Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Pagani O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med 2014;371:107-18. DOI: 10.1056/NEJMoa1404037

IBCSG SOFT and TEXT protocol documents for New England Journal of Medicine
April 3, 2014

1. SOFT Protocol (24-02)
   1.1. Original protocol
   1.2. Final protocol
   1.3. Summary of Amendment 1
   1.4. Summary of Amendment 2

2. TEXT Protocol (25-02)
   2.1. Original protocol
   2.2. Final protocol
   2.3. Summary of Amendment 1
   2.4. Summary of Amendment 2
   2.5. Summary of Amendment 3

3. SOFT and TEXT combined Statistical Analysis Plan. The original plans are within the individual protocols. The final plan for this combined analysis is included here.

INTERNATIONAL BREAST CANCER STUDY GROUP

IBCSG 24-02
BIG 2-02

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

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

Coordinating Group: International Breast Cancer Study Group (IBCSG)

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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Protocol Signature Page

IBCSG 24-02 / BIG 2-02

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

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

Signature on file

_____ _____

Date

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

Signature on file

_____ _____

Date

Principal Investigator and Co-investigator Protocol Signature Page

IBCSG 24-02 / BIG 2-02

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

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Name of Principal Investigator:_____

Signature:

_____ _____

Date

Name of Co-investigator:_____

Signature:

_____ _____

Date

Name of Co-investigator:_____

Signature:

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Date

Name of Co-investigator:_____

Signature:

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Date

Name of Co-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

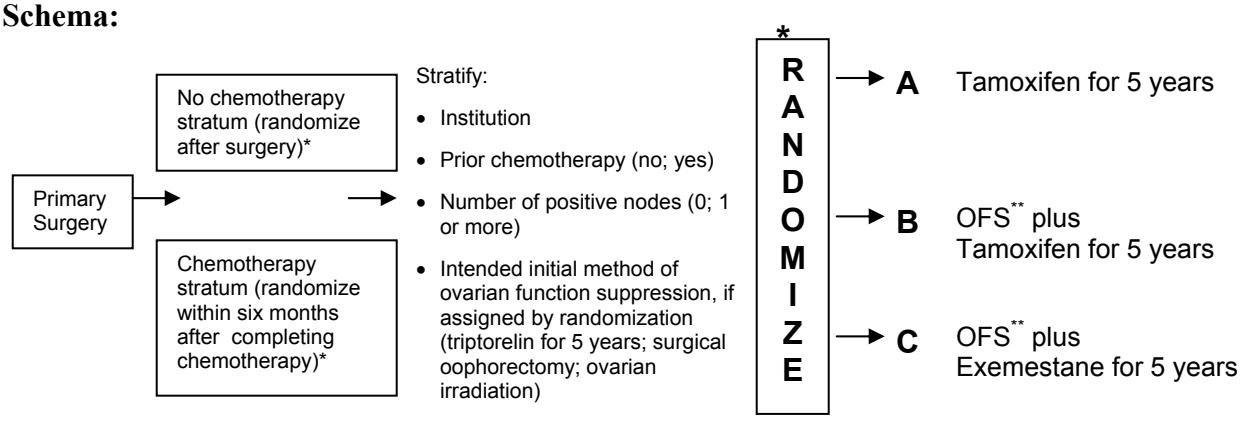
Patient Population: Premenopausal women (estradiol (E2) levels in the premenopausal range) with histologically proven, resected breast cancer with ER and/or PgR positive tumors who have received either no chemotherapy or remain premenopausal following completion of adjuvant and/or neoadjuvant chemotherapy.

Entry: Patients who do not receive chemotherapy should be randomized within 12 weeks after surgery; such patients must have estradiol (E2) levels in the premenopausal range following surgery. Patients who have received adjuvant and/or neoadjuvant chemotherapy should be randomized within 6 months of the final dose of chemotherapy as soon as premenopausal status is confirmed; such patients must have estradiol (E2) levels in the premenopausal range between 2 weeks and 6 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:



* 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 ≥ 2 months if an anthracycline was included (e.g. 4 cycles of EC or AC) or ≥ 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 6 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 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).

