INTERNATIONAL BREAST CANCER STUDY GROUP

IBCSG 24-02
BIG 2-02

Suppression of Ovarian Function Trial (SOFT)

Amendment 2

A Phase III Trial Evaluating the Role of Ovarian Function Suppression and the Role of Exemestane as Adjuvant Therapies for Premenopausal Women with Endocrine Responsive Breast Cancer

tamoxifen versus
ovarian function suppression + tamoxifen versus ovarian function suppression + exemestane

Coordinating Group: International Breast Cancer Study Group (IBCSG)

EudraCT number: 2004-000166-13

This protocol document includes information needed to conduct the study for all participating centers, with logistical details specific for IBCSG centers.

Cover pages added to the front of this protocol and Appendix VII contain logistical details that are needed for non-IBCSG participating groups and centers, including group specific contact information, randomization procedures, data submission procedures, serious adverse event reporting procedures, drug supply information and country-specific regulations and procedures.

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Supported by Pfizer, Inc.

GROUP SPECIFIC CONTACT INFORMATION

Please refer to Section 1 of Appendix VII for group-specific contact information to direct your inquiries about participation/eligibility/treatment for this trial.

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Protocol Amendment 2 Signature Page

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Suppression of Ovarian Function Trial (**SOFT**)

Approved by:
Director, Statistical and Data Management Center, International Breast Cancer Study Group
Prof. R.D. Gelber

Signature on file 14 July 2011

_____ _____
Date

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Protocol Amendment 1 Signature Page

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Suppression of Ovarian Function Trial (**SOFT**).

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

Signature on file 07 October 2005

_____ _____
Date

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

Signature on file 07 October 2005

_____ _____
Date

Protocol Signature Page

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-02

Suppression of Ovarian Function Trial (**SOFT**).

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

(Signature on file) 17Apr03

Date

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

IBCSG 24-02 / BIG 2

(Signature on file) 17Apr03

_____ _____

Date

Principal Investigator Protocol Signature Page Amendment 2

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Suppression of Ovarian Function Trial (**SOFT**).

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

Suppression of Ovarian Function Trial (SOFT)

A Phase III Trial Evaluating the Role of Ovarian Function Suppression and the Role of Exemestane as Adjuvant Therapies for Premenopausal Women with Endocrine Responsive Breast Cancer

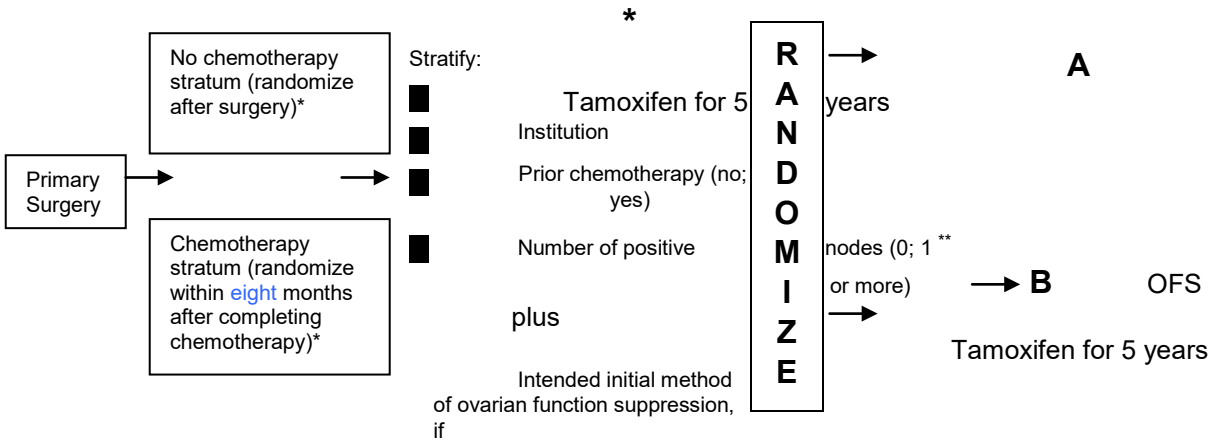
Patient Population: Premenopausal women (estradiol (E_2) levels in the premenopausal range) with histologically proven, resected breast cancer with ER and/or PgR positive tumors who have received either no chemotherapy or remain premenopausal following completion of adjuvant and/or neoadjuvant chemotherapy.

Entry: Patients who do not receive chemotherapy should be randomized within 12 weeks after surgery; such patients must have estradiol (E_2) levels in the premenopausal range following surgery. Patients who have received adjuvant and/or neoadjuvant chemotherapy should be randomized within 8 months of the final dose of chemotherapy as soon as premenopausal status is confirmed; such patients must have estradiol (E_2) levels in the premenopausal range between 2 weeks and 8 months after the final dose of chemotherapy.

Stratification Factors:
-Institution
-Prior adjuvant/neoadjuvant chemotherapy (no; yes)
-Number of positive axillary and/or internal mammary lymph nodes (0 – including pN0(sn), pN0(i+)(sn) and pNx; 1 or more – including pN1mi)
-Intended initial method of ovarian function suppression (triptorelin for 5 years; surgical oophorectomy; ovarian irradiation)

Sample Size: 3000 patients ~~(600 per year for 5 years with 1.9 years of additional follow-up)~~

Schema:



assigned by randomization **

(triptorelin for 5 years; surgical C OFS plus
oophorectomy; ovarian Exemestane for 5 years
irradiation)

* Patients may have received tamoxifen or anti-aromatase agent prior to randomization
** OFS = ovarian function suppression (triptorelin for 5 years OR surgical oophorectomy OR ovarian irradiation)

Treatment Schedules

Radiotherapy: Radiation therapy to the conserved breast is required. Radiation therapy to the chest wall following mastectomy is optional (if given, it may also include nodal fields). Radiation therapy may be given either after all chemotherapy or integrated into chemotherapy (if regimen is considered safe by the investigator). Radiation therapy may be concurrent with trial hormonal therapy.

Chemotherapy: Patients in the chemotherapy stratum must have completed adjuvant (and/or neoadjuvant) chemotherapy prior to randomization. A planned duration of [redacted] months if an anthracycline was included (e.g. 4 cycles of EC or AC) or [redacted]4 months if no anthracycline was given (e.g. 6 cycles of CMF) is recommended. If an anthracycline was used, an epirubicin-containing regimen is recommended. The final dose of chemotherapy must be less than 8 months prior to randomization.

Adjuvant Endocrine Therapy:

Tamoxifen: Tamoxifen 20 mg orally daily until 5 years from date of randomization, unless relapse or intolerance should occur earlier.

Exemestane: Exemestane (Aromasin®) 25 mg orally daily, preferably after food, until 5 years from date of randomization, unless relapse or intolerance should occur earlier. Exemestane should begin after initiating ovarian function suppression.

Triptorelin: Triptorelin (GnRH analogue) 3.75 mg by intramuscular injection every 28 days for 5 years from randomization, unless relapse or intolerance should occur earlier or surgical oophorectomy or ovarian irradiation is subsequently performed. Triptorelin (Decapeptyl Depot® intramuscular or Trelstar Depot® intramuscular) will be supplied by the study for use as GnRH analogue.

Surgical oophorectomy: Bilateral surgical oophorectomy via laparotomy or laparoscopy.

Ovarian irradiation: Bilateral ovarian irradiation. Biochemical verification of ovarian function cessation is required after two months (see Section 5.1.3).

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Appendices

1 Introduction

1.1 Adjuvant therapy for premenopausal women with receptor positive breast cancer

Chemotherapy, tamoxifen and ovarian ablation (by surgery or radiation) are individually effective adjuvant treatment modalities in women under 50 years of age with estrogen receptor positive (ER+) breast cancer [1,2].

Chemotherapy plus 5 years of tamoxifen is more effective than chemotherapy alone in women under 50 with ER+ breast cancer. The addition of 5 years of tamoxifen to adjuvant chemotherapy in this group results in an additional ~ 40% reduction in the odds of recurrence or death [3]. In women at relatively low risk for recurrence (NSABP B-20 trial in node negative ER+ breast cancer) chemotherapy plus tamoxifen resulted in a significant 44% reduction in the odds of recurrence compared to tamoxifen alone in women under 50 [4]. These data suggest that adjuvant combination chemo-endocrine strategies can improve results over single modality treatments.

In women under 50 with hormone receptor positive breast cancer who receive both adjuvant chemotherapy and 5 years of tamoxifen, it is unclear whether any additional benefit is derived from suppression of ovarian function as no trial has addressed this question to date.

Data from the Early Breast Cancer Trialists‟ Collaborative Group suggest that in the presence of chemotherapy the benefit from ovarian ablation appears smaller [2]. The magnitude of benefit from the addition of ovarian function suppression to chemotherapy may have been underestimated in previous trials due to inclusion of some women with ER-negative tumors and a predominance of women who would have been rendered permanently amenorrhoeic (postmenopausal) from the adjuvant chemotherapy alone. The majority of premenopausal women with breast cancer are at least 40 years of age and more than 80% of these women will develop amenorrhea following 6 cycles of classical CMF chemotherapy [5, 6]. By contrast, less than half of premenopausal women under age 40 develop amenorrhea with CMF. The prognosis of women who develop amenorrhea, even temporarily, from CMF chemotherapy tends to be better than those who continue to menstruate [7]. Shorter anthracycline-based regimens such as 4 cycles of doxorubicin and cyclophosphamide (AC) result in less frequent premature menopause compared with classic CMF (34% versus 69%) [8]. A recent report on the Canadian NCI trial indicated that the incidence of amenorrhea was significantly higher in the CEF arm compared to CMF: 73.9 vs 61.9% (p=0.005). According to the reported findings amenorrhea did not affect relapse free survival (RFS). The 7-year RFS was 53% and 49% for patients with and without amenorrhea, respectively (p=0.3 by log rank) [9]. It is unclear whether a subgroup analysis for women with endocrine responsive disease (excluding those with tumors not expressing hormone receptors) would have shown an association between amenorrhea and improved outcome.

