INTERNATIONAL BREAST CANCER STUDY GROUP
IBCSG 35-07
BIG 1–07
SOLE
Study of Letrozole Extension

A phase III trial evaluating the role of continuous letrozole versus intermittent letrozole following 4 to 6 years of prior adjuvant endocrine therapy for postmenopausal women with hormone-receptor positive, node positive early stage breast cancer

Coordinating Group: **International Breast Cancer Study Group (IBCSG)**

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Protocol Signature Page

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Study of Letrozole Extension - SOLE

Approved by:
CEO, International Breast Cancer Study Group
Prof. Dr. med. M. Castiglione

_____ _____

Date

Approved by:
Novartis representative(s)

_____ _____

Date

Approved by:
Group Statistician, International Breast Cancer Study Group
Prof. R.D. Gelber

_____ _____

Date

Principal Investigator Protocol Signature Page

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I have read the protocol and agree that it contains all necessary details for conducting this study. I will conduct the study as outlined in the following protocol and in compliance with GCP. I will provide copies of the protocol and all drug information relating to pre-clinical and prior clinical experience furnished to me by IBCSG, **to all physicians responsible to me who participate in this study. I will discuss this material with them to assure that they are fully informed** regarding the drug and the conduct of the study. I agree to keep records on all patient information (Case Report Forms and patient's informed consent statement), drug shipment and return forms, and all other information collected during the study for a minimum period of 15 years.

Name of Principal Investigator:_____

_____ _____

Signature Date

Protocol Summary and Schema
SOLE
Study of Letrozole Extension

A phase III trial evaluating the role of continuous letrozole versus intermittent letrozole following 4 to 6 years of prior adjuvant endocrine therapy for postmenopausal women with hormone-receptor positive, node positive early stage breast cancer

Patient population

Postmenopausal women who are disease-free following 4-6 years of prior adjuvant endocrine therapy with selective estrogen receptor modulator(s) (SERM) and/or aromatase inhibitor(s) (AI) for endocrine-responsive, node-positive operable breast cancer.

Rationale

In 2006, the standard duration of adjuvant endocrine therapy for breast cancer (either SERMs or AIs) is five years. Patients who receive extended adjuvant letrozole for five years following approximately five years of tamoxifen obtain further benefit compared with the five years of tamoxifen alone. Similarly, benefit has been demonstrated for switching from tamoxifen to an AI after 2 to 3 years of tamoxifen to complete five years of endocrine therapy, as well as initiating therapy with AI following surgery and administering the AI for five years.

Questions remain about the optimal duration and best schedule of AIs in the extended adjuvant setting. This trial tests the hypothesis that introducing 3-month treatment-free intervals during the course of five years of extended adjuvant letrozole will improve disease-free survival. This hypothesis is based on the theoretical principle that letrozole withdrawal for 3 months will permit some estrogenic stimulation which makes residual resistant disease susceptible to letrozole reintroduction.

Objective

To compare continuous letrozole for five years with intermittent letrozole over a five year period for postmenopausal women who are disease-free following 4-6 years of prior adjuvant endocrine therapy with SERM(s) and/or AI(s) for endocrine-responsive, node-positive, operable breast cancer.

Trial end points

Primary end point: Disease-free survival (DFS): time from randomization to local (including invasive recurrence restricted to the breast after breast conserving treatment), regional or distant relapse, contralateral breast cancer, appearance of a second (non-breast) malignancy, or death from any cause, whichever occurs first.

Secondary end points: overall survival (OS), distant disease-free survival (DDFS), breast cancer free interval (BCFI), sites of first failure, second (non-breast) malignancies, deaths without prior cancer events, and adverse events.

Statistical analysis

The randomization will be stratified according to participating center and prior SERM/AI endocrine therapy (SERM(s) alone, AI(s) alone, both SERM(s) and AI(s).

The primary analysis will be undertaken with the intention-to-treat population of all randomized patients. The primary endpoint is disease-free survival (DFS) and will be compared between treatment arms using a two-sided stratified logrank test with an overall experiment-wise alpha level equal to at most 0.05. Kaplan-Meier estimates of the DFS distributions will be calculated for each of the two treatment arms. Cox proportional hazards regression models will be used to investigate whether the treatment comparison is modified by adjustments for various covariates.

Sample size and anticipated trial duration

The sample size was determined to provide 80% power to detect a 20% reduction in the risk of an event defining DFS associated with intermittent letrozole compared with continuous letrozole (hazard ratio = 0.80; 25% increase in 4-year DFS from 90% to 91.917%) using a two-sided 0.05 level test of significance.

To achieve this goal requires 647 events defining DFS, assuming 4800 patients are accrued (1600 patients per year for 3 years), 5% non-assessability at 4 years, and approximately 5 years of additional follow-up. One year of start-up time, as participating centers obtain ethics committee approval and complete regulatory processes, is anticipated.

Procedures

All patients will be followed every 6 months for years 1 to 5, and thereafter yearly for assessment of disease status and for survival data collection.

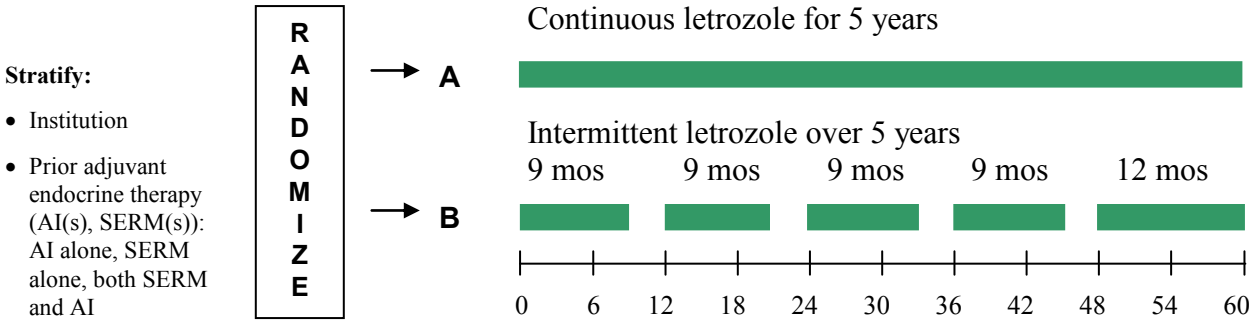
Risks and benefits

Adjuvant treatment with letrozole has been shown to have a favorable effect on time without recurrence of breast cancer. The adjuvant treatment with letrozole is generally well tolerated.

Trial Design

At completion of 4 to 6 years of prior adjuvant SERM/AI endocrine therapy, patients will be randomized to one of two treatment groups:

Schema



Extended Adjuvant Endocrine Therapy

Letrozole: A: Continuous letrozole 2.5 mg daily for 5 years
B: Intermittent letrozole 2.5 mg daily for the first 9 months of years 1 through 4, followed by 12 months in year 5

Randomization Timing

In principle, patients should start trial treatment as soon as possible after randomization. Trial treatment should begin no later than 6 weeks from the date of randomization.

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1. Introduction

1.1. Adjuvant treatment in breast cancer

Breast cancer is the most common malignant disease in women; and the most common form of cancer death in women in Europe with an estimated 370,100 new cases diagnosed and 129,900 deaths [1]. At diagnosis, 90% of the patients appear to have an operable breast cancer, that is, disease confined to the breast and to the ipsilateral axilla. More than 50% of these patients, however, die of metastatic disease. In fact, once metastases become overt, the disease is considered, with very few exceptions, incurable. Since the late nineteen-forties randomized trials of adjuvant systemic therapy (either endocrine or cytotoxic) have been conducted in an effort to reduce the number of relapses and to prolong the survival of patients with operable disease. The Oxford Overview summarizing the available results of all such trials indicated that adjuvant systemic treatments with chemotherapy, endocrine therapy, and combinations of both improved prognosis of patients with breast cancer [2].