TABLE OF CONTENTS

Section			Page
1	**Introduction**		10
2	**Trial objectives**		13
3	**Patient selection**		14
	3.1	Criteria for patient eligibility	14
	3.2	Criteria for patient ineligibility	16
4	**Randomization and stratification**		17
	4.1	Randomization timing	17
	4.2	Registration procedures	17
	4.3	Randomization help desk	18
	4.4	Randomized groups	19
	4.5	Stratification	19
5	**Treatment details**		20
	5.1	Trial treatments	20
	5.2	Side effects of study drugs	21
	5.3	Concomitant treatments	22
	5.4	Study drug supply	23
6	**End points and definitions of treatment failure**		24
	6.1	Trial end points	24
	6.2	Diagnosis of treatment failure	24
7	**Study parameters**		28
	7.1	Table of study parameters	28
	7.2	Adverse event reporting	30
	7.3	Serious Adverse Event (SAE) reporting	31
	7.4	Exposure in utero reporting	33
8	**Data submission**		33
	8.1	Case report forms schedule	33
	8.2	Pathology materials submission	35
	8.3	Data management	35
	8.4	Investigators' file	35
	8.5	Authorization log	36
	8.6	Patient identification log	36

9 Statistical considerations 37
9.1 Study design, objectives, and stratification 37
9.2 Data analyses 37
9.3 Sample size considerations 38
9.4 Interim monitoring 40
9.5 Data and safety monitoring committee 40

10 Quality of life (see Appendix V.) 40

11 Additional protocol-specific parameters 40
11.1 Hormone receptors 40
11.2 Pathology and pathology material banking 41
11.3 Family history 42

12 Ethics committee review and patient informed consent 42
12.1 Ethical Review Board/Ethics 42
12.2 Protection of human subjects 42
12.3 Informed consent procedures 43
12.4 Quality assurance 44

13 Administrative considerations 44
13.1 Insurance 44

14 References 44

Appendices

I. Requirements for Informed Consent
II. NCI Common Toxicity Criteria, Version 2 [available from the internet at: http://ctep.info.nih.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

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 $\geq$ 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 first results of the ATAC trial (anastrozole, tamoxifen and combination) in 9366 postmenopausal women with operable breast cancer were recently published. Among the 84% of patients with steroid hormone receptor positive disease, the hazard ratio for disease recurrence comparing anastrozole with tamoxifen was 0.78 (p=0.005) [26].

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

2.1.3 To compare OFS plus exemestane vs. OFS plus tamoxifen

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
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.

- Patients who received prior adjuvant and/or neoadjuvant chemotherapy should be randomized after completing chemotherapy and within 6 months of the final dose of chemotherapy as soon as premenopausal status is confirmed; such patients should have estradiol (E_2) in the premenopausal range between 2 weeks and 6 months after completing chemotherapy.

  Patients with temporary chemotherapy-induced amenorrhea who regain premenopausal status within six months of the final dose of chemotherapy are eligible. [Attention: under tamoxifen or aromatase inhibitors, even without evidence of menses, some women 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].

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. 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. Radiation therapy to the conserved breast is required.

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 positive axillary nodes require axillary dissection, except for patients with microscopically positive (pN1mi: micrometastasis ≤ 2mm) axillary sentinel nodes who are randomized in a clinical trial evaluating microscopically positive lymph 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 bilateral invasive breast cancer.

3.2.2d Patients with positive final margins (referring to only DCIS and invasive cancer, not LCIS).

3.2.2e Patients with clinically detectable residual axillary disease.

3.2.3 Patients with a history of prior ipsilateral or contralateral invasive breast cancer.

3.2.4 Patients with previous or concomitant malignancy EXCEPT adequately treated:
basal or squamous cell carcinoma of the skin
in situ carcinoma of the cervix or bladder,
contra- or ipsilateral *in situ* breast carcinoma.

3.2.5 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 or are planning oophorectomy within 5 years.

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.