1.2 The role of ovarian function suppression

This trial aims to focus the ovarian function suppression question on the subset of women who biologically would be most likely to benefit, i.e., women with hormone receptor positive breast cancer plus premenopausal status either following surgery alone or after completion of adjuvant/neoadjuvant chemotherapy. These women are likely to be on average younger than the median age for premenopausal breast cancer and will mostly be under 40 years of age. Analysis of women treated on IBCSG trials (I, II, V and VI) reveals that young women (under 35 years of age) with ER-positive tumors have a worse prognosis than premenopausal women ≥ 35 years old [10]. Paradoxically in these trials, women < 35 years old with ER-positive disease treated with adjuvant chemotherapy alone have a worse prognosis than women with ER-negative tumors in the same age group [11]. This young group of women with ER-positive disease may potentially benefit from receiving "maximal" adjuvant endocrine therapy in addition to chemotherapy.

Synthetic gonadotropin releasing hormone (GnRH) analogues administered by monthly injection have been shown to suppress ovarian function and result in a decline in estradiol levels to postmenopausal range with chronic administration [12]. GnRH analogues produce clinical responses in premenopausal women with advanced receptor positive breast cancer similar to those seen with conventional ovarian ablation and tamoxifen [13,14]. High levels of estradiol are known to occur in premenopausal women on tamoxifen alone [15] and the addition of a GnRH analogue can suppress these hormonal surges. GnRH analogues evaluated in breast cancer trials include goserelin, leuprorelin, buserelin and triptorelin.

Triptorelin has been shown to be efficacious as a single agent in the metastatic breast cancer phase II trial setting [16]. Twenty-seven premenopausal hormone receptor positive breast cancer patients were treated with 3.75 mg Decapeptyl Depot® IM q 28 days until progression. Tamoxifen was given for the first 4 weeks to cover a potential flare period induced by treatment stimulation of the pituitary gonadal axis by the LHRH. Prior treatment consisted of adjuvant chemotherapy in 7, adjuvant tamoxifen in 1 and no adjuvant treatment in 19. Six patients (18%) achieved CR, and a further 14 (52%) achieved PR for an overall response rate of 70%. Four patients had SD and four progressed. The median duration of response for CRs was 51 months and for PRs was 12 months; the median TTP for all patients was 15 months. Side effects were minimal and the most common complaint was hot flushes.

In a randomized study comparing the effect of goserelin with or without tamoxifen in 318 premenopausal patients with advanced breast cancer there was a modest benefit in favor of combination endocrine therapy in time to progression (p=0.03) and a non-significant improvement in median survival (13 weeks longer with combination p=0.25) [17]. The EORTC randomized 161 premenopausal patients to receive combination therapy with buserelin plus tamoxifen, compared to buserelin alone or tamoxifen alone, as first line treatment for metastatic breast cancer. The combined therapy arm resulted in a significant improvement in progression free survival (p=0.03) and overall survival (p= 0.01) compared with either single agent alone [18,19]. A meta-analysis of four randomized trials in premenopausal advanced breast cancer addressing the question of GnRH analogue alone versus GnRH analogue combined with tamoxifen reported a significant survival benefit for the combined endocrine approach [20]. It is important to test

whether the advantage seen with combination endocrine therapy in the advanced disease setting can be translated into meaningful differences for women in the adjuvant setting.

In a U.S. Intergroup randomized trial in premenopausal women with hormone receptor-positive node-positive breast cancer, the combination of tamoxifen plus goserelin for 5 years after chemotherapy significantly reduced recurrences compared with chemotherapy alone or chemotherapy plus goserelin. However, it remains unclear whether tamoxifen without goserelin after chemotherapy would have provided similar benefit as this treatment arm was not tested [21].

Although ovarian function suppression by GnRH analogues is thought to be similar to other forms of ovarian ablation (surgery or radiation) in the advanced disease setting, this may not be true in the adjuvant setting, particularly if administered for a relatively short duration in very young women in whom menstrual function may resume after cessation. Studies of efficacy of adjuvant endocrine therapy with tamoxifen suggest that duration is important [3] and this may also apply to GnRH analogues. In this trial, GnRH analogues, oophorectomy or ovarian irradiation (with biochemical confirmation of cessation of ovarian function) are all allowed; the method will be documented in the case report forms. There are case studies of failure of ovarian function suppression under GnRH analogue [22]. In such cases ovarian function suppression should be achieved by other means.

1.3 Anti-aromatase agents

There are two classes of aromatase inhibitors. Agents such as anastrozole and letrozole act by reversibly binding to the aromatase enzyme, which is responsible for the production of estrogens in postmenopausal 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 aromatase inhibitors, it cannot be displaced from the aromatase enzyme. Exemestane has been shown to significantly increase both median survival and median time to progression when compared to megestrol acetate as second line hormonal therapy in postmenopausal women with advanced breast cancer [23].

There is evidence in postmenopausal women with metastatic disease that aromatase inhibitors produce response rates and survival equivalent or superior to those seen with tamoxifen [24,25], and trials comparing aromatase inhibitors to tamoxifen for postmenopausal women in the adjuvant setting are awaiting maturity. The updated results of the ATAC trial (anastrozole, tamoxifen and combination) in 9366 postmenopausal women with operable breast cancer were recently published after a median follow-up of 68 months. Among the 84% of patients with steroid hormone receptor positive disease, the hazard ratio for disease-free survival comparing anastrozole with tamoxifen was 0.83 (p=0.005) [26, 46]. In the Intergroup Exemestane Study (IES), postmenopausal women with primary breast cancer who had received two to three years of adjuvant hormonal therapy with tamoxifen were randomized to either complete a total of 5 years of hormonal therapy with tamoxifen or to switch to exemestane for the remaining time. After a median follow-up of 30.6 months, switching to exemestane significantly improved the disease-free survival compared with

continuing tamoxifen (hazard ratio 0.68; p <0.001) [47,48]. The first results of the primary core analysis of the IBCSG 18-98/BIG 1-98 trial reported on 8010 postmenopausal women with endocrine-responsive breast cancer who were randomized to either tamoxifen or letrozole as adjuvant hormonal therapy. After a median follow-up of 25.8 months, letrozole significantly prolonged disease-free survival compared with tamoxifen (hazard ratio = 0.81; p=0.003) [49].

It is postulated that these promising results with aromatase inhibitors in postmenopausal women can also be obtained in premenopausal women who undergo ovarian function suppression.

Aromatase inhibitors at safe doses do not fully inhibit ovarian enzymes, and are not likely to be effective in premenopausal women [27]. However it has been shown that the combination of an aromatase inhibitor plus a GnRH agonist in premenopausal women can produce lower estrogen levels than a GnRH agonist alone [28,29]. In a small study, the combination of goserelin plus an aromatase inhibitor was found to result in objective responses or stable disease in 89% of premenopausal women with advanced breast cancer who had previously received goserelin plus tamoxifen [30].

Either the combination of a GnRH agonist (or oophorectomy or ovarian irradiation) with tamoxifen or the combination of a GnRH agonist with an aromatase inhibitor (exemestane) has the potential to improve survival in premenopausal women over that seen with tamoxifen alone.

This trial will compare the two tamoxifen containing arms to assess the role of ovarian function suppression, will compare the two ovarian function suppression arms to assess the role of exemestane compared with tamoxifen, and will compare the exemestane regimen to tamoxifen alone in premenopausal women with estrogen or progesterone receptor positive invasive breast cancer who either do not receive chemotherapy or who remain premenopausal at the end of their chemotherapy. The duration of hormonal treatment will be five years.

1.4 Bone mineral density

In a study of the effect of tamoxifen on bone mineral density in healthy premenopausal and postmenopausal women, tamoxifen treatment was associated with a significant loss of bone mineral density in premenopausal women, whereas it prevents loss of bone mineral density in postmenopausal women [31]. In an adjuvant breast cancer study assessing bone mineral density in premenopausal women receiving GnRH analogue (goserelin) for 2 years, there was a significant reduction in bone mineral content, while addition of tamoxifen to goserelin appears to compensate for the demineralizing effects of GnRH analogue [32]. A pre-clinical trial by Goss et al. [33] showed that in the ovariectomized rat, exemestane prevented bone loss. It is possible that the combination of exemestane and ovarian function suppression may result in less osteoporosis than the other hormonal therapies. Data on the use of bisphosphonates will be collected to assess the potential for confounding of the overall results.

2 Trial objectives

This trial will evaluate the worth of ovarian function suppression (achieved by either long-term use of GnRH analogue or surgical oophorectomy or ovarian irradiation) plus tamoxifen compared with tamoxifen alone for premenopausal women with steroid hormone receptor positive early invasive breast cancer who either receive no adjuvant chemotherapy or remain premenopausal following adjuvant and/or neoadjuvant chemotherapy. In addition, the worth of exemestane will be evaluated for this premenopausal patient population by comparing ovarian function suppression plus exemestane with tamoxifen alone and by comparing ovarian function suppression plus exemestane with ovarian function suppression plus tamoxifen.

2.1 Primary objectives

2.1.1 To compare ovarian function suppression (OFS: GnRH analogue or oophorectomy or ovarian irradiation) plus tamoxifen vs. tamoxifen alone

2.1.2 To compare OFS plus exemestane vs. tamoxifen alone (A secondary objective per Amendment 2)

2.1.3 To compare OFS plus exemestane vs. OFS plus tamoxifen (This comparison will combine data with the IBCSG 25-02 TEXT trial as the primary analysis for the TEXT trial)

2.2 Primary endpoint

2.2.1 Disease-free survival

2.3 Secondary endpoints

2.3.1 Overall survival
2.3.2 ~~Systemic disease-free survival~~ Breast cancer-free interval and distant recurrencefree interval
2.3.3 Quality of life
2.3.4 Sites of first treatment failure
2.3.5 Late side effects of early menopause
2.3.6 Incidence of second (non-breast) malignancies
2.3.7 Causes of death without cancer event

3 Patient selection

3.1 Criteria for patient eligibility

3.1.1 Premenopausal women [estradiol (E_2) in the premenopausal range (according to institution parameters)] who meet the following criteria:

- Patients who did not receive chemotherapy should be randomized within 12 weeks after definitive surgery. Such patients should have estradiol (E_2) in the premenopausal range following surgery; the only patients who do not require testing of estradiol (E_2) to confirm premenopausal status are those who have been menstruating regularly during the 6 months prior to randomization and have not used any form of hormonal contraception or any other hormonal treatments during the 6 months prior to randomization.