1.2. Letrozole

There are two classes of third generation AI(s). Agents such as anastrozole and letrozole act by reversibly binding to the aromatase enzyme, which is responsible for the production of estrogens in post menopausal women. Exemestane is an oral irreversible inactivator of aromatase that depletes plasma estrogen by more than 90% and whole body aromatization by 98%. Unlike reversible AI(s), it cannot be displaced from the aromatase enzyme. At clinically administered doses, the plasma half-lives of anastrozole (1 mg once daily), letrozole (2.5 mg once daily), and exemestane (25 mg once daily) were 41-48 hours, 2-4 days, and 27 hours, respectively. The time to steady-state plasma levels was 7 days for both anastrozole and exemestane and 60 days for letrozole. Androgenic side effects have been reported only with exemestane [3]. There is evidence in postmenopausal women with metastatic disease that AI(s) produce response rates and survival equivalent to or superior to those seen with tamoxifen [4, 5]. Letrozole is up to 150-250 times more potent than the first generation aromatase inhibitor aminoglutethimide (AG), *in vitro* and more than 10,000 times as potent as AG in inhibiting aromatase *in vivo* [6].

The high potency of letrozole is not accompanied by any significant effect on adrenal steroidogenesis *in vitro* or *in vivo* over its maximally effective dose range [7, 8]. Inhibition of adrenal steroidogenesis resulting in adrenal hypertrophy does occur with therapeutic doses of AG. The high potency and selectivity of letrozole explains its pharmacological profile and high therapeutic index. In postmenopausal patients with advanced breast cancer, daily doses of 0.1 mg to 5 mg letrozole suppressed plasma levels of estradiol, estrone and estrone sulfate to 75-95% from baseline [9]. Estrogen suppression was maintained throughout the treatment period of 28 days in all patients.

Letrozole is a highly selective inhibitor of the aromatase enzyme. No clinically relevant changes in the plasma levels of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxyprogesterone, ACTH

or plasma renin activity were found in postmenopausal patients treated with a daily dose of letrozole ranging from 0.1 to 5 mg [10, 11].

For postmenopausal women with endocrine responsive disease, the use of letrozole has been shown to yield some advantage in terms of treatment outcome as compared to tamoxifen in advanced disease [3] and preoperative setting where a double-blinded, randomized phase III trial of primary endocrine therapy was recently reported [12]. Letrozole 2.5 mg or tamoxifen 20 mg were given daily for 4 months to postmenopausal women with hormone receptor–positive breast cancer who were ineligible for breast-conserving surgery [12]. Among the 250 patients who received letrozole, 60% responded and 48% underwent successful breast-conserving surgery. The response to tamoxifen was significantly lower in terms of response rate (41%), and proportion of patients eligible for breast saving surgery. Differences in response rates between letrozole and tamoxifen were most striking for tumors that overexpressed ErbB-1 and/or ErbB-2 and were ER positive (88% *v*s 21%, p= .0004). In this study, the incidence of adverse events (AEs) was the same (57%) for the letrozole and tamoxifen groups. The most commonly reported AEs in both groups were hot flushes, headache, and nausea. The frequency of AEs suspected to be related to the study drugs was comparable for both groups (38% and 34% in the letrozole and tamoxifen groups, respectively). No other treatment-related effects with either of the study drugs were seen. Four patients discontinued study medication because of AEs (one patient in the letrozole group for a pulmonary embolism and 3 patients in the tamoxifen group for hepatitis C, erythema multiforme or cholestasis) [12].

1.3. Aromatase inhibitors in the adjuvant setting

Trials comparing AIs to tamoxifen for postmenopausal women in the adjuvant setting are mature. AIs have been studied in the adjuvant setting either as alternatives to tamoxifen or as sequential therapy after tamoxifen among postmenopausal women. The Arimidex, Tamoxifen Alone or in Combination (ATAC) trial compared primary use of an aromatase inhibitor, anastrozole, with either tamoxifen alone or the combination of the two as adjuvant therapy for early-stage breast cancer. The ATAC trial demonstrated improvements in disease-free survival (hazard ratio = 0.82) with use of anastrozole as monotherapy [13-15]. There was no benefit to combining the estrogen-deprivation effects of anastrozole with the antiestrogen effects of tamoxifen. Patients who were treated with anastrozole had significantly lower incidences of the following predefined adverse events compared with those treated with tamoxifen: hot flushes, vaginal bleeding, vaginal discharge, endometrial cancer, ischemic cerebrovascular events, venous thromboembolic events, and deep venous thromboembolic events. Women who were treated with anastrozole had significantly higher incidences of arthralgia and fractures than those treated with the bone-sparing agent tamoxifen; however, the risk ratio for fractures relative to tamoxifen has been shown to stabilize with treatment duration beyond two years.

The Breast International Group (BIG) 1-98 trial has recently reported on the use of the aromatase inhibitor letrozole compared with tamoxifen as primary therapy for early-stage breast cancer [16, 17]. 8028 women were randomized between March 1998 and May 2003 to receive five years of adjuvant endocrine therapy with letrozole, tamoxifen, or a sequence of these agents. Of these, the 4922 patients allocated continuous therapy with either letrozole or

tamoxifen were recently analyzed [16]. At a median follow-up of 51 months, 352 DFS events among 2463 patients allocated letrozole and 418 events among 2459 patients allocated tamoxifen were observed. This reflected an 18% reduction in the risk of an event (hazard ratio 0.82; 95 percent confidence interval 0.71 to 0.95; *P*= 0.007). Hazard ratios for the other defined endpoints were similar, though those for overall survival and systemic disease-free survival were not statistically significant. No subgroups showed significantly different relative efficacy; in particular, no significant heterogeneity was observed by nodal involvement status or progesterone receptor status.

Compared to patients receiving tamoxifen, more patients receiving letrozole reported at least one adverse event (AE) of any grade (2292 patients *vs* 2165 patients). Patients on tamoxifen experienced significantly more thromboembolic events, endometrial pathology, hot flushes, night sweats and vaginal bleeding. Patients on letrozole experienced significantly more bone fractures, arthralgia, low-grade cholesterol elevation, and cardiovascular events other than ischemic heart disease and cardiac failure. The relatively higher recording of low-grade cholesterol elevation on letrozole may be largely an artifact reflecting a cholesterol-lowering effect of tamoxifen. The overall incidence of cardiac failure did not differ significantly between the two arms.

Different trials have reported that the use of tamoxifen followed by aromatase inhibitor therapy may be clinically advantageous. The Intergroup Exemestane Study (IES) compared sequential treatment strategies. Patients in the IES trial had received 2 to 3 years of tamoxifen without evidence of tumor recurrence before random assignment to either ongoing tamoxifen treatment or to the aromatase inhibitor exemestane. Cross over from tamoxifen to exemestane yielded improved disease-free survival. Switching to exemestane was associated with a significantly lower incidence of gynecological symptoms, vaginal bleeding, muscle cramps and thromboembolic events compared with continued tamoxifen. However, switching to exemestane was associated with a significantly higher incidence of arthralgia, diarrhea and visual disturbances compared with continued tamoxifen. There was a suggestion towards increased osteoporosis (7.4% *vs* 5.7%; *P*=0.02) and higher fracture rates in the exemestane group than in the tamoxifen group (3.1% *vs* 2.3%; *P*=0.08) [18]. The updated safety data confirmed that patients switching to exemestane experienced fewer gynecological symptoms, vaginal bleeding, muscle cramps and thromboembolic events compared with continued tamoxifen. Switching to exemestane continued to be associated with a significantly higher incidence of diarrhea and arthralgia compared with continued tamoxifen. In addition, other musculoskeletal adverse events were more common with exemestane (with the exception of muscle cramps). Importantly, exemestane was associated with a higher incidence of myocardial infarction compared with tamoxifen, although it remains a possibility that this is attributable to the protective effects of tamoxifen, reducing the atherogenic risk profile. The Austrian Breast and Colorectal Cancer Study Group (ABCSG) Trial 8/Arimidex-Nolvadex (ARNO) 95 trial also examined sequential therapy, either switching patients from tamoxifen to anastrozole after 2 years or leaving patients on tamoxifen for a total of 5 years. The cross-over improvement resulting from sequential switching of treatment at 2 years in the ABCSG/ARNO trial was slightly more favorable than the improvement seen in the IES trial (hazard ratio, 0.60 *vs* 0.67, respectively) [19]. In the related but much smaller Italian Tamoxifen Anastrozole (ITA) trial

among women with lymph node–positive breast cancer who were free of recurrence after 2 to 3 years of tamoxifen treatment, patients were randomly assigned to either ongoing tamoxifen or cross over to anastrozole resulting in significantly improved disease free survival with the introduction of anastrozole [20].