3.2.9 Patients who received endocrine therapy (including neoadjuvant and adjuvant) for more than 6 months after their breast cancer diagnosis.

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.

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, which compromises ability to give informed consent for participation in this study.

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 6 months after the last dose of chemotherapy, as soon as premenopausal status is confirmed, as described in Section 3.1.1.

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) Core form. (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 Form QL 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.

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

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

4.4 Randomized groups

Randomization (1:1:1) 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, if assigned by randomization
- 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 injection every 28 days for 5 years, 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). Triptorelin will be supplied free of charge for patients randomized to ovarian function suppression in this study.

In case of intolerance to or unavailability of 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, FSH and LH. 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. Exemestane should begin 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.] 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.

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 anthracycline-treated 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 months if an anthracycline was included (e.g. 4 cycles of EC or AC) or ≥ 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 6 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 non-hormonal contraception should therefore be discussed.

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.

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

5.3.5 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 Pharmacia. Triptorelin will be provided by Pharmacia in North and South America, and by Beaufour 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 Beaufour 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 Pharmacia 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, Beaufour Ipsen and Pharmacia 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. Six-month 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 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.

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 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.

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

6.2.3 **Contralateral breast failure**

Acceptable: positive cytology or histology.
Suspicious: a visible or palpable lesion, suspicious mammogram, ultrasound, or MRI.

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

6.2.4 **Distant failure**

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

6.2.4.1 <u>Bone marrow</u>
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

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

Suspicious: evidence of enlarged lymph nodes by physical exam.

6.2.4.8 Other sites

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

Suspicious: clinical and radiological evidence of a tumor.

6.2.5 **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 (non-breast) 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	1 A	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
Estradiol[B]	x															
Adverse Events (AE)[C]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Late AEs[D]																x
Laboratory tests																
Hematology[E]	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Blood chemistry[F]	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-ray[H] (PA and lateral views)	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Bone scan[I]	y	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Abdominal US, CT or liver scan[J]	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Gynecological exam[K]	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Bone mineral densitometry[L]	y				y		y		y		y		y		y	
CRFs[M]																
Quality of Life[N]	x		x		x	x	x		x		x		x		x	
Forms B,C,H,F,P	x															
Form F	x	and at disease relapse														
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															

x = mandatory
y = recommended
v = if medically indicated

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 within 6 months after the final dose of chemotherapy, whichever is later (Section 3.1.1).

C. Adverse events should be graded using the NCI CTC version 2 (Appendix II). The following list gives targeted adverse events that should be recorded on the CRF at any time:
- Vaginal dryness/dyspareunia (pain or discomfort with intercourse) and/or treatment to alleviate
- Urinary incontinence
- Decreased libido (sexual interest)
- Vasomotor menopausal symptoms (hot flushes, night sweats) and/or treatment to alleviate
- Bone mineral densitometry
- Bone fracture or document osteoporosis and/or treatment to prevent/alleviate
- Musculoskeletal symptoms (myalgia, arthralgia (joint pain), stiffness not including bone fractures) and/or treatment to alleviate
- Depression
- Hypertension
- Cardiac ischemia/infarction
- Thrombosis and/or embolism
- CNS cerebrovascular ischemia
- Insomnia
- Fatigue
- Nausea
- Allergic reaction and/or hypersensitivity
- Injection site reaction
- Other Grade 3 or higher adverse events
- Use of antidepressants and primary reason for use
- Gynecologic surgery/procedures excluding PAP smears and procedures related to diagnosis of cervical carcinoma *in situ*
- Hyperplasia of the endometrium

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 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 5 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 Toxicity Criteria (CTC). The CTC should be labeled: CTC Version 2.0. The CTC is available for downloading on the internet at (http://ctep.info.nih.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	Lethal

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

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

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 Pharmacia 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 Pharmacia 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 24-QLC, 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.

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

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

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 and again if a hormone receptor analysis was done at recurrence.
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.
EVENT-DRIVEN FORMS		
Form 24-R	Radiotherapy Form	DataFax after completion of radiotherapy, or if radiotherapy was planned but not given.
Form 24-SAE-A	Serious Adverse Event Form (Section A)	DataFax within 24 hours when SAE occurs, see Section 7.3.
Form 24-SAE-B	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 procedures related to diagnosis of cervical carcinoma in situ). DataFax with the next scheduled Form 24-E.

