	221 (49%) (44 to 54%) 19	173 (38%) (34 to 43%) 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

	Letrozole		**tamoxifen**		
Baseline covariate	**CR + PR responses (n)**	**%**	**CR + PR responses (n)**	**%**	**Cochran Mantel Haenszel P-value**
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 $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)**.

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 post-menopausal 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 (FEM-INT-01, BIG-1-98, and MA-17) and a recently completed study (NJ-05) in breast cancer indications other than first-line, SAE tabulations are also provided. These studies include:

FEM-INT-01: second-line endocrine therapy comparing open-label letrozole 2.5 mg with anastrozole 1 mg until progression of breast cancer.

NJ-05: a double-blind study comparing letrozole 1 mg with fadrozole hydrochloride 1 mg in women with advanced breast cancer. Fadrozole hydrochloride (Afema®) is an approved oral non-steroidal aromatase inhibitor only in Japan for the treatment of advanced breast cancer.

BIG-1–98: a double-blind study comparing the monotherapies of letrozole 2.5 mg with tamoxifen 20 mg for 5 years, or the sequential treatment with letrozole or tamoxifen for 2 years followed by treatment with tamoxifen or letrozole for 3 years as adjuvant therapy for women with breast cancer

MA-17: a double-blind study comparing letrozole 2.5 mg with placebo as late adjuvant treatment in women with breast cancer after completion of 5 or more years of adjuvant tamoxifen.

The cutoff date for adverse event data for this ISS is March 8, 2000 (study 025), 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.

Table 22 **Number of patients with adverse events, regardless of study drug relationship, in most frequently affected primary system organ classes (³ 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 (³ 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 montherapy 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 (³ 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			

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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 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**.

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/5004/2766 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.

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 FEM-INT-01

This is an ongoing, open-label, randomized study comparing 1 mg anastrozole versus 2.5 mg letrozole as second-line therapy for patients with advanced breast cancer. As of the cutoff date, 345 patients in the letrozole group and 348 patients in the anastrozole group had been enrolled. In the SAERS database, 67 patients (19%) in the letrozole group and 62 patients (18%) in the anastrozole group had SAEs. The SAEs reported are similar to those seen previously in completed studies. The only SAEs reported for more than 2% of the patients in either treatment group were pleural effusion (3% and 2% of patients in the letrozole and anastrozole groups, respectively) and under general disorders, the SAE “condition aggravated” (7% and 6% of patients in the letrozole and anastrozole groups, respectively), the majority of which were due to progression of disease. There were 2 SAEs suspected to be related to the study medication, both related to letrozole treatment (thromboembolic event and dermatitis).

6.7.10.2 BIG-1-98

This is a double-blind study comparing the monotherapies of letrozole 2.5 mg with tamoxifen 20 mg for 5 years, or the sequential treatment with letrozole or tamoxifen for 2 years followed by treatment with tamoxifen or letrozole for 3 years as adjuvant therapy for women with breast cancer. Blinded SAEs are reported from SAERS for 2112 patients. There were 110 patients (5%) with SAEs and 22 patients (1%) with SAEs that were suspected to be related to the study drugs. The SAEs reported are similar to those seen previously in completed studies. The only SAEs suspected to be related to study drug and occurring in more than 2 patients were thromboembolic events in 5 patients (<1%) and pulmonary embolism in 3 patients (<1

6.7.10.3 NJ-05

This is a recently completed double-blind study comparing letrozole 1 mg with fadrozole hydrochloride 1 mg in women with advanced breast cancer. There were 78 patients in the letrozole group and 76 patients in the fadrozole group. Of these 154 patients, 33 received first-line therapy (15 in the letrozole group and 18 in the fadrozole group). There were 3 patients (4%) in the letrozole group with SAEs, one of which was considered related to study drug (sudden death, unexplained). There were 4 patients (5%) in the fadrozole group with SAEs, none of which was considered related to study drug.

6.7.10.4 MA-17

This is an ongoing double-blind, Phase III study of letrozole compared to placebo in patients with primary breast cancer completing 5 or more years of adjuvant tamoxifen. Planned number of patients is 2380, and as of February 29, 2000, 1100 patients had been enrolled. According to the agreement with oncology cooperative groups involved with this study sponsored by the National Cancer Institute of Canada (SWOG, ECOG, NCCTG, CALGB, EORTC, and IBCSG), only unexpected, treatment-related SAEs were to be reported. As of February 29, 2000, no treatment-related SAEs had been reported.