1.4. Extended treatment with letrozole after 5 years of tamoxifen

The MA.17 trial, led by the National Cancer Institute of Canada, was open to women who had completed 5 years of tamoxifen as primary adjuvant therapy for early-stage breast cancer and who were without clinical evidence of recurrence. These patients were randomly assigned to either extended adjuvant therapy with the aromatase inhibitor, letrozole, or placebo. After 2 to 3 years of follow-up, extended treatment with letrozole after 5 years of tamoxifen demonstrated a reduction in the risk of both locoregional and distant breast cancer recurrence compared with placebo. For the sequential strategy of 5 years of tamoxifen followed by an aromatase inhibitor, the recurrence rate associated with cross over to an aromatase inhibitor was 43% lower than the recurrence rate of tamoxifen alone (hazard ratio = 0.57) [21]. Letrozole was associated with a significantly higher incidence of hot flushes, arthritis, arthralgia and myalgia, but a significantly lower incidence of vaginal bleeding compared with placebo. There were no significant differences between letrozole and placebo in the incidence of osteoporosis (5.8% *vs* 4.5%; P=0.07) or fracture rates (3.6% *vs* 2.9%; P=0.24). Efficacy and safety data from an update of the MA.17 trial (median follow-up of 2.5 years) were consistent with the initial analysis. In addition, newly diagnosed osteoporosis was higher in the letrozole group compared with placebo (P=0.003), although the incidence of bone fractures was similar for both groups (P=0.25) [22].

1.5. Optimal sequence of endocrine therapy in a low estrogen environment

Recent evidence suggests that estradiol is capable of inducing programmed cell death (i.e., apoptosis) in breast cancer cells that have developed resistance following extensive antihormonal therapy. In particular, cells that are maintained estrogen-free for years initially start to grow spontaneously; in this case, even minimal concentrations of estrogen produce a cytocidal effect on cells that are exhaustively deprived of estrogen [23-25]. An antitumor action was observed also for physiological levels of estradiol on breast tumors grown in athymic mice [26].

Clinical observations also indicate an antitumor activity of estradiol, supporting a role for intermittent treatment with antiaromatase therapy. In fact, a small study of high-dose estrogen therapy following exhaustive antihormonal therapy was recently reported. Evaluation of response was performed after 3 months on therapy. On 26 evaluable patients, 4 patients obtained complete response and 6 patients partial response. In addition, two patients had stable disease for ≥6 months duration. [27].

These new data suggest a rational approach for the treatment of patients with ER-positive breast cancer during extensive antihormonal therapy. Low-dose estrogen levels (achievable through interruptions of treatment with AIs) could be used to induce apoptosis in breast cancer cells that might have developed resistance following extensive antihormonal therapy.

The 3 months interruption after 9 months of letrozole is based on the prolonged estradiol and estrone suppression observed after a single administration of letrozole in healthy postmenopausal women. In these subjects estradiol was maintained suppressed 2 weeks after a single dose of letrozole [28]. Moreover, the maximal response to estradiol of breast tumors transplanted into athymic mice was observed after 4 weeks of treatment [29]. Finally, as mentioned above, a clinical effect of high-dose estrogen therapy following exhaustive antihormonal therapy was observed after 3 months of treatment.

1.6. Cost-effectiveness of intermittent delayed letrozole

Modelled analyses from the UK and the US suggest that, in postmenopausal women with hormone-receptor-positive early-stage breast cancer, letrozole as extended adjuvant therapy after tamoxifen, rather than no further treatment, is a cost-effective treatment strategy. Sensitivity analyses have shown these results to be robust [30]. However, a recent study compared the efficiency of adjuvant therapy with AIs or with tamoxifen in postmenopausal women with operable breast cancer and positive estrogen receptors. The follow-up of a hypothetical cohort of women starting treatment at 63 years of age was simulated during 10 and 20 years. The probabilities and costs of transition between health states and quality adjusted life years (QALYs) were evaluated. The cost of gaining one QALY was lower with the introduction of exemestane after tamoxifen than with letrozole after 5 years of tamoxifen, indicating that the latter option might be less cost-effective [31]. The introduction of a regimen that decreases to 75% the yearly amount of letrozole may improve the cost-effectiveness of extended letrozole administration.

2. Trial objectives

This trial will compare continuous letrozole for five years with intermittent letrozole over a five year period for postmenopausal women who are disease-free following 4-6 years of prior adjuvant endocrine therapy with SERM(s) and/or AI(s) for endocrine-responsive node-positive operable breast cancer.

2.1. Primary endpoint

Disease-free survival (includes second (non-breast) malignancies and deaths)

2.2. Secondary endpoints

2.2.1. Overall survival

2.2.2. Distant disease-free survival

2.2.3. Breast cancer free interval (events are reappearance of invasive breast cancer at any site including contralateral disease)

2.2.4. Sites of first DFS failure

2.2.5. Second (non-breast) malignancies

2.2.6. Deaths without prior cancer event

2.2.7. Adverse events

3. Patient selection: criteria for patient eligibility/ineligibility

3.1. Patient characteristics

3.1.1. Patients must be postmenopausal using any one of the following criteria. Because letrozole is not effective in pre- or perimenopausal patients, and may stimulate ovarian function, definitive confirmation of postmenopausal status is required.

- Patients of any age who have had a bilateral oophorectomy (including radiation castration AND amenorrheic for > 3 months)
- Patients 56 years old or older. If the patient has any evidence of ovarian function, biochemical evidence of definite postmenopausal status (defined as estradiol, LH, and FSH in the postmenopausal range) is required.
- Patients 55 years old or younger must have biochemical evidence of definite postmenopausal status (defined as estradiol, LH, and FSH in the postmenopausal range. Patients who have received prior LHRH analogue within the last year are eligible if they have definite evidence of postmenopausal status as defined above.

3.1.2. Patients must be accessible for follow-up.

3.2. Disease characteristics

3.2.1. At diagnosis, patients must have had operable, non-inflammatory breast cancer.

3.2.2. Patients must be clinically disease-free at randomization. (Note: It is recommended but not required that disease-free status be verified by abdominal ultrasound, chest x-ray, and bone scan (if symptomatic). A mammogram within one year prior to randomization is recommended.)

3.2.3. Patients must have had steroid hormone receptor positive tumors (ER and/or PgR), determined by immunohistochemistry, after primary surgery and before commencement of prior endocrine therapy.

3.2.4. Following primary surgery, eligible patients must have had evidence of lymph node involvement either in the axillary or internal mammary nodes, but not supraclavicular nodes.

3.2.5. There must have been no evidence of recurrent disease or distant metastatic disease at any time prior to randomization.

3.2.6. Not eligible: Patients who have had bilateral breast cancer.

3.3. Prior surgery and radiotherapy

3.3.1. Patients must have had proper local treatment including surgery with or without radiotherapy for primary breast cancer with no known clinical residual loco-regional disease.

3.4. Prior/concurrent disease and conditions

3.4.1. Patients must have clinically adequate hepatic function.

3.4.2. Not eligible: Patients who have had a bone fracture due to osteoporosis at any time during the 4-6 years of prior endocrine SERM/AI therapy.

3.4.3. Not Eligible: Patients who have had any previous or concomitant malignancy EXCEPT adequately treated: basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix or bladder, contra- or ipsilateral in situ breast carcinoma.

3.4.4. Not eligible: Patients who have had any other non-malignant systemic diseases (cardiovascular, renal, lung, etc.) that would prevent prolonged follow-up.

3.4.5. Not eligible: Patients with psychiatric, addictive, or any disorder which compromises compliance with protocol requirements.

3.5. Prior treatment

3.5.1. Patients must have completed 4 to 6 years of prior adjuvant endocrine therapy with SERM(s), aromatase inhibitor(s), or a sequential combination of both. When calculating 4-6 years, neoadjuvant endocrine therapy should not be included.

3.5.2. Patients must have stopped prior endocrine SERM/AI therapy, and must be randomized within 12 months (1 year) of the last dose of prior endocrine SERM/AI therapy.

3.5.3. Patients may have received any type of prior adjuvant therapy, including but not limited to neoadjuvant chemotherapy, neoadjuvant endocrine therapy, adjuvant chemotherapy, trastuzumab, ovarian ablation, GnRH analogues, lapatinib.