- Patients who received prior adjuvant and/or neoadjuvant chemotherapy should be randomized after completing chemotherapy and within 8 months of the final dose of chemotherapy as soon as premenopausal status is confirmed; all such patients should have premenopausal status confirmed by an estradiol (E_2) in the premenopausal range between 2 weeks and 8 months after completing chemotherapy.

  Adjuvant trastuzumab (Herceptin ®) is allowable, and is not considered to be chemotherapy for eligibility timing determination.

  Patients with temporary chemotherapy-induced amenorrhea who regain premenopausal status within eight months of the final dose of chemotherapy are eligible. [Please note that some patients taking tamoxifen or aromatase inhibitors, even without evidence of menses, may have ovarian function recovery following chemotherapy and resume estradiol secretion.] Premenopausal levels of serum estradiol may persist after chemotherapy-induced amenorrhea despite prolonged amenorrhea [34]. Therefore in patients wishing to participate in the study, with postmenopausal hormone levels shortly after chemotherapy, it is recommended to recheck their estradiol level at a later timepoint within 8 months of completing chemotherapy, even in the absence of return of menses.

3.1.2 Histologically proven, resected breast cancer. Pathology material should be available for submission for central review as part of the quality control measures for this protocol.

3.1.3 Patients must have hormone receptor positive tumors. If there is more than one breast tumor, each tumor must be hormone receptor positive. Hormone receptors must be determined using immunohistochemistry. ER and/or PgR must be greater than or equal to 10% of the tumor cells positive by immunohistochemical evaluation. Biochemical determination alone is not acceptable. Detailed guidelines for assessments of ER and PgR are given in the Appendix III.

3.1.4 The tumor must be confined to the breast and axillary nodes without detected metastases elsewhere, with the exception of tumor detected in internal mammary chain nodes by sentinel node procedure. Patients who received neoadjuvant therapy must have had operable disease prior to neoadjuvant treatment to be eligible. Patients who had a pathological evaluation with tru cut or core biopsy of invasive breast cancer prior to neoadjuvant therapy and were found to have no invasive tumor in the pathological specimen from definitive surgery are eligible. For these patients, pre-neoadjuvant tumor characteristics will be used for defining eligibility. In case of persistent disease, pathology findings from the definitive surgery should be used.

3.1.5 Patients must have had proper surgery for primary breast cancer with no known clinical residual loco-regional disease:

- A total mastectomy. Radiotherapy is optional after mastectomy.

OR

- A breast-conserving procedure (lumpectomy, quadrantectomy or partial mastectomy with margins clear of invasive cancer and DCIS). The local pathologist must document negative margins of resection in the pathology report. If all other margins are clear, a positive posterior (deep) margin is permitted, provided the surgeon documents that the excision was performed down to the pectoral fascia and all tumor has been removed. Likewise, if all other margins are clear, a positive anterior (superficial; abutting skin) margin is permitted provided the surgeon documents that all tumor has been removed. Radiation therapy to the conserved breast is required; patients may be randomized before, during or after completion of radiation therapy to the breast.

3.1.6 Either axillary lymph node dissection (pathological examination of at least 6 nodes recommended) or a negative axillary sentinel node biopsy [pN0(sn)] is required. Patients with negative or microscopically axillary positive sentinel nodes (pN1mi: micrometastasis none > 2.0mm) do not require further axillary therapy. Those with positive sentinel nodes must have either an axillary dissection or radiation of axillary nodes.

3.1.7 For IBCSG centers, patients must have completed baseline Quality of Life (QL) Forms prior to randomization. The only exceptions are cognitive or physical impairment that interferes with QL assessment or inability to read any of the languages available on IBCSG QL forms. For non-IBCSG centers, extent of participation in the QL study is to be determined at the activation of the trial for each cooperative group (see Appendix VII for Group-specific guidelines).

3.1.8 Written informed consent must be signed and dated by the patient and the investigator prior to randomization.

3.1.9 Patients must be accessible for follow-up.

3.1.10 Patients must be informed of and agree to data and tissue material transfer and handling, in accordance with national data protection guidelines.

3.2 Criteria for patient ineligibility

3.2.1 Patients who are postmenopausal (i.e., do not have an estradiol (E2) level in the premenopausal range) after surgery or after chemotherapy, whichever is later.

3.2.2a Patients with distant metastatic disease.

3.2.2b Patients with locally advanced inoperable breast cancer including inflammatory breast cancer or supraclavicular node involvement or with enlarged internal mammary nodes (unless pathologically negative) are not eligible. Patients with involved internal mammary nodes detected by sentinel node biopsy that are not enlarged are eligible.
3.2.2c Patients with positive final margins (referring to only DCIS and invasive cancer, not LCIS), except as noted in section 3.1.5. DCIS at a margin is permitted if a complete mastectomy has been performed.

3.2.2d Patients with clinically detectable residual axillary disease.

3.2.3 Patients with a history of prior ipsilateral or contralateral invasive breast cancer. Patients with synchronous bilateral invasive breast cancer (diagnosed histologically within 2 months) are eligible if the bilateral disease meets all other eligibility criteria (see section 8.1.2 for data management for such patients).

3.2.4 Patients with previous or concomitant invasive malignancy are not eligible. The exceptions are patients with the following (and only the following) malignancies (previous or concomitant) who are eligible if adequately treated:

- basal or squamous cell carcinoma of the skin *in situ* non-breast carcinoma without invasion contra- or ipsilateral *in situ* breast carcinoma non-breast invasive malignancy diagnosed at least 5 years ago and without recurrence: ○ stage I papillary thyroid cancer ○ stage Ia carcinoma of the cervix ○ stage Ia or b endometrioid endometrial cancer ○ borderline or stage I ovarian cancer

3.2.5 Patients with other non-malignant systemic diseases (cardiovascular, renal, hepatic, lung, etc.) that would prevent prolonged follow-up. Patients with previous thrombosis (e.g., DVT) and/or embolism can be included only if medically suitable.

3.2.6 Patients who have had a bilateral oophorectomy or ovarian irradiation. Patients who will be recommended to undergo oophorectomy within 5 years (e.g., BRCA1 / 2 gene carriers) and therefore for whom randomization to a treatment arm without OFS is inappropriate.

3.2.7 Patients with a history of noncompliance to medical regimens and patients who are considered potentially unreliable.

3.2.8 Patients who are pregnant or lactating at the time of randomization or who desire a pregnancy within 5 years. Patients planning to use additional hormonal therapy apart from the randomized treatment (see Section 5.3.1) during the next five years including all types of hormonal contraception. A pregnancy test is recommended for women of child-bearing potential who are sexually active and not using reliable contraceptive methods.

3.2.9 Patients who received endocrine therapy (including neoadjuvant and adjuvant) for more than 8 months after their breast cancer diagnosis. Patients who are receiving endocrine therapy at

randomization (and have received it for less than 8 months) may continue such therapy until protocol-specified tamoxifen/exemestane is initiated (see section 5.1).
3.2.10 Patients who were taking tamoxifen or other SERM (e.g. Raloxifene) or hormone replacement therapy (HRT) within one year prior to their breast cancer diagnosis. Prior oral contraceptives are allowed.

3.2.11 Patients who have received GnRH analogues as part of their breast cancer treatment prior to randomization.

3.2.12 Patients with psychiatric, addictive, or any disorder that would prevent compliance with protocol requirements.

4 Randomization and stratification

This trial will use a web-based randomization system. Each Participating Group will determine how its 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 be enrolled in the study and randomized as close as possible to the start of protocol treatment. In this trial, patients who do not receive chemotherapy should be randomized within 12 weeks after surgery and those who receive adjuvant/neoadjuvant chemotherapy should be randomized between 2 weeks and 8 months after the last dose of chemotherapy, as soon as premenopausal status is confirmed, as described in Section 3.1.1.

Adjuvant trastuzumab is allowable and is not considered to be chemotherapy for eligibility timing determination.

4.2 Registration procedures

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

4.2.1 Verify eligibility.

4.2.2 Obtain informed consent form signed and dated by patient and investigator.

4.2.3 Complete baseline Quality of Life (QL) Forms; QLC, QLM, and, for English speaking centers, Form QLS. (Required for IBCSG participating centers; for other Groups, participation in

the QL study is according to Group-specific guidelines, see Appendix VII.) See Section 3.1.7 for exceptions.

4.2.4 Complete Confirmation of Registration Form (A).

4.2.5 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.

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

4.2.6 When randomization is complete, fill in Confirmation of Registration Form (A) and fax Form A, and Forms QLC, QLM, and, for English speaking centers, Form QLS, to an IBCSG DataFax number. This completed Form A is considered the essential document for regulatory purposes. It should be filed at your institution.

4.2.7 File your copy of the completed Confirmation Form (A) and Informed Consent Form. Do not mail these 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.

Normal Business Hours: Monday – Friday 00:00-18:00 US Eastern Time

FSTRF Randomization Help Desk
Frontier Science & Technology Research Foundation (FSTRF)
4033 Maple RD, Amherst, NY 14226 USA
Phone: +1 716 898 7301
Fax: +1 716 898 7082 Email:
bc.helpdesk@fstrf.org

The telephone information may also be used after business hours for urgent issues.