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.

8.2 Pathology materials submission

The following material must be sent to the IBCSG Coordinating Center within three months of randomization: 1 tumor tissue block, 1 normal tissue block, 1 representative H&E slide from each of the blocks (see Appendix IV). 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. See Section 11 for more information.

8.3 Data management

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

8.4 Investigators' file

Each 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
- 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

8.5 Authorization log

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

8.6 Patient identification log

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

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

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

9 Statistical considerations

9.1 Study design, objectives, and stratification

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 three primary treatment comparisons 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 three arms. Cox proportional hazards regression models will be used to investigate whether the three treatment comparisons are modified by adjustments for various covariates. To guarantee the overall alpha level of at most 0.05 for all three tests, each of the pairwise hypotheses will be tested at the two-sided 0.0167 level.

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, and ER/PgR subgroup. These analyses will be considered as secondary and descriptive.

The following additional secondary outcomes will be assessed: overall survival, systemic disease-free survival, 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, node-positive disease who received chemotherapy plus tamoxifen. Premenopausal women with ER-positive, 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.

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%, 98%, and 99%, 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.

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].

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) 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 ER-positive and/or PgR-positive tumors are eligible.

The following items are required for all patients:

1. Completed Hormone Receptor Form
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

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 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 Coordinating Center Office in Bern (**IBCSG Coordinating Center, Effingerstrasse 40, CH-3008 Bern**). The Australia-New Zealand Group will maintain a tumor bank within Australia. The H&E section is sent to Prof. Gusterson's laboratory in Glasgow for central pathology review, and then returned to Bern for storage. Central pathology review reports will be available to institution pathologists who wish to see them. 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 Ethics committee review and patient informed consent

12.1 Ethical Review Board/Ethics

All protocols and the patient informed consent forms must have the approval of a properly constituted committee or committees responsible for approving clinical trials. The ERB/IRB written, signed approval letter/form must contain approval of the designated investigator, the institution, the protocol (identifying protocol title and version number), and of the patient informed consent template, as well as the composition of the Ethical Committee (names of members) that approved such documents. Documentation of ethical committee approval should be sent to the IBCSG Coordinating Center prior to enrollment of the first patient. The IBCSG Ethical Committee also reviews the protocol annually.

12.2 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 12.3. Additional institution-specific sections should be added to Appendix I as described in Section 12.3.

The medical record must be available for review by the IBCSG audit team as described in Section 12.4.

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

12.3 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/17-c_e.html) 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.

12.4 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

The IBCSG through the SIAK/SAKK has a Public and Products Liability Insurance. All persons, acting on behalf of the Named Insured, are covered as Additional Insured. The scope of coverage is Comprehensive Swiss Form.

This insurance does not cover any liability resulting from medical malpractice. Specifically the negligence in the application of the protocol and/or treatment of the patients is excluded.
The IBCSG insurance does NOT cover patients from the United States of America or from Canada. Each group will be responsible for obtaining proper insurance coverage.

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Appendices

I. Requirements for Informed Consent
II. NCI Common Toxicity Criteria, Version 2 [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

IBCSG Trial 24-02/BIG Trial 2-02

Appendix I

IBCSG PATIENT INFORMATION AND INFORMED CONSENT

1) This 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.

2) This template can be edited to incorporate information specific to your institution and the final version should receive the Institutional Review Board/ Local Ethical Committee approval in advance of use.

3) Following the ICH-GCP guidelines, the Informed Consent should contain information about the following items:
   a) The trial involves research
   b) Purpose of the trial
   c) Trial treatment (s) and the probability of random assignment
   d) The subject's responsibilities
   e) The aspects of the trial that are experimental
   f) Risks
   g) Benefits
   h) Alternative treatments available
   i) Compensation/Expenses
   j) Subject's participation is voluntary/right to withdraw
   k) Confidentiality
   l) Information about course of the trial
   m) Circumstance under which trial may be terminated
   n) Contact persons for further information or in case of injury
   o) The approximate number of subjects involved in the trial
   p) Duration of subject's participation in the trial

4) This 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.