3.6. Concurrent treatment

3.6.1. Patients must have stopped hormone replacement therapy (HRT), bisphosphonates

(except for treatment of bone loss), or any investigational agent at randomization. (Note: These agents are also not permitted during trial treatment.)

3.7. Protocol requirements before randomization

3.7.1. Pathology material from the primary tumor must be available for submission for central review as part of the quality control measures for this protocol.

3.7.2. Written Informed Consent (IC) must be signed and dated by the patient and the investigator prior to randomization.

3.7.3. Written consent to pathology material submission, indicating the patient has been informed of and agrees to tissue material use, transfer and handling, must be signed and dated by the patient and the investigator prior to randomization.

4. Randomization and stratification

This trial will use a web-based randomization system. Each Participating Group will determine how its Participating Centers will access the randomization system, either through a Group Randomization Center, or directly from the Participating Center. The following procedures should be used in either case. Specific details for randomizing are in the "IBCSG Registration/Randomization Procedures Manual," which is available on the IBCSG website (www.ibcsg.org).

4.1. Randomization timing

In principle, patients should start trial treatment as soon as possible after randomization. Trial treatment should begin no later than 6 weeks from the date of randomization.

4.2. Registration procedures

Complete the following steps to randomize a patient on this trial.

4.2.1. Verify eligibility.

4.2.2. Obtain written informed consent both for the clinical trial and the pathology material submission, signed and dated by the patient and physician

4.2.3. Complete Confirmation of Registration Form (A). The date the Informed Consent Form and the consent to pathology material submission section of the Informed Consent Form were signed by the patient and the date signed by the investigator are both required to complete randomization.

4.2.4. Depending on your Group's choice, either

- Telephone or fax your Randomization Center to review the eligibility and randomization information. Your Randomization Center will access the IBCSG Registration/Randomization System.
- Directly access the IBCSG Registration/Randomization System.

In the former case, the Randomization Center will provide the Participating Center with the following information. In the latter case the Randomization System will provide this information via e-mail.

- Randomization number (patient ID)
- Treatment assignment
- Date of randomization

4.2.5. When randomization is complete, fill in Confirmation of Registration Form (A) with the information above and fax Confirmation of Registration Form (A) and Pathology Material Consent Form (PMC) to an IBCSG DataFax number. These forms are considered the essential documents for regulatory purposes. They should be filed at your institution.

4.2.6. File original of all forms.

4.3. Randomization help desk

The IBCSG Data Management Center (located at FSTRF) is responsible for developing and maintaining the IBCSG Registration/Randomization System. The Randomization Help Desk includes technical personnel and administrators of the randomization programs at the Data Management Center in Amherst, NY, USA.

Business Hours: 7:30-18:00 US Eastern Time

FSTRF Randomization Help Desk
Frontier Science & Technology Research Foundation (FSTRF)
4033 Maple Rd, Amherst, NY 14226 USA
Phone: +1 716 834 0900 ext. 301
Fax: +1 716 834 8432
Email: bc.helpdesk@fstrf.org

4.4. Randomized groups

Randomization (1:1) to 2 groups:

Arm A: Continuous letrozole for 5 years

Arm B: Intermittent letrozole over a 5 year period

4.5. Stratification

4.5.1. Institution

4.5.2. Prior endocrine SERM/AI therapy (SERM(s) and aromatase inhibitor(s) only)

- SERM(s) alone (without AI(s))
- AI(s) alone (without SERM(s))
- Both SERM(s) and AI(s), each for at least 1 month

5. Treatment details

5.1. Trial treatments

Arm A: Continuous letrozole 2.5 mg daily for 5 years

Arm B: Intermittent letrozole 2.5 mg daily for the first 9 months of years 1 through 4, followed by 12 months in year 5

Compliance: At each visit, patients should return the last dispensed drug container. The investigator or designee will count the remaining pills and record the information on the CRF.

5.2. Side effects of letrozole

5.2.1. Adverse effects [6]

Safety data of letrozole are available from a wide range of clinical trials in first-line and second-line advanced breast cancer, with adjuvant and extended adjuvant treatment as well as from post-marketing experience.

Approximately one third of the patients with metastatic breast cancer treated with 2.5 mg letrozole, 40% of the patients under adjuvant letrozole and 70-75% of the patients under letrozole following standard adjuvant tamoxifen (extended adjuvant therapy) experienced adverse events.

The most frequent adverse experiences reported during the course of clinical trials irrespective of causality were hot flushes, musculoskeletal disorders (bone pain, back pain, arthralgia), nausea, dyspnea, and fatigue.

The following adverse reactions were observed during clinical trials and in the postmarketing phase:

Very common (≥ 10%): Arthralgia, hot flushes.

Common (1 – 10%): Myalgia, bone pain, osteoporosis, bone fractures, fatigue, peripheral edema, elevated serum cholesterol, increased appetite, weight gain, anorexia, depression,

headache, dizziness, nausea, vomiting, dyspepsia, constipation, diarrhea, alopecia, increased sweating, rash.

Uncommon (0.1 – 1%): Arthritis, thrombophlebitis (including superficial and deep vein thrombosis), hypertension, ischemic cardiac events (including angina pectoris, myocardial infarction, cardiac failure), palpitations, tachycardia, cerebrovascular accident, somnolence, insomnia, memory impairment, dysesthesia, taste disturbance, general edema, cataract, eye irritation, blurred vision, anxiety, dyspnea, increased hepatic enzymes, weight loss, abdominal pain, stomatitis, dry mouth, vaginal bleeding, vaginal discharge, vaginal dryness, breast pain, pruritus, dry skin, urticaria.

Rare (0.01 – 0.1%): Pulmonary embolism, arterial thrombosis, transient ischemic attack (cerebrovascular infarction).

For the extended adjuvant therapy after standard adjuvant tamoxifen no significant qualitative differences with respect to the general safety profile were found. The most frequently observed adverse events were hot flushes (49.7%), fatigue (33.6%), arthralgia/arthritis (28.7%) night sweats (24.2%), edema (18.4%), headache (20.1%) hypercholesterolemia (15.5%), dizziness (14.2%), constipation (11.3%), nausea (8.6%), and myalgia (6.7%). Of these common adverse events, hot flashes (49.7 % vs. 43.3%), arthralgia/arthritis (27.7 % vs. 22.2 %) and myalgia (9.5% vs. 6.7 %) occurred at a significantly higher incidence under letrozole than placebo.

In the adjuvant setting, hot flashes (33.7%), arthralgia/arthritis (21.2%), night sweating (13.9%), weight increase (10.7%), nausea (8.8%), bone fractures (5.7%) and fatigue (5.3%) were the most common reported adverse events. Compared to tamoxifen, bone fractures (5.7% vs 4%), arthralgia (21.2% vs 13.5%) and – although a rare event – osteoporosis (2.0% vs 1.1%) were significantly more frequent under letrozole. Conversely, the incidence of hot flashes, night sweats, thromboembolic events (1.2% vs 2.8%), endometrial cancer (0.2% vs 0.4%) and endometrial proliferative disorders (0.3% vs 1.8%) was higher for tamoxifen. Myocardial infarctions were seen at similar rates (0.6% vs 0.4%).

Patients receiving letrozole had less secondary malignancies reported at any time after randomization (1.9% vs 2.4%) with endometrial cancer being the most common (0.4 vs 0.2%).

Of the non-breast cancer related deaths, deaths related to other second (non-breast) malignancy and cardiovascular cause were most frequently reported.

5.2.2. Drug Interactions

Letrozole inhibits in vitro the cytochrome P450-isoenzymes 2A6 and moderately 2C19, however, CYP2A6 does not play a major role in drug metabolism. In in vitro experiments letrozole did not substantially inhibit the metabolism of diazepam (a substrate of CYP2C19) at concentrations approximately 100-fold higher than those observed in plasma at steady-state. Thus, clinically relevant interactions with CYP2C19 are unlikely to occur. Nevertheless, caution should be used in the concomitant administration of drugs whose disposition is mainly dependent on these isoenzymes and whose therapeutic index is narrow.