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)**.

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)

Table 29 Summary of adverse events suspected of being related to study treatment (³ 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**.

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 100,000. SAEs are summarized in **Table 31**.

Table 31 Serious adverse events reported during commercial use

Country	Age	Reaction description
AUS	55	polyarthritis
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 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.

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

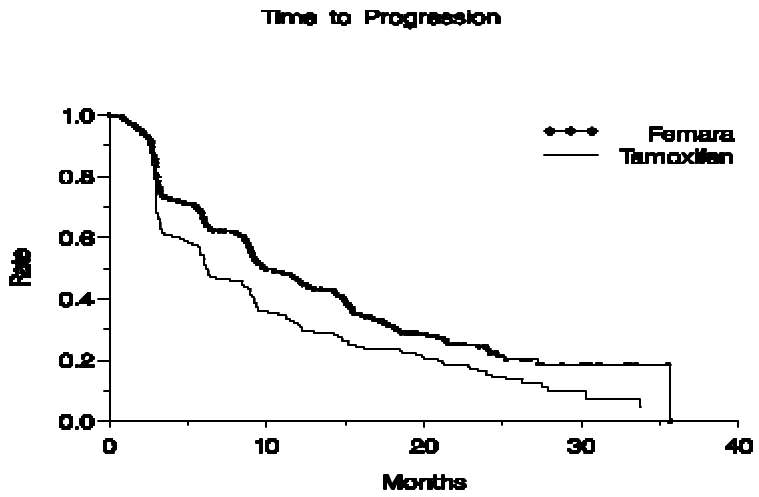
7.2.1 Time to progression

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
Tamoxifen	6.15	(5.79-8.45)		((0.61-0.84)

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		
	Number	Percent	Number	Percent	p
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.

Table 35 First-lineTamoxifen 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)*

* $P^2 = 14.9$ p=0.0002

7.2.4 Response rate after cross-over

The protocol specified that patients progressing on their primary hormone therapy would crossover to receive the opposite therapy. **Table 39** presents response rates of women who received the crossover treatment. As indicated the response rate of women receiving letrazole after tamoxifen progression was higher than that of women receiving tamoxifen after letrazole progression.

Table 39 Response rate after crossover treatment

	# pts crossed over	Response rate #	(%)	Type of response CR/PR
Tam to Letrozole	169	17	(10)	2/15
Let to Tamoxifen	155	10	(6)	0/10

Response durations of crossover treatment are illustrated in **Table 40**. The median duration of response to letrazole as second line hormone treatment was 12+ months versus 8+ months for tamoxifen as second line hormone treatment.

Table 40 Response duration - crossover treatment

Tamoxifen to Letrazole		Letrozole to Tamoxifen	
5+	15+	6+	9
8+	19+	6+	12
9+	20+	7+	12
11+	21+	7+	13
11+	21+	7+	13
12+	24+		
12+	25+		
12	28+		
12			

7.3 Safety

Duration of time on therapy for patients receiving letrozole or tamoxifen is summarized in **Table 41**. 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 41 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 42** 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 42 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 femara 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 letrazole and tamoxifen manifest a similar toxicity spectrum.

The number of patients with cardiovascular, cerebrovascular and peripheral vascular adverse events listed in **Table 42** 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 43 and 44**.

Table 43 Terms for Fracture

Term	Sponsor Included	FDA Included
Fractures Femoral neck fracture 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	X	X
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

Table 44 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 45**. 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 45 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, Dr. M. Ellis, Georgetown University, indicated that he had received grants and income from the sponsor. Georgetown University accrued 3 patients to the study.

Forty-three USA institutions participated in study 025. 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, Tunesia, 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 Mouridsen, 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 $ 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 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. At progression 169 letrozole treated patients and 155 tamoxifen treated patients crossed over to the alternative therapy. Response rates were 10% (T û L) and 6% (L ûT), with 2 CR's in the letrozole treated group. Response durations were longer for responders crossed over from tamoxifen to letrozole than for the opposite crossover. In an exploratory analysis 110 of 344 letrozole treated patients (32%) improved their performance status ($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 letrazole 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 is submitted to the December 13, 2000 ODAC meeting.

13.0 Recommendation

Pending ODAC discussion

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