4.4 Randomized groups

Randomization (1:1:1) to 3 groups:

4.4.1 Tamoxifen alone for 5 years.

4.4.2 Ovarian function suppression (triptorelin for 5 years or surgical oophorectomy or ovarian irradiation) plus tamoxifen for 5 years.

4.4.3 Ovarian function suppression (triptorelin for 5 years or surgical oophorectomy or ovarian irradiation) plus exemestane for 5 years.

4.5 Stratification

4.5.1 Institution.

4.5.2 Prior adjuvant/neoadjuvant chemotherapy
- No
- Yes

4.5.3 Number of positive axillary and/or internal mammary lymph nodes
- 0 (including pN0(sn), pN0 (i+)(sn) and pNx)
- 1 or more (including pN1mi)

Patients with less than 6 axillary lymph nodes dissected, all of which were negative and without a sentinel node assessment will be classified as pNx in secondary statistical analyses. For purposes of stratification, disease will be regarded as node-negative if all examined axillary and/or internal mammary lymph nodes were proven to be pathologically negative or if a sentinel axillary and/or internal mammary lymph node biopsy result was negative. Isolated tumor cells (less than or equal to 0.2mm) in a sentinel node is classified as node negative [i.e., pN0(i+)(sn)]. Microscopic disease (pN1mi: > 0.2mm and less than or equal to 2.0mm) in a sentinel axillary and/or internal mammary node is categorized as node positive.

4.5.4 Intended initial method of ovarian function suppression, in the event the patient is randomized to ovarian function suppression:
- Triptorelin for 5 years
- Surgical oophorectomy
- Ovarian irradiation

5 Treatment details

5.1 Trial treatments

5.1.1 Triptorelin (GnRH analogue) 3.75 mg by intramuscular injection every 28 (±3) days for 5 years from the date of randomization, unless relapse or intolerance should occur earlier or bilateral surgical oophorectomy or bilateral ovarian irradiation is subsequently performed. (Triptorelin: Decapeptyl Depot® intramuscular or Trelstar Depot® intramuscular). The responsible investigator may authorize another qualified person to administer triptorelin. Triptorelin will be supplied free of charge for patients randomized to ovarian function suppression in this study.

In case of intolerance to triptorelin, goserelin (Zoladex®) 3.6 mg by subcutaneous injection every 28 days may be used as an alternative to triptorelin but will not be provided by the study. GnRH analogues administered at 3 monthly intervals are not approved in this trial due to uncertainty concerning the duration of ovarian function suppression in women with this schedule.

There are case studies of failure of ovarian function suppression under GnRH analogue [22]. In such cases ovarian function suppression should be achieved by other means, providing the patient accepts an alternative method.

5.1.2 Bilateral surgical oophorectomy via laparotomy or laparoscopy. For patients randomized to an ovarian function suppression treatment group, oophorectomy may be performed initially, after GnRH analogue has been administered for some time, or not at all.

5.1.3 Bilateral ovarian irradiation. For patients randomized to an ovarian function suppression treatment group, ovarian irradiation may be performed initially, after GnRH analogue has been administered for some time, or not at all. Target volume: small pelvis (previous ultrasound pelvic examination with skin marks of the ovarian position is recommended). Standard ovarian irradiation regimen is recommended, using megavoltage energy and scheduling as follows: 3 Gy per fraction in 4 fractions (total dose = 12 Gy) or 3 Gy per fraction in 5 fractions (total dose = 15 Gy). Biochemical verification of ovarian function cessation is required after two months by measurement of estradiol (E_2). If biochemistry shows that radiation was not successful in achieving ovarian function suppression, then this should be achieved by alternate means.

5.1.4 Tamoxifen 20 mg orally daily until 5 years from date of randomization, unless relapse or intolerance should occur prior to 5 years.

5.1.5 Exemestane (Aromasin®) 25 mg orally daily, preferably after food, until 5 years from date of randomization, unless relapse or intolerance should occur prior to 5 years. It is suggested that exemestane begin approximately 6 to 8 weeks after initiation of ovarian function suppression; however, it may begin immediately after, but no later than 10 weeks after, initiation of ovarian function suppression. [Note that exemestane administered to a premenopausal woman in the absence of ovarian function suppression (i.e., if GnRH analogue is discontinued) is not an effective treatment.] Patients who were receiving tamoxifen therapy at the time of randomization may continue such therapy until exemestane is initiated. Exemestane will be provided free of charge.

5.1.6 Radiotherapy: The role of radiotherapy is not assessed in the present trial but radiotherapy should be used according to accepted guidelines. Radiation therapy to the conserved breast is required.

- Radiation therapy to the chest wall following mastectomy is optional and nodal fields may be treated together with the conserved breast or the chest wall.
- Radiation therapy may be given either after all chemotherapy or integrated into chemotherapy (if the combination is considered safe by the investigator).
- Radiation therapy may be concurrent with trial hormonal therapy or given before starting tamoxifen or exemestane, according to institutional practice. A patient may be randomized prior to completing radiation therapy in order to meet the time frame for randomization (section 3.1.1) and then initiate oral trial hormonal therapy when radiation therapy is completed if this is institutional practice. However, patients randomized to ovarian function suppression and planning to receive triptorelin (GnRH analogue) injections should commence those as soon as randomized.

Radiation therapy is well documented to reduce the risk for local and regional recurrence and may decrease breast cancer mortality. These beneficial effects may be counteracted by increased morbidity and mortality from causes other than breast cancer. The morbidity (e.g. lymphedema and reduced mobility of the shoulder, and cardiac morbidity) should be minimized by stringent indications for chest wall and nodal irradiation and by careful planning of the treatment. It is recommended to restrict such treatment to patients who are at high risk of local recurrence (e.g. 20% or more) such as those with breast-conserving surgery, four or more metastatic axillary lymph nodes, and some patients with tumors larger than 5 cm [35,36].

Increased morbidity or mortality could occur after cardiac exposure to chest wall or breast irradiation, and there is a common feeling that this risk might be enhanced for anthracyclinetreated patients. Although the risk for cardiac morbidity and mortality in recent trials which use modern radiotherapy techniques appears to be less than in older studies, information on late adverse effects is limited. There is evidence that the risk is related to the volume of the irradiated heart [37]. It is therefore strongly advised to use 3-D-planning to avoid excessive cardiac exposure. If another system for treatment planning is used, the radiation oncologist should be aware that patients may receive anthracyclines and/or other cardiotoxic drugs as part of adjuvant chemotherapy.

Tamoxifen may mediate enhancement of radiation-induced lung fibrosis [38]. The clinical relevance of the observed changes is unknown and is unlikely to be severe. No change in current practice is recommended and institutions are encouraged to further study lung and skin fibrosis in patients receiving tamoxifen or exemestane together with radiotherapy.

5.1.7 Chemotherapy: Patients in the chemotherapy stratum must have completed adjuvant (and/or neoadjuvant) chemotherapy prior to randomization. A planned duration of 2 [redacted]nths if an anthracycline was included (e.g. 4 cycles of EC or AC) or 4 m[redacted]ths if no anthracycline was given (e.g. 6 cycles of CMF) is recommended. If an anthracycline was used, an epirubicincontaining

regimen is recommended. The final dose of chemotherapy must be less than 8 months prior to randomization.

5.2 Side effects of study drugs

5.2.1 GnRH analogue: The most common side effects are hot flushes, sweating, amenorrhea, fertility impairment, decreased libido and vaginal dryness and/or dyspareunia. Less frequent side effects are headache, tiredness, mood changes, sleep disturbance, nausea, back or joint pain, local injection site reaction, weight gain and slight rise in cholesterol. Loss of bone mineral density can occur.

In clinical trials in advanced disease adverse events (AEs) were generally mild to moderate and rarely severe enough to require discontinuation of treatment. Adverse experiences that have been seldom reported include: skin rash, allergic and anaphylactic reactions including angioedema, hypo- or hypertension, and elevated liver enzymes.

GnRH analogue is contraindicated in pregnancy and lactation. Cases of pregnancy have occurred in women receiving regular injections of GnRH analogue [22]. The role of nonhormonal contraception should therefore be discussed.

Following a safety review of several published studies in men with prostate cancer receiving GnRH agonists, on 20 October 2010, the US FDA required manufacturers of GnRH agonists to add new safety information about increased risk of diabetes and certain cardiovascular diseases in men receiving GnRH agonist for the treatment of prostate cancer to the Warnings and Precautions section of the drug labels. The FDA"s 3 May 2010 Drug Safety Communication, last updated 4 January 2011, about the Ongoing Safety Review of GnRH Agonists noted, "There are no known comparable epidemiologic studies evaluating the risk of diabetes and cardiovascular disease in women taking GnRH agonists." (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm209842.htm; accessed 21 February 2011) Therefore, no changes are recommended concerning the management of patients on this study. Nevertheless, in addition to the cardiovascular and other targeted adverse events already collected, we will prospectively capture adverse event information specifically on hyperglycemia and glucose intolerance (diabetes) and the use of anti-diabetic drugs as concomitant medications.

5.2.2 Tamoxifen: The most common side effects are hot flushes, night sweating, vaginal discharge, irregular menses, vulvar itching and nausea. Fluid retention and skin rash have been reported. Tamoxifen is known to increase the risk of thromboembolic disease. Ocular alterations such as corneal damage, cataract or retinopathy are rare. Patients should avoid pregnancy as tamoxifen may cause fetal harm. There may be an increased risk of endometrial cancer, polyps and hyperplasia associated with the estrogen agonist action of tamoxifen. Rare cases of uterine sarcoma have been reported. Tamoxifen may be associated with loss of bone mineral density in premenopausal women while it prevents bone mineral density loss in the low estrogen

(menopausal) state. Modification of tamoxifen dosage is rarely indicated. No standard dose modifications are prescribed.