There was no evidence of other clinically relevant interaction in patients receiving other commonly prescribed drugs (e.g. benzodiazepines; barbiturates; NSAIDs such as diclofenac sodium, ibuprofen; paracetamol; furosemide; omeprazole).

Clinical interaction studies with cimetidine and warfarin indicated that the coadministration of letrozole with these drugs does not result in clinically significant drug interactions, even though cimetidine is a known inhibitor of one of the cytochrome P450 isoenzymes capable of metabolising letrozole in vitro.

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

5.3. Concomitant treatments

5.3.1. Patients may not receive HRT, bisphosphonates (except for the treatment of bone loss) or any other investigational agent during trial treatment.

5.3.2. Patients may not receive any SERMs or AIs except for protocol-specified letrozole during trial treatment.

5.4. Study drug supply

Study drug will be supplied by Novartis. Details of drug supply, drug accountability and compliance are described in Appendix V.

6. End points and definitions of treatment failure

6.1. Trial end points

6.1.1. Primary Endpoint:

Disease-free survival (DFS) is defined as the time from randomization to local (including invasive recurrence restricted to the breast after breast conserving treatment), regional or distant relapse, contralateral breast cancer, appearance of a second (non-breast) malignancy, or death from any cause, whichever occurs first. Appearance of DCIS or LCIS either in the ipsilateral or in the contralateral breast will not be considered as an event for DFS (but must be reported on the Follow-Up Form (E)). See Section 6.3 for other exceptions.

6.1.2. Secondary end points:

- Overall survival (OS) is defined as the time from randomization to death from any cause.
- Distant disease-free survival (DDFS) is defined as the time from randomization to any recurrent or metastatic disease in distant sites (i.e., other than the local mastectomy scar/chest wall/skin, the ipsilateral breast in case of breast conservation,

or the ipsilateral axilla and internal mammary lymph nodes), second (non-breast) malignancy, or death from any cause, whichever occurs first.

- Breast cancer free interval (BCFI) is defined as the time from randomization to local (including recurrence restricted to the breast after breast conserving treatment), regional, or distant relapse, or contralateral breast cancer. In calculating BCFI, second (non breast) malignancies are ignored and deaths without cancer event are censored at the time of death as a competing event. Appearance of DCIS or LCIS either in the ipsilateral or in the contralateral breast is not considered a BCFI event, but should be recorded on the Follow-up Form (E).
- Sites of first DFS failure.
- Second (non-breast) malignancies
- Deaths without prior cancer event
- Adverse events

6.2. Diagnosis of Events

The diagnosis of failure event depends on evidence of recurrent disease which can be classified as either suspicious or acceptable. In either case, this should be specified and reported. Acceptable evidence of failure according to site is defined below. Any events not included in this section are considered unacceptable as evidence of recurrent disease. Failures include: local, regional, contralateral breast, and distant failures, second (non-breast) primaries, and deaths without recurrence. Histological confirmation of cytological evidence of recurrence is recommended in easily accessible lesions.

The date of failure event is the time of first appearance of a suspicious lesion, later proven to be a definitive recurrence or metastasis. All events described below should be recorded on the Follow-up Form (E).

6.2.1. Local failure

Local failure is defined as a tumor recurrence in any soft tissues of the ipsilateral, conserved breast or the chest wall, mastectomy scar, and/or skin.

Acceptable for recurrence in conserved breast: positive cytology or histology.

Acceptable for recurrence in chest wall, mastectomy scar, and/or skin: positive cytology or histology or evidence of new lesions (by CT or MRI) without any obvious benign etiology.

Suspicious: a visible or palpable lesion.

Appearance of DCIS or LCIS either in the ipsilateral or in the contralateral breast is not considered a BCFI event, but should be recorded on the Follow-up Form (E).

6.2.2. Regional Failure

Regional failure is defined as a tumor recurrence in the ipsilateral axillary lymph nodes, extranodal soft tissue of the ipsilateral axilla, ipsilateral internal mammary lymph nodes, and/or ipsilateral supraclavicular lymph nodes.

Acceptable: positive cytology or histology or evidence of new lesions by CT or MRI without a benign etiology.

Suspicious: a visible or palpable lesion.

6.2.3. Contralateral breast failure

Acceptable: positive cytology or histology.

Suspicious: a visible or palpable lesion, suspicious mammogram, ultrasound, or MRI.

Appearance of DCIS or LCIS in the contralateral breast is not considered an event for DFS.

6.2.4. Distant failure

Tumors in all areas other than those defined above are considered distant metastases. The following criteria apply:

6.2.4.1. Bone marrow

Acceptable: positive cytology, aspiration, or biopsy.

Suspicious: unexplained depression of peripheral blood counts and/or a leucoerythroblastic blood picture.

6.2.4.2. Lung

Acceptable: positive cytology or histology or a positive CT or MRI without obvious benign etiology or evidence of progressive disease. (Progressive disease is confirmed by two consecutive X-rays with the second showing worsening disease.)

Suspicious: new radiological lesion(s).

6.2.4.3. Pleura

Acceptable: positive cytology or histology.
Suspicious: new pleural effusion.

6.2.4.4. Bone

Acceptable: positive cytology or histology or a positive X-ray, MRI, or CT, one bone scan with new multiple lesions and no obvious benign etiology.

Suspicious: skeletal symptoms or positive scan showing only one new lesion (until confirmed by other imaging study).

6.2.4.5. Liver

Acceptable: positive cytology or histology, or positive CT or MRI without an obvious benign etiology, or evidence of progressive disease by ultrasound. (Progressive disease in this case is confirmed by two ultrasounds with the second showing worsening disease).

Suspicious: any two of the following: hepatomegaly on physical examination, equivocal ultrasound and abnormal liver function test.

6.2.4.6. Central nervous system

Acceptable: positive cytology or histology. Positive MRI or CT when the clinical picture is suspicious.

Suspicious: any other clinical findings suggestive of this diagnosis.

6.2.4.7. Distant lymph nodes

Acceptable: positive cytology or histology, or enlarged lymph nodes in CT or MRI, or progressive disease by physical exam without an obvious benign etiology.

Suspicious: evidence of enlarged lymph nodes by physical exam.

6.2.4.8. Other sites

Acceptable: positive cytology or histology or evidence of progressive disease if only indirect means of diagnosis were used (e.g., X-ray).

Suspicious: clinical and radiological evidence of a tumor.

6.3. Other Events

6.3.1. Second (non-breast) malignancy

Any positive diagnosis of a second (non-breast) malignancy other than basal cell or squamous cell carcinoma of the skin, cervical carcinoma *in situ,* or bladder cancer *in situ* is considered an DFS event and should be reported on the Follow-up Form (E) and on the Serious Adverse Event Forms (SAE-A and SAE-B).

6.3.2. Death without prior cancer event

Any death without a prior cancer event described in 6.2.1 through 6.2.4 above is considered a DFS event. The death, date, and the cause should be reported on the Follow-up Form (E) regardless of whether it occurs during or after trial treatment, and on the Serious Adverse Event Forms (SAE-A and SAE-B) if occurring during trial treatment.

6.3.3. Other noteworthy events

These events are NOT considered endpoints in this trial, but must be recorded on the Follow-up Form (E).

- Ipsilateral and contralateral breast cancer *in situ*
- Cervical carcinoma in situ, bladder cancer *in situ*
- Basal or squamous cell carcinoma of the skin

7. Study parameters

7.1. Table of study parameters

Visit	1A	2	3	4	5	6	7	8	9	10	11	Yearly until death
Year	0	1	1	2	2	3	3	4	4	5	5	
Trial month	0	6	12	18	24	30	36	42	48	54	60	
Informed consent and pathology material consent	x											
Check of inclusion & exclusion criteria	x											
History	x											
Physical examination including weight	x	x	x	x	x	x	x	x	x	x	x	x
Estradiol, FSH, LH[B]	m											
Adverse Events (AE)[C]	x	x	x	x	x	x	x	x	x	x	x	
Late AEs[D]												x
Laboratory tests												
Hematology[E]	r	m	m	m	m	m	m	m	m	m	m	
Blood chemistry[F]	r	m	m	m	m	m	m	m	m	m	m	
Investigations												
Mammogram[G]	r		r		r		r		r		r	
Chest-X-ray[H] (PA and lateral views)	r	m	m	m	m	m	m	m	m	m	m	
Bone scan[I]	m	m	m	m	m	m	m	m	m	m	m	
Abdominal US, CT or liver scan[J]	r	m	m	m	m	m	m	m	m	m	m	
Gynecological exam[K]	m		m		m		m		m		m	
Bone mineral densitometry[L]	m		m		m		m		m		m	

x = mandatory
r = recommended
m = if medically indicated

Legend to Table 7.1

A. The day of randomization is considered Day 0 for the purpose of follow-up.

B. Biochemical evidence of definite postmenopausal status, defined as estradiol, FSH, and LH in the postmenopausal range, is required at study entry for some patients as defined in section 3.1.1.