5) In order to assist in the preparation of your customized version, an electronic file in Word will be distributed via e-mail to all Principal Investigators or IBCSG members may download it from the IBCSG web site (www.ibcsg.org).

PATIENT INFORMATION SHEET AND INFORMED CONSENT APPENDIX I

IBCSG PATIENT INFORMATION SHEET FOR CLINICAL RESEARCH

You are being asked to participate in a clinical research study. The doctors at different centers of the International Breast Cancer Study Group (IBCSG) throughout the world study the nature of breast cancer and attempt to develop improved methods of diagnosis and treatment. This is called clinical research. In order to decide whether or not you should agree to be part of this research study you should understand enough about its risks and benefits to make an informed judgment. This process is known as Informed Consent.

This Patient Information Sheet gives detailed information about the research study which your doctor will discuss with you. Once you understand the study, if you wish to participate, you will be asked to sign the Patient Informed Consent. You will have a copy of this document and of the Patient Informed Consent to keep as a record.

PROPOSAL FOR A NEW CLINICAL RESEARCH STUDY

The clinical research study being proposed to you is:

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

PURPOSE OF THE RESEARCH STUDY

You have been diagnosed with a type of breast cancer that is known to respond to hormonal treatment in the majority of patients. Hormonal therapy has been shown to help prevent breast cancers from coming back after they have been removed by surgery if the breast cancer has hormone receptors. Standard hormonal treatment used consists of tamoxifen, an estrogen modulator, which is usually given for five years. More recently, another family of hormonal drugs called aromatase inhibitors, to which the drug exemestane (Aromasin®) belongs, has shown initial promising results. In addition, premenopausal patients also benefit from suppression of the ovaries to simulate menopause. This ovarian function suppression can be achieved by either radiation therapy, surgical resection of the ovaries or by a class of drugs knows as the GnRH analogues, given as monthly injections. It has also been shown that suppressing (shutting down) the ovaries (which stops them from making hormones such as estrogen) helps prevent breast cancers from coming back in women who are premenopausal (women whose ovaries are still producing hormones).

Tamoxifen is the standard therapy. Exemestane is a drug which is approved for use in advanced breast cancer for postmenopausal women, but its use in combination with ovarian suppression in premenopausal women with operable (early stage) breast cancer is experimental.

This study is being done to see if shutting down the ovaries plus giving tamoxifen is better at preventing the return of breast cancer than giving tamoxifen alone in premenopausal women. It will also test whether the newer hormone exemestane plus suppression of the ovaries is better than either tamoxifen alone or tamoxifen plus suppression of the ovaries. In addition the side effects of these different treatments will be studied.

DESCRIPTION OF THE CLINICAL RESEARCH STUDY

Patients will be assigned randomly (similar to the toss of a coin) to receive tamoxifen, tamoxifen plus ovarian suppression or exemestane plus ovarian suppression. This study will permit the estimation of the effects of the treatment on the patients' likelihood of recurrence and death from breast cancer on their quality of life. About 3000 women from centers around the world are expected to be enrolled in this study.

Your participation in this research trial is entirely voluntary and you will be given sufficient time to decide whether you wish to participate.

TREATMENT

It is not clear at this time, which of the hormonal treatments will be better for you. For this reason, the treatment offered to you will be chosen by a method called randomization. Randomization is a method similar to the "flip of a coin" to assign at random (by chance) a treatment for you. Your chances of receiving tamoxifen, tamoxifen plus ovarian suppression or exemestane plus ovarian suppression are equal (1/3 chance of receiving any one of the treatments). Neither you nor your doctor will choose a treatment for you, but at random (by chance), you will be assigned to receive one of the following treatment programs:

Arm A: Tamoxifen for five years.

Arm B: Ovarian function suppression plus tamoxifen for five years.

Arm C: Ovarian function suppression plus exemestane for five years.