5.2.3 Exemestane: The most common side effects seen with exemestane in clinical trials in advanced disease are hot flushes, nausea, increased sweating, fatigue, hair thinning, dizziness and skin rash. Exemestane lowers plasma estrogen levels, which may result in loss of bone mineral density. The best data for comparing the side effects of exemestane with tamoxifen comes from the Intergroup Exemestane Study (IES) in postmenopausal women receiving adjuvant hormonal therapy, in which exemestane was compared to tamoxifen for two to three years (after two to three years of prior tamoxifen). The following adverse events were reported in similar percentages of patients: hot flushes and sweating, aches or pains, fatigue, insomnia, headaches, dizziness, depression, nausea and cardiovascular disease other than myocardial infarction. Adverse events that were significantly more common with exemestane than tamoxifen included visual disturbances, arthralgias and diarrhea and there was a trend to an increase in osteoporosis. Adverse events that were significantly more common with tamoxifen than exemestane were gynecologic symptoms and vaginal bleeding, muscle cramps and thromboembolic disease [47]. In a subsequent updated oral presentation of this trial [48], a nonsignificant excess of myocardial infarctions was noted in those treated with exemestane compared with tamoxifen in the population (mean age 64 years).

5.3 Concomitant treatments

5.3.1 Additional hormonal treatments (either oral or transdermal) including estrogen, progesterone, androgens, aromatase inhibitors, hormone replacement therapy, oral or other types of hormonal contraceptives (including implants and depot injections), raloxifene or other SERMS are not allowed while on study. For women with vaginal dryness and/or dyspareunia, use of vaginal moisturizers and lubricants should be considered [39]. If these non-hormonal measures are insufficient to relieve symptomatic vaginal dryness then a local vaginal estrogen treatment, preferably with minimal systemic absorption, is allowed (e.g., Estring®).

5.3.2 Women who are distressed by vasomotor symptoms (e.g., hot flushes and night sweats) requiring medical intervention should be treated with non-hormonal treatments (e.g., serotonin reuptake inhibitors) [40].

5.3.3 Bisphosphonates are not allowed UNLESS bone density has been documented to be at least 1.5 standard deviations below the young adult normal mean or the patient is participating in a randomized clinical trial testing bisphosphonates in the adjuvant breast cancer setting. The administration of vitamin D3 and calcium supplements is allowed. Considering the potential increased risk of osteoporosis in women in this study, patients should be advised about adequate calcium intake and weight bearing exercise.

5.3.4 Patients for whom it is clinically indicated may receive neoadjuvant/adjuvant therapy with trastuzumab (Herceptin®) prior to and/or while on study. When determining eligibility, trastuzumab should not be considered as chemotherapy.

5.3.5 Patients should be advised that a low risk of pregnancy remains despite GnRH analogue therapy [22].

5.3.6 Patients will not receive other investigational agents while on study except as described in Section 5.3.3.

5.4 Study drug supply

Exemestane will be provided by Pfizer. Triptorelin will be provided by Pfizer in North and South America, and by Ipsen in all other areas.

Tamoxifen, chemotherapy and goserelin will not be provided by the study and must be prescribed by the patient's physician. The drugs should be obtained as if the patient were receiving standard treatment and not participating in a clinical trial.

The coordination of the drug supply-related activities for all clinical centers in all countries will be performed by the IBCSG Coordinating Center in Bern, Switzerland. Exemestane and triptorelin will be provided via a central distribution mechanism. The central clinical supply facility from Ipsen in France will be responsible for the distribution of both drugs in countries outside North and South America and a central clinical supply facility nominated by Pfizer in the United States will be responsible for the distribution in North and South America.

Prior to the shipment of exemestane and triptorelin to a participating clinical center, the necessary ethics and regulatory approvals must be transmitted to the IBCSG Coordinating Center. Upon approval by IBCSG, Ipsen and Pfizer will proceed with the shipment of a certain amount of drug as start up reserve in order to have medication on site before patients are randomized by the investigator. Shipment of additional Six-month to one-year supplies of exemestane and triptorelin will occur automatically based upon randomization assignment. Sixmonth to one-year supplies of exemestane and triptorelin will be re-supplied automatically on a continuous basis for patients continuing treatment. New packages should only be dispensed to patients at the scheduled protocol visits.

Logistics for transmitting ethics and regulatory approvals to the IBCSG Coordinating Center and for study drug supply for different parts of the world are described in detail in Appendix VII: Participating Group Specific Logistical Information.

Destruction of drug: Expired or useless drugs at any clinical center may be destroyed on site and a certificate of destruction provided to IBCSG. If this is not feasible, the expired or useless drugs should be sent back to the supplier for destruction. Any supplied study drug returned by patients at study completion may not be reused and should be destroyed or returned as above.

6 End points and definitions of treatment failure

6.1 Trial end points

6.1.1 **Primary end point:** First confirmation of relapse (local, regional, or distant), contralateral breast cancer, second (non-breast) primary tumor, and/or death.

Disease-free survival (DFS) is defined as the time from randomization to local (including recurrence restricted to the breast after breast conserving treatment), regional or distant relapse, contralateral breast cancer, appearance of a second (non-breast) primary tumor, 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). See Section 6.2.7 for other exceptions.

6.1.2 **Secondary end points:** Overall survival (OS) is defined as the time from randomization to death from any cause.

~~Systemic relapse is defined as any recurrent or metastatic disease in sites other than the local mastectomy scar/chest wall/skin, the ipsilateral breast in case of breast conservation, or the contralateral breast.~~

~~Systemic disease-free survival (SDFS) is defined as the time from randomization to systemic relapse, appearance of second (non-breast) primary tumor, or death, whichever occurs first. See Section 6.2.7 for exceptions.~~

Breast cancer-free interval (BCFI) is defined as the time from randomization to the earliest time of invasive breast recurrence (local, regional or distant relapse) or a new invasive breast cancer in the contralateral breast. Deaths without a prior breast cancer event are censored. The appearance of a second (non-breast) primary tumor is not considered as an event.

Distant recurrence-free interval (DRFI) is defined as the time from randomization to the earliest time of distant recurrence. Deaths without a prior breast cancer event are censored. The appearance of a second (non-breast) primary tumor is not considered as an event.

Quality of life.
Sites of first treatment failure.
Late side effects of early menopause.
Incidence of second (non-breast) primaries.
Causes of death without cancer event.

6.2 Diagnosis of treatment failure

The diagnosis of first treatment failure 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 treatment failure according to site is defined below. Any events not included in this section are considered unacceptable as evidence of recurrent disease. Treatment failures include: local, regional, contralateral breast, and distant failures, second (non-breast) primaries, and deaths without cancer events. The date of treatment failure 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 (or in the case of bilateral, either) conserved breast or the chest wall, mastectomy scar, and/or skin.

Acceptable for recurrence in ipsilateral 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 treatment failure.

6.2.1.1 Treatment after local relapse for patients who received breast-conserving surgery. Patients may continue to receive the protocol treatment after resection of a relapse in the ipsilateral conserved breast, an option that reflects the controversy concerning therapy for reappearance of disease in the ipsilateral breast. Continued treatment is only allowed when there is no evidence of loco-regional disease outside the breast or of distant disease at the time of breast relapse. Details of the local treatment for the conserved breast relapse must be recorded on the Follow-up Form (E). Patients who develop a local relapse other than a relapse in the ipsilateral conserved breast should change therapy.

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. For patients with bilateral breast cancer at randomization, failure in the previously-listed regional nodes should be recorded as regional failure (rather than distant) on the Follow-Up Form E. The side (right or left) of the nodes should be recorded.

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. For patients with bilateral breast cancer at randomization, contralateral breast failure cannot be defined.

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 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, not including ipsilateral supraclavicular lymph nodes, or, for cases with bilateral invasive cancers, supraclavicular or axillary nodes on either side.
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.

For patients with bilateral breast cancer at randomization, failure in the axillary lymph nodes, extranodal soft tissue of the axilla, internal mammary lymph nodes, and/or supraclavicular lymph nodes on either the right or left side should be recorded as regional failure (rather than distant) on the Follow-Up Form E. The side (right or left) of the recurrence should be recorded.

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.

6.2.5 **Second (non-breast) primary**
Any positive diagnosis of a second (non-breast) primary other than basal cell or squamous cell carcinoma of the skin, cervical carcinoma *in situ* or bladder cancer *in situ* is considered a treatment failure. Patients may continue to receive the protocol treatment after a second (nonbreast) primary is diagnosed.

6.2.6 Death without cancer event
Any death without a prior cancer event described in 6.2.1 through 6.2.5 above is considered a treatment failure.

6.2.7 **Other noteworthy events**
The following events should be recorded on the Follow-up Form (E). These events are NOT considered treatment failures, but must be recorded. 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	12	13	14	15	Yearly until death
Year	1	1	1	1	1	2	2	3	3	4	4	5	5	6	6	
Trial month	0	3	6	9	12	18	24	30	36	42	48	54	60	66	72	
Informed 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	x	x	x	x
EstradiolB	x															
Adverse Events (AE)C	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Late AEsD																x
Laboratory tests																
HematologyE	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Blood chemistryF	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Investigations																
Mammogram[G]	x				y		y		y		y		y		y	
Chest-X-rayH (PA and lateral views) or chest CT	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Bone scanI	y	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Abdominal US, CT or liver scanJ	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Gynecological examK	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Bone mineral densitometryL	y				y		y		y		y		y		y	
CRFsM																
Quality of LifeN	x		x		x	x	x		x		x		x		x	
Forms B,C,H,F,P	x															
Form F	x	and at disease relapse (Form RF)														
Form AE, CCM	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Form E		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Form OFS, TE (while receiving OFS, tamoxifen or exemestane)		x	x	x	x	x	x	x	x	x	x	x	x			
Forms R, SAE, EIU, GYN	as needed per protocol															
Forms BC, BF, BP and BR	Submit for patients with synchronous bilateral breast cancer as required per protocol.															

x = mandatory **y = recommended** **v = if medically indicated**

*Physical exam and history may be completed up to two months prior to randomization. A pregnancy test is recommended for women of child-bearing potential who are sexually active and not using reliable contraceptive methods.