C. Adverse events should be graded using the NCI CTCAE V.3 (Appendix II). The following targeted adverse events should be recorded on the CRF during the reporting period in which they occur:

- Hot flashes/flushes
- Osteoporosis

- Bone fracture
- Musculoskeletal symptoms (myalgia, arthralgia (joint pain), stiffness not including bone fractures)
- Mood alteration / depression
- Hypertension
- Cardiac ischemia/infarction
- Thrombosis / thrombus / embolism
- CNS cerebrovascular ischemia
- Hemorrhage, CNS
- Insomnia
- Fatigue
- Bone pain
- Other Grade 3 or higher adverse events

D. Late adverse events (adverse events occurring after trial treatment is completed) should be recorded on Follow-up Form (E).

E. Hematology is recommended within 2 months prior to randomization and should be done whenever medically indicated.

F. Blood chemistry (includes liver function tests with alkaline phosphatase) is recommended within 2 months prior to randomization and should be done whenever medically indicated.

Radiological assessments

G. A bilateral mammography is recommended within one year prior to randomization. A mammography of the conserved and contralateral breast is recommended at yearly intervals or should be done according to national standards or hospital specific requirements.

H. A chest X-ray is recommended prior to randomization. A chest X-ray should be performed any time it is medically indicated or according to specific local requirements. Both PA view and lateral view should be done.

I. A bone scan should be done at baseline if clinically indicated. A bone scan should be performed during treatment with trial drug if alkaline phosphatase is significantly elevated (e.g. > 3 x ULN) or if medically indicated otherwise (e.g. bone pain). If the bone scan showed areas suspicious for tumor then these areas should be confirmed by X-ray or CT or MRI.

J. Abdominal ultrasound or liver scan or abdominal CT is recommended prior to randomization or during treatment if liver function tests are significantly abnormal or if medically indicated or according to specific local requirements.

Other procedures

K. In the event of a pelvic complaint (i.e., abnormal vaginal bleeding) patients should have a gynecological examination.

L. Bone densitometry by DEXA should be done at baseline and then yearly for 5 years if medically indicated.

7.2. Adverse event reporting

The main criterion for tolerability is the occurrence of toxicities and adverse events. The severity and causality will be classified according to the NCI CTCAE Version 3.0. The CTCAE is available for downloading on the internet at (http://ctep.cancer.gov/reporting/ctc.html).

An adverse event is defined as any untoward medical occurrence that occurs from the first dose of study medication until 30 days after the final dose, regardless of whether it is considered related to a medication.

In addition, any known untoward event that occurs subsequent to the adverse event reporting period that the investigator assesses as possibly related to the protocol treatment should be considered an adverse event.

Symptoms of the targeted cancer (if applicable) should not be reported as adverse events.

The adverse event severity grade provides a qualitative assessment of the extent or intensity of an adverse event, as determined by the investigator or as reported by the subject. The severity grade does not reflect the clinical seriousness of the event, only the degree or extent of the affliction or occurrence (e.g. severe nausea, mild seizure), and does not reflect the relationship to study drug.

Severity grade for other adverse events, not covered in the toxicity grading scale:

1 = Grade 1	Mild
2 = Grade 2	Moderate
3 = Grade 3	Severe
4 = Grade 4	Life-threatening
5 = Grade 5	Fatal

7.3. Serious Adverse Event (SAE) reporting

7.3.1. Definition

An SAE is defined in general as any undesirable medical occurrence/adverse drug experience that occurs during or within 30 days after stopping study treatment that, at any dose, results in any of the following:

- is fatal (any cause)
- life-threatening,
- requires or prolongs inpatient hospitalization,
- results in persistent or significant disability/incapacity
- is an unexpected grade 4 toxicity
- is a congenital anomaly or birth defect
- is a secondary (non-breast) malignancy

- requires significant medical intervention

Second (non-breast) malignancies are always considered SAEs, no matter when they are diagnosed. These events should be reported on the Serious Adverse Event Forms (SAE-A and SAE-B) and on the Follow-Up Form (E).

Other significant/important medical events which may jeopardize the patient are also considered serious adverse events.

Serious also includes any other event that the investigator or the IBCSG Safety Office judges to be serious or which is defined as serious by the regulatory agency in the country in which the event occurred.

An unexpected adverse event is one that is not listed as a known toxicity of the investigational drug in the summary of product characteristics.

A related adverse event is one for which the investigator assesses that there is a reasonable possibility that the event is related to the investigational drug. All adverse events judged as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.

7.3.2. Exceptions to the definition

Any death or serious adverse event that occurs more than 30 days after stopping study treatment but is considered to be at least possibly related to previous trial treatment is also considered an SAE. All serious adverse events must also be reported for the period in which the trial protocol interferes with the standard medical treatment given to the patient. Cases of second (non-breast) malignancies and congenital abnormalities are to be regarded as SAEs, regardless of whether they occur during or after study treatment.

Events not considered to be serious adverse events are hospitalizations occurring under the following circumstances:

- elective surgery;
- occur on an outpatient basis and do not result in admission (hospitalization < 24 h);
- are part of the normal treatment or monitoring of the studied treatment;
- progression of disease.

7.3.3. Reporting SAEs

Any serious adverse event occurring in a patient after providing informed consent must be reported. Information about all serious adverse events will be collected and recorded on the IBCSG Serious Adverse Event Report Forms (SAE–A and SAE-B).

To ensure patient safety, the IBCSG must learn of each SAE using the procedures described below:

- The investigator/MD responsible for the patient must FAX a signed Serious Adverse Event Form (SAE-A) in English within 24 hours to the DataFax data submission fax number for the Participating Center. A copy is automatically forwarded to the IBCSG Coordinating Center for medical review.
- Follow-up information should be completed on the Serious Adverse Event Form (SAE-B) within 15 days of the initial report and must be faxed to the DataFax data submission fax number for the Participating Center. A copy is automatically forwarded to the IBCSG Coordinating Center. If the event is not resolved within 15 days, submit an additional Serious Adverse Event Form (SAE-B) to report the final resolution.
- If a non-serious adverse event becomes serious, this and other relevant follow-up information must also be provided within 24 hours.

The original Serious Adverse Event Forms (SAE-A and SAE-B) and the fax confirmation sheet(s) must be kept with the CRFs at the Participating Center.

The IBCSG Coordinating Center will inform Novartis Corporation and other appropriate persons about all SAEs related to trial medication (per either investigator or IBCSG medical review) within 24 hours of receipt at the IBCSG Coordinating Center.

The IBCSG Coordinating Center will record the SAE and prepare a summary report of all SAEs received at the end of each month. Principal Investigators will receive the summary report on a monthly basis, and these reports can be found on the IBCSG web site (www.ibcsg.org).