Tamoxifen is taken in tablet form by mouth each day. Exemestane is taken as a tablet by mouth each day.

If you are randomized to ovarian function suppression (Arm B or Arm C), you and your physician may choose to have your ovaries removed surgically, shut down by radiation treatments, or suppressed by getting a monthly intramuscular

injection of a drug called GnRH analogue for five years. Surgery and radiation result in permanent menopause. With the monthly injection of the GnRH analogue, the ovaries may recover their function when injections are stopped. The injections will be given into the muscle (intramuscular). The drug given as a monthly injection to suppress the ovaries on this study is triptorelin and its use in early stage breast cancer is experimental. In rare circumstances your physician may suggest a different drug for injection (goserelin), but it will not be provided by the study. If you choose to suppress the ovaries by radiation, treatments will be given once a day for four or five days.

You will have a full medical history and physical examination taken at the time you enter the study and every 3 months for the first year, every 6 months for the second to sixth year, and once a year thereafter. You will also have blood tests (about one tablespoon). A mammogram and a chest x-ray will be done at the time you enter the study if they have not already been done in the past 12 months. Your doctor may suggest other tests, such as a bone scan, regular mammograms and a test for bone density.

At specified intervals during the study, you will be asked to fill out questionnaires that ask you how well you feel and what side effects you are having from the treatment. You will be given Quality of Life Questionnaires before you begin the study, every 6 months during the first and second years and once a year during years 3 to 6. If, for any reason, a question makes you feel very uncomfortable, you may leave the question unanswered. However, we would like to encourage you to answer all of the questions because your answers may help us better understand how the treatment influences the quality of patients' everyday life.

If your surgery was a lumpectomy and you have not yet had radiation therapy, you will be given radiation therapy to the breast, regardless of which hormone treatment you are on. Radiation therapy to the chest wall may also be given for some patients who have had a mastectomy. Your doctor will talk this over with you.

You will receive the hormone treatment (tamoxifen or exemestane) for 5 years unless there is evidence of disease recurrence. However you will continue to be followed on this study for the remainder of your life to determine if your cancer ever comes back.

If during the course of the study, information becomes available to clearly identify that one of the treatment options is better, you will be informed and further treatment will be discussed.

You can choose to stop participating in this study at any time. However, if you decide to stop participating in the study, we encourage you to talk your doctor first. It is possible, though not likely, that your participation in this study will be ended by your doctor or the investigators running the trial without your consent,

either because it is felt to be in your best interest or because the study is being stopped.

As described in detail below, hormone treatments produce some side effects. It is possible that your physician will recommend medications to help with these side effects. For women with vaginal dryness and/or dyspareunia (pain with intercourse) vaginal moisturizers and lubricants may be used. If these do not help the symptoms, local vaginal estrogens may be considered. If you have troublesome hot flushes your doctor might recommend a serotonin reuptake inhibitor medication. Because any of the treatments in this study may increase the risk of osteoporosis, adequate calcium intake or supplements and weight bearing exercise may be recommended for women on this trial. Women who have evidence of bone density loss (osteoporosis) may be recommended to have specific treatments for osteoporosis, such as alendronate (Fosamax).

RISKS AND DISCOMFORTS

While on the study, you are at risk for side effects, as discussed below. You should discuss these with your doctor. There may also be other side effects that we cannot predict. Other drugs may be given to make some of these side effects less serious and uncomfortable. Many side effects go away shortly after the drugs are stopped, but in some cases side effects can be serious, long lasting or permanent. There may also be unexpected risks (risks not known about).

Triptorelin or goserelin injections (GnRH analogue):
The most common side effects include the usual symptoms experienced during menopause. These side effects are hot flushes, stopping of menstrual periods, inability to have children, decrease in sex drive, and vaginal dryness and/or dyspareunia (painful intercourse). Infertility and other menopausal side effects may be reversible after ceasing the injections. Less frequent side effects are headache, tiredness, mood changes, sleep disturbance, nausea, back or joint pain, local irritation where the shots are given and slight rise in cholesterol. Loss of bone mineral density (osteoporosis) may occur and may lead to broken bones. Rare side effects include skin rash, allergic reactions, changes in blood pressure and elevated liver blood tests. Anaphylactic shock, a very severe allergic reaction that can cause death, is very rare but has occurred.