Legend to Table 7.1

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

B. Estradiol must be in the premenopausal range within 12 weeks of surgery or for patients who have received chemotherapy between 2 weeks and 8 months after the final dose of chemotherapy (Section 3.1.1). It is recommended to determine E_2 level as close to randomization as possible. The only patients who do not require testing of estradiol (E_2) to confirm premenopausal status are those who did NOT receive chemotherapy and who have been menstruating regularly during the 6 months prior to randomization and have not used any form of hormonal contraception or any other hormonal treatments during the 6 months prior to randomization.

C. Adverse events should be graded using the NCI CTCAE version 3.0 (Appendix II). The following list gives targeted adverse events that should be recorded on the CRF at any time:

- Vaginal dryness and/or treatment to alleviate
- Decreased libido (sexual interest)
- Urinary incontinence
- Vasomotor menopausal symptoms (hot flashes/flushes, night sweats) and/or treatment to alleviate
- Osteoporosis and/or treatment to prevent/alleviate
- Bone fracture
- Dyspareunia (pain or discomfort with intercourse) and/or treatment to alleviate
- Musculoskeletal symptoms (myalgia, arthralgia (joint pain), stiffness not including bone fractures) and/or treatment to alleviate
- Depression
- CNS cerebrovascular ischemia
- CNS hemorrhage
- Hypertension
- Cardiac ischemia/infarction
- Thrombosis and/or embolism
- Nausea
- Insomnia
- Sweating
- Fatigue
- Allergic reaction and/or hypersensitivity
- Injection site reaction
- Glucose Intolerance (Diabetes) and/or anti-diabetes treatment
- Hyperglycemia
- 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 must be done within 2 months prior to randomization and whenever medically indicated.

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

Radiological assessments

G. A bilateral mammography must be taken 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 or chest CT is required within one year prior to randomization. A chest X-ray must 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 is recommended within one year prior to randomization. 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 (i.e. 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 required 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 because of increased risk of uterine cancer in patients receiving tamoxifen. It is recommended that all patients receive gynecological assessment according to standard local practice for patients on tamoxifen.

L. Bone densitometry by DEXA is recommended within one year prior to randomization and then yearly for 6 years. Bisphosphonates may be used for patients who demonstrate a BMD T-score at least 1.5 standard deviations below the young adult normal mean.

M. See Section 8 for details on CRF schedule and submission. Details on CRF completion are available in the Trial 24-02 Data Management Manual.

N. Quality of Life self-assessment forms must be completed and submitted according to guidelines in Appendix V.

All patients must be followed every 3 months for the first year and every 6 months for years 2 to 6, and thereafter yearly for assessment of disease status and for survival data collection.

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 Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE should be labeled: 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 toxicity 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**

A serious adverse event is defined in general as any undesirable medical occurrence/adverse drug experience that occurs during or within 4 weeks 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 or
is an unexpected grade 4 toxicity is a
congenital anomaly or birth defect is
a secondary cancer
requires significant medical intervention

Other significant/important medical events, which may jeopardize the patient, or may require significant medical intervention to prevent one of the other serious outcomes listed above, are also considered a serious adverse event.
Serious adverse event also includes any other event that the investigator or company 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 package insert or the investigator‟s brochure.

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.

7.3.2 **Exceptions to the definition**

Any death or serious adverse event that occurs more than 4 weeks after stopping study treatment but is considered to be at least possibly related to previous study treatment is also considered an SAE. All serious adverse events must also be reported for the period in which the study protocol interferes with the standard medical treatment given to the patient. Cases of second primaries 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 (planned before entry into the clinical study); occur on an outpatient basis and do not result in admission; 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 Form (Form 24-SAE).

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 SAE Form 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 original SAE Form 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.
- The IBCSG Coordinating Center will inform Pfizer Corporation and all appropriate parties about all SAEs related to study medication (per either investigator or IBCSG medical review) within 24 hours of receipt at the IBCSG Coordinating Center.

The original Serious Adverse Event Form and the fax confirmation sheet must be kept with the case report forms at the participating center.

IBCSG Coordinating Center will medically review all SAEs with respect to seriousness, causality and expectedness. The Safety Office will prepare and distribute notifications of those SAEs subject to expedited reporting (suspected, unexpected serious adverse reactions, SUSARs), to the appropriate persons and regulatory authorities.

The IBCSG Coordinating Center will 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. These reports can also be found on the IBCSG web site (www.ibcsg.org).

7.4 Exposure in utero reporting

If any trial subject becomes or is found to be pregnant while receiving protocol treatment or within 4 weeks of discontinuing protocol treatment, the investigator must FAX an Exposure in Utero Form (Form 24-EIU) to the DataFax data submission fax number for the participating center. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of birth or pregnancy termination. A copy of the form is automatically forwarded to the IBCSG Coordinating Center for medical review and for transmission to Pfizer Corporation.

The investigator will follow the subject until completion of the pregnancy and report the outcome within 5 days or as specified below by completing the follow-up portion of the initial Exposure in Utero Form. The completed form must be faxed to the DataFax data submission fax number for the participating center. A copy is automatically forwarded to the IBCSG Coordinating Center for medical review and for transmission to Pfizer Corporation.

If the outcome of the pregnancy meets the criteria for classification as a serious adverse event (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator should follow the procedure for reporting serious adverse events as described in Section 7.3.3, and submit the follow-up Exposure in Utero Form as described above.

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—SOFT

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

RANDOMIZATION FORMS		
Form IC	Informed Consent Form	Obtain before randomization and keep with patient records.
Forms 24QLC, 24-QLM, 24-QLS	QL Core and QL Module Forms; QL Supplement Form (for English-speaking Centers only).	DataFax baseline QL forms (see exceptions in Section 3.1.7). These forms are also required during follow-up (see instructions below).
Form 24-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 24-B	Clinical Form	DataFax within 1 month of randomization.
Form 24-C*	Surgery Form	DataFax within 1 month of randomization.
Form 24-H	Prior Treatment History Form	DataFax within 1 month of randomization.
Form 24-F*	Hormone Receptor Form	DataFax within 1 month of randomization with the hormone receptor report.
Form 24-P*	Pathology Form	DataFax within 1 month of randomization with a copy of the original pathology report.
Form 24-AE	Adverse Event Form	Complete prior to starting protocol treatment (tamoxifen, exemestane, OFS) and DataFax within 1 month of randomization. This form is also required at follow-up (see instructions below.)
Form 24-CCM	Concomitant Medications Form	Complete prior to starting protocol treatment (tamoxifen, exemestane, OFS) and DataFax within 1 month of randomization. This form is also required at follow-up (see instructions below.)
FOLLOW-UP FORMS		
Form 24-E	Follow-Up Form	DataFax every 3 months in Year 1, every 6 months during Years 2-6, and yearly thereafter.
Form 24-OFS	Ovarian Function Suppression Form	DataFax at each follow-up period until completion of OFS.
Form 24-TE	Tamoxifen/Exemestane Form	DataFax at each follow-up period until the completion of tamoxifen and/or exemestane.
Form 24-AE	Adverse Event Form	DataFax at each follow-up period during protocol therapy (tamoxifen, exemestane, OFS), and with Form 24-E at 6 and 12 months after the last dose of protocol therapy. This form is also required at baseline.
Form 24-CCM	Concomitant Medications Form	DataFax at each follow-up period during protocol therapy (tamoxifen, exemestane, OFS), and with Form 24-E at 6 and 12 months after the last dose of protocol therapy. This form is also required at baseline.

Forms 24-QLC, 24-QLM	QL Core and QL Module Forms	DataFax on schedule in QL Appendix V: months 6, 12, 18, 24, 36, 48, 60, 72. These forms are also required at baseline.
Form 24-QLS	QL Supplement Form (for English-speaking Centers only)	DataFax on schedule in QL Appendix V: months 6, 12, 24. This form is also required at baseline.
Form 24-MQL	Missed QL Form	DataFax if scheduled QL Core, Module and/or Supplement Form(s) is/are not obtained.

8.1 Case report forms schedule—SOFT (continued on next page)

8.1 Case report forms schedule—SOFT (continued from previous page)

EVENT-DRIVEN FORMS		
Form 24-R*	Radiotherapy Form	DataFax after completion of radiotherapy, or if radiotherapy was planned but not given.
Form 24-SAEA	Serious Adverse Event Form (Section A)	DataFax within 24 hours when SAE occurs, see Section 7.3.
Form 24-SAEB	Serious Adverse Event Form (Section B)	DataFax within 15 days of the initial report and/or at the definitive SAE outcome, see Section 7.3.
Form 24-EIU	Exposure in Utero Form	DataFax if patient becomes pregnant during protocol therapy (tamoxifen, exemestane, OFS), and when pregnancy outcome is known.
Form 24-GYN	Gynecologic Procedures Form	Use to report gynecologic surgery, procedures and/or diagnostic imaging (excluding PAP smears and minor procedures related to diagnosis of cervical carcinoma in situ). DataFax with the next scheduled Form 24-E.
Form 24 RF	Relapse Hormone Receptor Form	DataFax if a hormone receptor analysis was done at relapse.

* For patients with bilateral breast cancer Forms BC, BF, BP and BR should be submitted for the second breast/side (see section 8.1.2)

8.1.1 Signing and submitting forms

All forms should be signed by the Principal Investigator or designee. An authorization log (see Appendix VI.) should be completed at each participating center. The Pathology Form (P) must be signed by the pathologist who reviewed the case or the Principal Investigator.

For IBCSG Participating Centers: Forms 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 case report forms.

For non-IBCSG Participating Centers: Please consult your Participating Group Specific Logistical Information (Appendix VII) for special instructions about how to submit data from your center.