8. Data submission

We will conduct the trial according to the ICH Good Clinical Practice (GCP) guidelines. Keeping accurate and consistent records is essential to a cooperative study. The following forms are to be submitted at the indicated times by the participating institutions for each patient:

8.1. Case report forms schedule

RANDOMIZATION FORMS		
Informed Consent Form	Consent to participation in clinical trial	Obtain before randomization and keep with patient records.
Pathology material consent	Consent to submission of pathology material	Obtain before randomization and keep with patient records.
Form PMC	Pathology Material Consent Form	DataFax after randomization with Form 35-A.
Form 35-A	Confirmation of Registration Form	Fill in before contacting your Randomization Center or entering the IBCSG Registration/Randomization system to randomize. DataFax completed form for all patients randomized.
BASELINE FORMS		
Form 35-H	History Form	DataFax within 1 month of randomization.
Pathology Report	Pathology Report of original diagnosis	DataFax within 1 month of randomization. See Section 10 for pathology material requirements.
Form 35-AE	Adverse Event Form	Complete prior to starting protocol treatment (letrozole) and DataFax within 1 month of randomization. This form is also required at follow-up (see instructions below).
Form 35-CCM	Concomitant Medications Form	Complete prior to starting protocol treatment (letrozole) and DataFax within 1 month of randomization. This form is also required at follow-up (see instructions below).
FOLLOW-UP FORMS		
Form 35-E	Follow-Up Form	DataFax every 6 months during Years 1-5, and yearly until death.
Form 35-L	Letrozole Form	DataFax at each follow-up period until the completion of letrozole.
Form 35-AE	Adverse Event Form	DataFax at each follow-up period during protocol therapy (letrozole). This form is also required at baseline.
Form 35-CCM	Concomitant Medications Form	DataFax at each follow-up period during protocol therapy (letrozole). This form is also required at baseline.
EVENT-DRIVEN FORMS		
Form 35-SAE-A	Serious Adverse Event Form (A)	DataFax within 24 hours when SAE occurs, see Section 7.3.
Form 35-SAE-B	Serious Adverse Event Form (B)	DataFax within 15 days of the initial report and/or at the definitive SAE outcome, see Section 7.3.

The Data Managers' Manual for this trial contains instructions for submitting forms using the DataFax system.

8.2. Signing and submitting forms

All forms should be signed by the Principal Investigator or designee. An authorization log (see Appendix IV) should be completed at each participating center.

CRFs should be faxed to an IBCSG DataFax number. SAE Forms should also be faxed to an IBCSG DataFax number for automatic transmission to the IBCSG Coordinating Center. Full instructions on submitting forms will be distributed to each Participating Center and are available on the IBCSG website (www.ibcsg.org). Also available on the website is a list of fax numbers that are available for faxing CRFs.

For Centers participating through a Group: Please consult your Participating Group Specific Logistical Information (Appendix VI) for special instructions about how to submit data.

8.3. Data management

Data collected in this trial will be sent to the IBCSG Data Management Center in Amherst, NY USA. The Data Management Center will process the data and will generate queries and forms requests. The IBCSG Coordinating Center in Bern, Switzerland will provide medical review and summary of SAEs. The IBCSG Statistical Center in Boston, MA USA will perform the data analysis.

8.4. Investigators' file

Each Participating Center should keep documentation about this trial in an investigators' file, which should include the following documents:

- Protocol and appendices
- Amendments
- Signed Protocol Signature Pages
- Sample CRFs including blank SAE Forms
- Data Managers' Manual
- Obvious Corrections Document
- Randomization Manual
- Patient information and Informed Consent templates approved by Ethics Committee
- Investigator's Brochure and updates
- Ethics Committee approval of protocol, Patient Information Sheet and IC, amendments
- Ethics Committee review of SAE, investigators' alert, and other documents
- Correspondence with Ethics Committee
- Malpractice insurance information
- Agreement with IBCSG
- Correspondence with IBCSG Coordinating Center, Data Management Center
- SAE reports from IBCSG Coordinating Center
- Accrual reports from IBCSG
- Normal laboratory values

- Laboratory Certifications
- CV of Principal Investigator and co-investigators
- Authorization log
- Patient identification log
- Drug accountability log (incl certificates of destruction if applicable)
- ICH GCP guidelines/Declaration of Helsinki and updates
- Audits/monitoring reports

8.5. Authorization log

The Principal Investigator (PI) should identify the other members of the Clinical Trial Team who are supervised by the PI and approved to provide information in CRFs, queries, etc. (See template in Appendix IV.)

8.6. Patient identification log

As per GCP, patients have the right to confidentiality. Therefore, no patients' names should be used in CRFs or any other documentation transmitted to IBCSG central offices. Items that are used to identify a patient include initials of patient's name, date of birth, randomization number. When no names are used, at least 2 of the above are usually required to identify the patients' records. It is therefore imperative that the local data manager keeps an identification log for all patients entered in this trial including:

- Patient's name
- Patient's initials
- Randomization number
- Date of birth

Other items that could be included are date of randomization and treatment arm.

9. Statistical considerations

9.1. Study design, objectives, and stratification

The SOLE trial is a multinational Phase III randomized clinical trial designed to compare continuous letrozole for 5 years with intermittent letrozole over a 5-year period among postmenopausal women who are disease-free following 4 to 6 years of prior adjuvant endocrine therapy with SERM(s) and/or AI(s) for endocrine-responsive node-positive operable breast cancer. The hypothesis is that introducing 3 month treatment-free intervals during the course of five years of extended letrozole will improve disease-free survival.

Randomization will be stratified according to participating center and prior SERM/AI endocrine therapy use (SERM(s) alone, AI(s) alone, both SERM(s) and AI(s)).

9.2. Data analyses

The primary analysis will be undertaken with the intention-to-treat population of all randomized patients. The primary endpoint is disease-free survival (DFS: Section 6.1.1) and will be compared between treatment arms using a two-sided stratified logrank test with an overall experiment-wise alpha level equal to at most 0.05. Kaplan-Meier estimates of the DFS distributions will be calculated for each of the two treatment arms. Cox proportional hazards regression models will be used to investigate whether the treatment comparison is modified by adjustments for various covariates.

Other factors will be used to characterize the patients enrolled in the study and to provide descriptive statistics of outcomes according to subgroups of the population. These factors include age at randomization, body mass index, tumor size, tumor grade, number of positive lymph nodes, ER/PgR and HER2 status of the primary tumor, type of prior endocrine therapy, interval of time since the cessation of prior endocrine therapy. These analyses will be considered as secondary and descriptive.

The following secondary endpoints will be assessed: overall survival, distant disease-free survival, breast cancer-free interval, sites of first DFS failure, incidence of second (non-breast) malignancies, deaths without prior cancer event, incidence of targeted adverse events.

9.3. Sample size considerations

Postmenopausal women with hormone receptor positive early breast cancer continue to be at risk for disease recurrence following completion of 4 to 6 years of adjuvant endocrine therapy. The MA.17 trial provides an estimate for the baseline risk of an event defining DFS for patients enrolled in the continuous letrozole group. Overall, the 4-year DFS in the update of MA.17 was 94.4% [22]. Among the subgroup of patients with node-positive disease, the 4-year DFS was 91.8% [32]. DFS in the MA.17 trial considered only breast cancer recurrence and contralateral breast cancer as events; specifically it did not consider deaths prior to recurrence or second (non-breast) malignancies as events. Therefore, in the eligible population of patients with node-positive disease at initial diagnosis, the baseline risk following randomization used for sample size determination is assumed to be 90% at 4 years.

The sample size was determined to provide 80% power to detect a 20% reduction in the risk of an event defining DFS (Section 6) associated with intermittent letrozole compared with continuous letrozole (hazard ratio = 0.80; 25% increase in 4-year DFS from 90% to 91.917%) using a two-sided 0.05 level test of significance.

To achieve this goal requires 647 events defining DFS, assuming 4800 patients are accrued (1600 patients per year for 3 years), 5% non-assessability at 4 years, and approximately 5 years of additional follow-up [33]. One year of start-up time, as Participating Centers obtain Ethics Committee approval and complete regulatory processes, is anticipated.

9.4. Interim monitoring

A group sequential design with two interim analyses and one final analysis is used [33]. The target number of events for the final analysis is 647, and interim analyses are planned after 40% and 70% information (259 and 453 events observed respectively). At each interim analysis and at the final analysis, testing will be performed using O'Brien-Fleming boundaries [34].

9.5. Data and Safety Monitoring Committee (DSMC)

The study will be presented for review by the IBCSG Data and Safety Monitoring Committee (DSMC) at each of their semi-annual meetings. Accrual, safety, events, and deaths will be monitored. Analyses of efficacy according to randomization group will be presented only at the time points specified for formal interim analysis. The DSMC will also make recommendations concerning potential modifications to the design criteria for this study if the assumptions used in the design are found to be inaccurate. A formal review of the accrual rate will be performed two years after study activation to assess whether modifications are required.

