

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: NDA 20-726/S-006

MEDICAL/STATISTICAL REVIEW

sNDA 20-726

FDA MEDICAL AND STATISTICAL ODAC REPORT

Drug Name: Femara® Letrozole tablets
Applicant: Novartis
Date Submitted: July 11, 2000
Date Received: July 12, 2000
Date of Review: November 14, 2000

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1. General Information

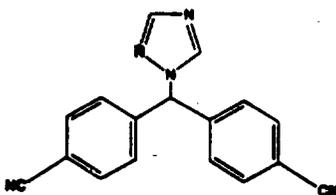
1.1. Pharmacological class

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. These include the following:

- For the analysis of the primary endpoint TTP, a supportive analysis adjusted for receptor status, prior adjuvant therapy, and dominant site of disease were presented.
- Additional exploratory analyses investigating the influence of other baseline covariates such as previous chemotherapy for advanced disease, performance status, duration of adjuvant anti-estrogen therapy, washout of adjuvant anti-estrogen therapy, age class, body mass index and bisphosphonate use were performed.
- Further exploratory analyses were conducted using the covariates receptor status, prior adjuvant therapy, and dominant site of disease as stratification factors for the estimation of TTP. Treatments were compared by the stratified logrank test."

Corresponding analyses were done for overall response (logistic regression/stratified analysis).

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-erbB-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 benzydryl triazole 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 and 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 letrozole 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 (

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 mg 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

This section describing the pivotal trial protocol reflects the original protocol and Amendment 1 only. Please note that changes were subsequently implemented with Amendments 2-4 and are not described below. Importantly, the statistical plan and requirement for a peer review were revised. For details of these amendment changes please refer back to Section 2.5

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 overall objective tumor response rate (CR + PR), overall clinical benefit rate (CR + PR + NC \geq 24 weeks), duration of overall response, duration of 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.
- b. To compare the tolerability and toxicity of the two treatment arms.
- c. 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 (extension phase).

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 1 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 tamoxifen 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 carcinomatosis 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 ≥ 11.6 mg/dL (or ≥ 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 ≥ 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 will 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 hypercalcemia. 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.

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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 | | | | | | |
|---|-------------------------------|--------|--------|--------|--------|-----------|---------------|
| | 1 0 | 2 1 | 3 3 | 4 6 | 5 9 | ≥6 ≥12 | Term Visit |
| Visit ^a | | | | | | | |
| 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 | X | X | X | X | X | X | X |
| Adverse Experiences | | 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 | X | | X | X | X | X | X |
| -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 |
| LABORATORY TEST | X | | X | X | X | X | X |
| -Hematology | | | | | | | |
| -Blood Chemistry | | | | | | | |

- 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 Statistical 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 \geq 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 performance 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:

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: 1 cm 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.

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5.4 Investigators

Table 3 Investigators

| Investigator | Study | Center # | City | Country |
|------------------------------|------------|--------------|------------------------------|--------------|
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| | | | | |
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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 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 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%) |

¹The 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 were similar for the two major treatment arms. A summary is provided in Table 7.

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Table 7 Relevant medical history or concomitant medical conditions (≥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.

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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 |