8.1.2 Data submission for patients with synchronous bilateral breast cancer at randomization

Patients with synchronous bilateral breast cancer are eligible for the SOFT Trial providing both tumors meet the eligibility criteria. Because of the presence of tumors in both breasts, information for both left and right breasts must be collected for these patients. Report the information for one breast/side on the Surgery, Receptor, Pathology and Radiotherapy Forms, and the other breast/side on the following forms:

- [redacted] Bilateral Surgery Form BC
- Bilateral Hormone Receptor Form BF
- Bilateral Pathology Form BP
- Bilateral Radiotherapy Form BR
- All relevant pathology and Hormone Receptor Reports

See section 11 for pathology material submission requirements.

8.2 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.

8.3 Investigators' file

Each 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 Management manual
Quality-of-Life manual
Randomization manual
Patient information and Informed Consent templates approved by Ethical Committee
Investigator's Brochure and updates
Ethical Committee approval of protocol, Patient Information sheet and IC, amendments
Ethical Committee review of SAE, investigators' alert, and other documents
Correspondence with Ethical Committee
Health Authority Approval
Correspondence with Health Authority
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
ICH GCP guidelines/Declaration of Helsinki and updates
Audits/monitoring reports
Obvious Corrections document

8.4 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 VI.).

8.5 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

This study is a multi-national, Phase III, randomized clinical trial designed to evaluate five years of tamoxifen versus a combination of five years of tamoxifen plus ovarian function suppression (OFS: five years of GnRH analogue or surgical oophorectomy or ovarian irradiation) versus a combination of five years of exemestane plus OFS. The trial is designed to answer the following three questions for premenopausal patients with hormone-receptor positive breast cancer who either receive no adjuvant chemotherapy or who remain premenopausal after adjuvant and/or neoadjuvant chemotherapy:

- Do results differ between five years of tamoxifen alone and ovarian function suppression (OFS: five years of GnRH analogue or surgical oophorectomy or ovarian irradiation) plus five years of tamoxifen?
- Do results differ between five years of tamoxifen alone and OFS plus five years of exemestane?
- Do results differ between OFS plus five years of tamoxifen and OFS plus five years of exemestane?

The randomization will be stratified according to participating institution, use of adjuvant/neoadjuvant chemotherapy (no; yes), number of positive axillary and/or internal mammary lymph nodes (0 – including pN0(sn), pN0(i+)(sn) and pNx; 1 or more – including pN1mi) and intended method of ovarian function suppression (GnRH analogue x 5 years; surgical oophorectomy; ovarian irradiation).

9.2 Data analyses

The treatment comparisons for primary objectives will be based on disease-free survival (DFS: Section 6.0) using two-sided stratified logrank tests to determine if the treatment groups are different, 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 treatment arms. Cox proportional hazards regression models will be used to investigate whether the a 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, type and schedule of initial chemotherapy, type of surgery, use of post mastectomy radiation, tumor size, tumor grade, hormone receptor proportion score, ER/PgR subgroup, use of trastuzumab, and Her2 subgroup. These analyses will be considered as secondary and descriptive.

The following additional secondary outcomes will be assessed: overall survival, breast cancer- free interval, distant recurrence-free interval, quality of life, sites of first recurrence, late side effects of early menopause, causes of death without recurrence, incidence of second (non-breast) malignancies.

9.3 Sample size considerations

~~The protocol allows the entry of patients who did not receive chemotherapy, but we do not expect to enroll many such patients. Hence our DFS estimates are based on a patient population receiving chemotherapy. From IBCSG Trial VIII (CMF x 6 arm: 355 patients), 15.6% of patients maintained menses following chemotherapy. The age distribution and the probability of maintaining menses are shown in Table 9.1.~~

~~Table 9.1. Maintaining Menses following CMF x 6 in IBCSG Trial VIII~~

~~Age Group~~	~~Number of Patients~~	~~Maintained Menses~~
~~<=35~~	~~27~~	~~78%~~
~~36-40~~	~~55~~	~~35%~~
~~41-45~~	~~120~~	~~10%~~
~~>45~~	~~153~~	~~2%~~

~~Patients who remain premenopausal following chemotherapy are likely to have an outcome similar to that observed for patients <=35, as the majority of patients in this age group maintain menses. A recent review of data from IBCSG, NSABP, ECOG and SWOG indicated that women under age 35 with ER-positive, node-positive disease who were treated with chemotherapy alone had about a 40% 5-year DFS [11]. Assuming a 40% reduction in risk of relapse by adding tamoxifen [3], the baseline 5-year DFS for patients with node-positive disease who receive chemotherapy plus tamoxifen is estimated to be 58%. This estimate agrees with the 59% 5-year DFS based on 109 women in CALGB 9344 under age 35 with ER positive, nodepositive disease who received chemotherapy plus tamoxifen. Premenopausal women with ERpositive, node-negative disease in IBCSG Trial V had a 70% 5-year DFS without tamoxifen (results were the same for either no chemotherapy or a single perioperative cycle of CMF). Adding tamoxifen should improve this to 81%. If we assume that a little over 60% of the cases enrolled in this trial will be node-positive,~~

~~the baseline risk for the tamoxifen alone control group (with or without prior chemotherapy) is estimated to be 67%.~~

~~The three treatment comparisons will be performed annually starting when 200 events have been observed in the three arms, for a total of 5 analyses over 6.9 years. Table 9.2 shows the operating characteristics of three alternative designs that would allow the detection of 20%, 25%, and 30% reduction in hazard by adding OFS to tamoxifen compared with tamoxifen alone.~~

~~Table 9.2. Operating characteristics for the OFS + tamoxifen versus tamoxifen alone comparison.~~

~~Reduction in hazard~~	~~20%~~	~~**25%**~~	~~30%~~
~~Tamoxifen alone 5-yr DFS~~	~~67%~~	~~**67%**~~	~~67%~~
~~OFS + tamoxifen 5-yr DFS~~	~~72.6%~~	~~**74.1%**~~	~~75.6%~~
~~Two-sided alpha level~~	~~.0167~~	~~**.0167**~~	~~.0167~~
~~Power~~	~~.80~~	~~**.80**~~	~~.80~~
~~Required number of events for two arms*~~	~~861~~	~~**522**~~	~~343~~
~~Accrual rate for two arms (pts/year)~~	~~400~~	~~**400**~~	~~400~~
~~Total accrual time (yrs)~~	~~5.5~~	~~**5**~~	~~4.5~~
~~Sample size (two arms)~~	~~2200~~	~~**2000**~~	~~1800~~
~~Total study duration with 4 interim + 1 final analyses (yrs)*~~	~~9.8~~	~~**6.9**~~	~~5.4~~
~~Total sample size (all 3 arms)~~	~~3300~~	~~**3000**~~	~~2700~~

~~* Under the alternative hypothesis with 4 interim analyses and 1 final analysis [41].~~

~~For planning purposes, we will target a 25% reduction in hazard for each of the three comparisons. This will require recruitment for the three arms of **3000 patients** (600 patients per year for 5 years with 1.9 years of additional follow-up). Accrual of premenopausal patients with ER-positive tumors to IBCSG Trials VI (N+) and VIII (N-) averaged 222 per year. Applying the 15.6% rate of maintaining menses following chemotherapy to this cohort, we anticipate approximately 35 patients per year from IBCSG institutions. Global participation including the Breast International Group (BIG) and the US Intergroup is required to successfully complete this trial.~~

~~The same operating characteristics apply to the second comparison (OFS plus exemestane versus tamoxifen alone) and to the third comparison (OFS + exemestane versus OFS + tamoxifen), when testing for an improvement in 5-year DFS from the baseline value of 67%. If one assumes a 25% reduction in hazard due to the addition of OFS to tamoxifen (and thus an estimated 74.1% 5-year DFS for the OFS + tamoxifen arm), then a further 25% reduction in the hazard for OFS + exemestane compared with OFS + tamoxifen (to 79.8% 5-year DFS) would be detected with 68% power, if the final analysis is performed at 6.9 years from the activation of the study.~~

The originally planned sample size was 3000. It was projected that 5 years of accrual, plus 1.9 years of additional follow up would be sufficient to observe the 783 target number of DFS events (522 needed for each pairwise comparison). This number of events would provide 80% power to detect a hazard ratio of 0.75 for GnRH + tamoxifen versus tamoxifen alone (74.1% versus 67.0%

5-yr DFS, respectively) using a 2-sided, 0.0167 level test (adjusting for multiple tests). The study opened to enrollment in August 2003. In January 2011, enrollment was closed with 3066 patients randomized. Due to agreements with pharmaceutical partners and financial constraints, it is not possible to increase patient enrollment.

As of October 2010, the overall DFS event rate was substantially lower than originally anticipated: approximately 2% per year compared with the protocol-specified 8% per year. Consequently, at the October 2010 estimated event rate, an additional thirteen (13) years of follow up (end of 2023) would be required to observe the protocol-specified 783 target number of the DFS events (at which time the median follow up would be 15 years). The Steering Committee considered this delay in the reporting of the trial results (20 years after first enrollment compared with the originally anticipated 7 years) to be unacceptably long, and decided to revise the analysis plan so that the first results of the study could be reported within 3 years of completing enrollment (median follow up approximately 5 years). This decision was endorsed by the IBCSG Data and Safety Monitoring Committee (DSMC). Outcome according to treatment group was not available to either the Steering Committee or the DSMC.

By revising the timing for the first report of results from an „event-driven" plan (783 DFS events in SOFT) to a „time-driven" plan (with a data cut-off defined for the fall of 2013), the Steering Committee recognized that the statistical power for the original three pairwise comparisons at the time of first report will be substantially reduced. Therefore, the Steering Committee decided to focus the primary analysis from the SOFT trial on the unique comparison: OFS + tamoxifen versus tamoxifen alone, and to test this comparison at the 2-sided 0.05 level with no interim analyses planned. We estimate that the power to detect hazard ratios of 0.80, 0.75, and 0.70 at the 2013 timing of the first analysis to be 34%, 52%, and 69%, respectively. A hazard ratio of 0.665 for OFS + tamoxifen versus tamoxifen alone would be detected with power of 80%. The comparison of OFS + exemestane versus tamoxifen alone is considered of secondary importance in the SOFT patient population. The comparison of OFS + exemestane versus OFS + tamoxifen will be assessed primarily in the originally-planned combined analysis of SOFT and the Tamoxifen and Exemestane Trial (TEXT) described below.