10. Additional protocol-specific evaluations

10.1. Pathology and pathology material banking

10.1.1. Pathology requirements

The work of the pathologist is basic to the success of all studies. Each Participating Center should identify a pathologist responsible for study patients. The pathologist determines the diagnosis, classification, and grading of the primary tumor; and evaluates the non-tumor breast tissue and local or regional spread as found in the biopsy and/or mastectomy specimen, including precise documentation of tumor size, margins of the primary, the total number of lymph nodes examined, and the number of nodes involved. All lymph nodes must be examined from each patient. If the patient has received a sentinel node biopsy, each sentinel node must be evaluated. The central review pathologist will review the submitted specimens and complete the central pathology review.

The following items are required for all patients:

1. Pathology Reports (including steroid hormone receptor determination)
2. Tumor block for banking (Ideally the block should contain at least some invasive tumor taken from the periphery of the tumor.)
3. Normal tissue block for banking
4. Representative H & E sections of the above blocks

The tissue blocks may be returned to the Participating Center upon request after 4 1mm cores have been taken for preparing tissue micro-arrays (TMAs).

All reports, slides, and blocks must be marked with the randomization number. If materials are not properly marked, we cannot guarantee that the slides and blocks will be forwarded to the

Central Pathology Review Office. Please ensure that the blocks and slides are carefully packaged as otherwise they could easily get damaged during transport. The slides should be sent in customized slide boxes and should be wrapped with tissue paper to prevent any movement. The slides and blocks have not been packed securely enough if they move around when the box is shaken.

10.1.2. Pathology material banking

The IBCSG has established a central repository for tissue blocks and slides from every patient enrolled in IBCSG clinical trials. The required pathological material (described in the previous section) is submitted to, catalogued, and maintained in the IBCSG Coordinating Center Office in Bern (**IBCSG Coordinating Center, Pathology Coordinating Office, Effingerstrasse 40, CH- 3008 Bern**). The primary tumor H&E section and block are sent for central pathology review to the European Institute of Oncology in Milan, Italy, and then returned to the IBCSG Tissue Bank in Bern for storage. Central pathology review reports will be available to institution pathologists who wish to see them. Central pathology review will include histopathological parameters (tumor type and grade, occurrence of peritumoral vascular invasion), hormone receptors (estrogen and progesterone receptors), HER2 status and the tumor proliferative fractions (Ki-67 immunolabelling). Testing for genes which may be inherited is not a part of the central pathology review of this study. The blocks will be available for prospective and retrospective studies approved by the IBCSG Biological Protocols Working Group and by the IBCSG Ethics Committee.

The IBCSG requires a suitable tissue bank for application of the newer assays which are likely to become available in the very near future. In particular, IBCSG expects that novel predictive parameters will be identified by gene expression profiling. This will open at least one of the following possibilities:

1. The application of gene expression profiling to paraffin embedded material
2. The identification of specific mRNAs which could be detectable by molecular biology assays (RT-PCR, in situ hybridization, etc) in paraffin-embedded tissue
3. The identification of protein molecules detectable by immunohistochemistry.

These assays will most likely require a comparison between neoplastic and normal tissue, and this is why IBCSG is banking two sets of samples per patient. In many cases (but not all) normal tissue may be found around the invasive tumors. Separate blocks are necessary for extractive techniques in order to avoid neoplastic cells contaminating the normal sample.

10.2. Patient Reported Symptoms and Quality of Life Substudy

Some of the Participating Centers will participate in the ancillary study of Patient Reported Symptoms and Quality of Life. Details of the rationale, logistics, and statistical considerations are in Appendix III.

11. Regulatory approval procedures and Patient Informed Consent

11.1. Ethical Review Board/Ethics Committee

All protocols and the patient informed consent forms must have the approval of a properly constituted committee or committees responsible for approving clinical trials. The ERB/IRB written, signed approval letter/form must contain approval of the designated investigator, the protocol (identifying protocol title and version number), and of the patient informed consent. Documentation of Ethics Committee approval must be sent to the IBCSG Coordinating Center prior to enrollment of the first patient. The IBCSG Ethics Committee also approves the protocol and reviews it annually.

11.2. Regulatory approval procedures

If applicable, in addition to the approval of the Ethics Committee according to national legislation, the protocol, other protocol related documents including patient information and informed consent and other documents as required locally must be submitted to and be approved by the health authority. Documentation of health authority approval must be sent to the IBCSG Coordinating Center prior to Participating Center activation.

11.3. Protection of human subjects

The IBCSG has an Office for Human Research Protection (OHRP) Federal Wide Assurance (FWA00009439) and follows all of the policies and procedures that are part of that assurance. All potential subjects for this trial will receive a full explanation of the trial, its purpose, treatments, risks, benefits, and all of the other items listed in Section 11.4. Additional institution-specific sections should be added to Appendix I as described in Section 11.4.

The medical record must be available for review by the IBCSG audit team as described in Section 11.5.

Serious adverse event (SAE) reports are distributed monthly. In addition they are available on the IBCSG website (www.ibcsg.org) for IBCSG member institutions.

11.4. Informed consent

Informed consent for each patient will be obtained prior to initiating any trial procedures in accordance with the “IBCSG Patient Information and Informed Consent." (See Appendix I.) One signed and dated copy of the informed consent must be given to each patient and the original copy must be retained in the investigator's trial records. The informed consent form must be available in the case of data audits. Verification of signed informed consent and the date signed are required for randomization to this trial.

The "Declaration of Helsinki" (http://www.wma.net/e/policy/b3.htm) recommends that consent be obtained from each potential patient in biomedical research trials after the aims, methods, anticipated benefits, and potential hazards of the trial, and discomfort it may entail, are

explained to the individual by the physician. The potential patient should also be informed of her right to not participate or to withdraw from the trial at any time. The patient should be told that material from her tumor will be stored and potentially used for additional studies not described in this protocol.

If the patient is in a dependent relationship to the physician or gives consent under duress, the informed consent should be obtained by an independent physician. If the patient is legally incompetent (i.e., a minor, or mentally incompetent), informed consent must be obtained from the parent, legal guardian, or legal representative in accordance with the law of the country in which the trial is to take place. By signing this protocol, the investigator agrees to conduct the trial in accordance with Good Clinical Practice and the "Declaration of Helsinki."

The IBCSG recognizes that each institution has its own local, national, and international guidelines to follow with regard to informed consent. Therefore, we provide a template information sheet and informed consent form (Appendix I), which can be downloaded and edited to incorporate information specific to your institution (see www.ibcsg.org) for IBCSG members. The template Patient Information Sheet and Informed Consent has been written according to ICH guidelines which state the Informed Consent should adhere to GCP and to the ethical principles that have origin in the “Declaration of Helsinki”. The final version should receive the Institutional Review Board/ Local Ethics Committee approval in advance of its use.

11.5. Quality Assurance

The IBCSG conducts trials according to the ICH Good Clinical Practice (GCP) guidelines. The Study Data Manager reviews each CRF as it is received. In addition, the IBCSG Medical Reviewer reviews each case at specific timepoints. The IBCSG conducts periodic audit visits to ensure proper trial conduct, verify compliance with GCP, and perform source data verification.

12. Administrative Considerations

12.1. Insurance

The IBCSG will contract the appropriate liability insurance for this trial. Patients who suffer injuries due to the trial should report them immediately to their physician. The local group/institution should report all alleged claims immediately to the IBCSG Coordinating Center.

The IBCSG insurance does NOT cover patients from the United States of America or from Canada. Each group will be responsible for obtaining proper insurance coverage.

12.2. Steering Committee

A Steering Committee will be constituted for this trial. The primary responsibilities of the Steering Committee are twofold. First, the Steering Committee is responsible for maintaining the scientific integrity of the trial, for example, by recommending changes to the protocol in

light of emerging clinical or scientific data from other trials. Second, the Steering Committee is responsible for translation of recommendations of the IBCSG Data and Safety Monitoring Committee into decisions (see section 9.5.). Membership will include IBCSG officials, study chair and co-chairs, trial statisticians, representatives from some participating institutions and groups, and representatives from Novartis.

General partition of responsibilities:

The Steering Committee has the authority to make and implement any final decisions, such as substudies of the trial or amendments to the trial protocol, and may recommend the termination of the trial.

The IBCSG Executive Committee is responsible for the implementation of all final decisions taken by the Steering Committee.

The IBCSG Foundation Council decides on the termination of the trial.

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