Surgery to remove the ovaries (oophorectomy):
The most common side effects are those of menopause including hot flushes, stopping of menstrual periods, inability to have children, decrease in sex drive, and vaginal dryness and/or dyspareunia (painful intercourse). Less frequent side effects are headache, tiredness, mood changes, sleep disturbance, nausea, back or joint pain, and slight rise in cholesterol. Loss of bone mineral density (osteoporosis) may occur and may lead to broken bones. Rare side effects include complications of the anesthesia or surgery itself, such as a wound infection. These will be described in more detail in a separate surgery consent.

Radiation to the ovaries:
The most common side effects are those of menopause including hot flushes, stopping of menstrual periods, inability to have children, decrease in sex drive, and vaginal dryness and/or dyspareunia (painful intercourse). Less frequent side effects are headache, tiredness, mood changes, sleep disturbance, nausea, back or joint pain, and slight rise in cholesterol. Loss of bone mineral density (osteoporosis) may occur and may lead to broken bones. The radiation might result in nausea or tiredness.

Tamoxifen:
The most common side effects are hot flushes, night sweating, vaginal discharge or dryness, irregular periods, vulvar itching and nausea. Tamoxifen may be associated with loss of bone mineral density in pre-menopausal women while it decreases bone mineral density loss in the menopausal state. Rare side effects of tamoxifen include retaining fluid, skin rash, and hair thinning. An infrequent side effect is abnormal occurrence of thromboembolic events. A blood clot in the leg can cause serious problems, including death, if it travels to the lungs. If you have had a history of thromboembolic events you might not be suitable to take part in this study. Women taking tamoxifen may be at a slightly higher risk for getting cataracts or rarely other eye problems. Tamoxifen can raise sensitivity to blood thinners such as coumadin.

Tamoxifen may cause changes in the lining of the uterus (endometrium). In addition, for every 1000 patients who take tamoxifen each year, 1-2 patients have developed cancer of the uterine lining (endometrial cancer), and even fewer have developed a cancer of the uterine muscle (uterine sarcoma). There may be also an increased risk of polyps and hyperplasia. In women receiving ovarian function suppression any vaginal bleeding should be reported to your doctor. In the event of abnormal vaginal bleeding or pelvic pain, you should have a gynecological (female) examination because of the increased risk of uterine cancer in women receiving tamoxifen.

Exemestane:
The most common side effects are hot flushes, nausea, increased sweating, fatigue, hair thinning, dizziness and skin rash. Exemestane may result in loss of bone mineral density (which can lead to broken bones).

Reproductive risks (all treatments):
Treatment under this study may involve unforeseeable risks to an unborn child if a woman should become pregnant during the course of this study treatment. In general, if your ovaries are suppressed, you will not be able to become pregnant, but you cannot be certain about that. For this reason, women are advised to use effective non-hormonal contraception during participation in this study. Hormonal contraception of any type is not allowed while on this study. You should not breast feed while taking study treatment. You should not participate in this study if you are pregnant or wish to become pregnant within the next 5 years.

Your physician will be checking you closely to see if any of the side effects are occurring. Physical exam, routine blood tests and other tests (depending on the choice of therapy) will be done to monitor the effects of treatment.

Your doctor may prescribe medication to keep these side effects under control. Schedules and dosages may be also altered to reduce their frequency and intensity.

You should report any side effect or symptom that you experience to your physician. Moreover, it is important that you tell your physician about additional medication that you take during or after the treatment.

Your physician may also decide to stop the treatment early in case of thromboembolic events, vaginal bleeding, abnormal blood counts (white blood cells, red blood cells, platelets, neutrophils), impaired functioning of the kidneys or liver, severe gastrointestinal symptoms or any other serious toxicity.