We prospectively plan to combine the data available for the two OFS-containing arms with the data available from the Tamoxifen and Exemestane Trial (TEXT: BIG 3-02; IBCSG 25-02) that is being conducted as a complementary study with SOFT. We note that SOFT and TEXT differ with respect to patient selection and treatment for women who receive chemotherapy; SOFT enrolls patients who remain premenopausal following chemotherapy and initiates OFS (GnRH analogue, surgical oophorectomy or ovarian irradiation) following the completion of chemotherapy, while TEXT enrolls patients following surgery and uses concurrent GnRH analogue and chemotherapy. Nevertheless, the combined analysis will provide a statistically powerful comparison of exemestane versus tamoxifen as adjuvant therapy for premenopausal women. The two studies are scheduled to open simultaneously. The power of such a combined analysis (at the 0.05 two-sided level) to detect a 20%, 25%, or 30% reduction in hazard with OFS + exemestane versus OFS + tamoxifen would be at least ~~88~~63%, ~~98~~84%, and ~~99~~95%, respectively, assuming that both SOFT and TEXT ~~recruit as planned and that the combined~~ ~~analysis is~~

~~performed 6.9 years from the opening of the two studies.~~ are first reported based on data available in the fall of 2013 and the October 2010 estimated event rates in the two trials continue.

Updates of efficacy results will be prepared and reported approximately every 2 years after the first report.

9.4 Interim monitoring

~~A group sequential design with four interim analyses and one final analysis will be used [41]. Under the hypothesis of a 25% reduction in hazard between the tamoxifen alone arm and one of the two OFS arms, the target number of events for the final analysis is 783. Formal interim analyses are planned yearly starting when 200 events have been observed in the three arms. At each interim analysis and at the final analysis testing for each comparison will be performed using O'Brien-Fleming boundaries [42].~~

Originally the protocol included a group sequential design with four interim and one final efficacy analysis. Due to the lower than anticipated DFS event rate, no interim efficacy analysis has been performed. Because the number of events is so much lower than anticipated, the DSMC determined that the first analysis planned for 2013 would be sufficient, and that interim monitoring for efficacy was not required.

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, toxicity, 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 (annually from the 200th event).~~ 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 Quality of Life

See Appendix V for a complete description of the quality-of-life study to be conducted in conjunction with this protocol. See Appendix VII for non-IBCSG Group-specific guidelines for participating in the quality-of-life study.

11 Additional protocol-specific parameters

11.1 Hormone receptors

11.1.1 Hormone receptor determination

Immunohistochemical measurements of estrogen receptor (ER) and progesterone receptor (PgR) of the invasive component of the tumor are required for this protocol. The measurements should be expressed as percent of positive cells. Patients with greater than or equal to 10% of cells positive are considered hormone receptor positive. For this trial, only patients with either ERpositive and/or PgR-positive tumors are eligible. For patients with bilateral breast cancer, all tumors must meet the above criteria.

The following items are required for all patients:

1. Completed Hormone Receptor Form F
2. Steroid Hormone Receptor Report

For patients with bilateral breast cancer, the following items are required for the second breast/side:

1. Completed Bilateral Hormone Receptor Form BF
2. Steroid Hormone Receptor Report

11.1.2 Quality assurance

It is mandatory that all laboratories conducting immunohistochemical measurements participate in a program for quality assurance. One such system is the NEQAS Scheme, which has been validated by the IBCSG pathologists.

More information on immunohistochemical measures and the NEQAS system is available in the Hormone Receptor Guidelines (Appendix III).

11.1.3 Central review

Tissue bank material will be used for central review of hormone receptors. The original histological report must be available.

11.2 Pathology and pathology material banking

11.2.1 Pathology requirements

The work of the pathologist is basic to the success of all studies. Each 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 (CPR) form. See Appendix IV, “Pathology Guidelines” for more information.

The following items are required for all patients:

1. Completed Pathology Form P
2. Pathology Report
3. Tumor block for banking
4. Normal tissue block for banking
5. Representative H & E sections of the above blocks

For patients with bilateral breast cancer, the following items are required for the second breast/side:

1. Completed Bilateral Pathology Form BP
2. Pathology Report
3. Tumor block for banking

4 Representative H & E section of the above block

The tissue blocks, particularly in case of small tumors, may be returned to the participating center upon request. ~~If for some reason blocks can not be provided, 20 unstained slides of the primary tumor and 10 unstained slides of the normal tissue must be submitted.~~

All reports, slides, and blocks must be marked with the randomization number~~. If materials are not properly marked, we cannot guarantee that the slides will be forwarded to the Central Pathology Review Office.~~ The IBCSG ~~Coordinating Center~~ has received broken slides in the past and asks that they be sent in customized boxes especially made for slides. They should be packed with tissue paper to prevent any movement. The slides have not been packed securely enough if they move around when the box is shaken.

11.2.2 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 Central Pathology Office and IBCSG Tissue Bank in Milan ~~Coordinating Center Office in Bern~~ (**IBCSG Central Pathology Office, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy ~~Coordinating Center, Effingerstrasse 40, CH-3008 Bern~~**). The Australia-New Zealand Group will maintain a tumor bank within Australia. Immunohistochemistry characterization is done as part of ~~The H&E section is sent for~~ central pathology review, and the respective sections are stored in the central repository thereafter. ~~then returned to 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 proliferative fractions (Ki-67 immunostaining). 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 Biological Protocols Working Group and by the IBCSG Ethical Committee.

11.3 Family history

Information on patients‟ family history of breast cancer is being collected on Clinical Form B to evaluate its impact on prognosis. A positive family history of breast cancer has been shown to be associated with an increased risk of contralateral tumors [43] and second primaries [44]. In addition, research is ongoing to determine whether genetically-associated breast cancer responds differently to treatment [45].

12. Regulatory approval procedures and patient informed consent

12.1 Ethics Review Board/Ethics Committee

All protocols and the patient informed consent (IC) Forms must have the approval of a properly constituted committee or committees responsible for approving clinical trials. The Ethical Review Board (ERB)/Institutional Review Board (IRB) written, signed approval letter/form must contain approval of the designated investigator, the institution, the protocol (identifying protocol title and version number), and of the patient IC template, as well as the composition of the Ethics Committee (names of members) that approved such documents. Documentation of ethics committee approval should 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.

12.2. Regulatory approval procedures

The protocol, other protocol related documents including patient information and IC, and other documents as required locally must be submitted to and approved by health authorities according to national regulations.

12.3. Requirements for Center Activation

Prior to activation, the Centers have to submit all required regulatory documents as specified in the activation letter including Ethics Committee approval, Health authority approval, and approved patient information/IC to the IBCSG ~~Coordinating Center~~.

Logistics for transmitting regulatory documents and ethics and health authority approvals for participating groups are described in Appendix VII.

12.4 Protection of human subjects

The IBCSG has an Office for Human Research Protection (OHRP) assurance (#T-4777) 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 12.5. Additional institution-specific sections should be added to Appendix I as described in Section 12.5.

The medical record must be available for review by the IBCSG audit team as described in Section 12.6.

SAE reports are distributed monthly. In addition they are available on the IBCSG website (www.ibcsg.org).

IBCSG will promptly notify the appropriate persons of all SAE reports subject to expedited reporting. Investigators are responsible to forward such safety information to their Ethics Committee.

12.5 Informed consent procedures

Informed consent for each patient will be obtained prior to initiating any trial procedures in accordance with the statement entitled "Requirements for 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. There must be verification on Form A and in the randomization system that informed consent was obtained and the date obtained.

The "Declaration of Helsinki" (http://www.wma.net/e/policy/b3.htm) and its updates recommend 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 a minor, 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, available from the IBCSG website in Microsoft Word, which can be downloaded and edited to incorporate information specific to your institution (www.ibcsg.org). The final version should receive the Institutional Review Board/ Local Ethical Committee approval in advance of its use.

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."
Following the ICH-GCP guidelines, the Informed Consent should contain information about the following items:

- The trial involves research
- Purpose of the trial
- Trial treatment (s) and the probability of random assignment
- The subject"s responsibilities
- The aspects of the trial that are experimental
- Risks
- Benefits
- Alternative treatments available
- Compensation/Expenses
- Subject"s participation is voluntary/right to withdraw
- Confidentiality
- Information about course of the trial
- Circumstances under which trial may be terminated
- Contact persons for further information or in case of injury
- The approximate number of subjects involved in the trial
- Duration of subject"s participation in the trial

The template has been designed to cover the above items. If the IRB/Local Ethical Committee requires modifications, none of the above items should be completely excluded, nor should the meaning of the highlighted areas be modified.

12.6 Quality assurance

The IBCSG conducts trials according to the ICH Good Clinical Practice (GCP) guidelines. The Study Data Manager reviews each Case Report Form as they are received. In addition, the Study Chair and/or 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.

Data Management manuals are available from the IBCSG website (www.ibcsg.org).

13 Administrative considerations

13.1 Insurance

IBCSG as the Sponsor of the Study, contracts adequate Clinical Trial Insurance, in accordance with all relevant legal requirements, laid down by local regulations where the Study takes place. This insurance provides compensation to participants of the study.

Patients who suffer injuries due to the trial should report them immediately to their doctor.

The local group must report all alleged claims immediately to IBCSG.

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Appendices

I. Requirements for Informed Consent II. NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
[available from the internet at: http://ctep.cancer.gov/reporting/ctc.html]
III. Hormone Receptor Guidelines IV. Pathology Protocol V. Quality-of-Life Protocol VI. Authorization Log VII. Participating Group Specific Logistical Information
VIII. IBCSG Guidelines for Publication and Presentations