This clinical research protocol has been approved by (*please insert name of local Ethical Committee that has approved the protocol*). This committee is responsible for making sure that research with patients is appropriate and that, in your community, the patient's rights and welfare are protected.

BENEFITS

The ultimate goal of conducting clinical research studies in breast cancer patients is to understand better the behavior of breast cancer and to find better ways of treatment. We hope that the treatment under this clinical research study will be of benefit to you and/or that it will help others, although we cannot guarantee this.

ALTERNATIVE TREATMENTS

Instead of being in this study, your doctor may recommend that you receive hormonal therapy with tamoxifen for 5 years or some other form of hormonal therapy not given as part of this study.

EXPENSES

You will receive no payment for taking part in this study. Exemestane and triptorelin will be supplied to you on this study free of charge if you are randomized to a treatment using one of those drugs. All other expenses, including the cost of tamoxifen, chemotherapy, surgery or radiation and routine standard examinations will be handled similarly as if you were receiving standard treatment and not participating in a clinical trial.

INSURANCE

IBCSG has a public and products liability insurance. All persons, acting on behalf of the named insured, are covered as additional insured. The scope of

coverage is comprehensive Swiss form. This insurance does not cover any liability resulting out of medical malpractice; especially the negligence in the application of the respective protocol and/or treatment of the patients is excluded.

CONFIDENTIALITY

Medical records of patients are maintained under strict confidentiality as required by law. Confidentiality will be maintained during and after your participation in the study. Data collected during the study will be stored and analyzed by computer. It will be stored for a prolonged period (over 15 years). If at any time you wish to withdraw from the study and have the data relating to your case destroyed, please notify the IBCSG directly or through your doctor by submitting a written statement. Data will be analyzed exclusively for the purposes of research in breast cancer. Neither your name nor anything that could identify you will be used in any reports or publications that result from this study. During their required reviews, representatives of IBCSG, the health authorities, the pharmaceutical company representatives or subcontractors (Pharmacia/Pfizer Oncology) and the local ethics committee may have access to medical records that contain your identity. This will be done only under the formal agreement that confidentiality will be respected in all cases.

COLLECTION OF BIOLOGICAL MATERIAL

If you participate in this study, it is planned that a sample of tissue obtained at the time of your surgery for breast cancer will be sent to a central laboratory or institute for pathology review, and at a later stage for use in research projects to investigate biologic properties of breast cancer. Samples may be collected and stored at the IBCSG Coordinating Center. The use of the material for research will be under the supervision of the Scientific Committee of the IBCSG and will be submitted to the appropriate Ethical Committees.

You may decide to grant advance authorization for possible future new studies on your stored tissue specimens, with the understanding that their confidential nature will be fully protected and that a prior approval of an appropriate ethics committee will be obtained. Alternatively, you will be asked to consent to any such future study. On the other hand, you have the right to refuse consent to storage and further research on your tissue specimens except for the needs of the present study.

There will be no advantage or disadvantage to you as a result of such studies, and you will not incur additional cost as a result of obtaining the above-mentioned samples.

VOLUNTARY PARTICIPATION/RIGHT TO REFUSE OR WITHDRAW

The choice to enter or not to enter this study is yours. You are in a position to make a decision if you understand what the doctor has explained and what you

have read about the research study and other possible forms of care. If you begin the study, you will have the right to withdraw at any time without giving any reason. This will not affect in any way your future medical assistance. If you should withdraw from study treatment, you will be offered other available care which suits your needs and medical condition. In this case, we request your agreement to periodically contact you or your treating physician to provide basic information about your medical status. If instead you chose to withdraw from both treatment and follow-up, you may be asked to have a last examination before you withdraw.

TERMINATION OF THE STUDY

You might stop receiving study treatment without your consent for the following reasons:

a) If your breast cancer recurs.

b) If the doctors treating you detect side effects that they consider dangerous.

c) If you refuse to have the treatments or follow-up examinations and tests needed to determine whether the treatment is safe and effective.

d) If you become pregnant.

e) If the early analyses of trial data show a significant potential benefit or harm for one of the three arms.

NEW INFORMATION ARISING FROM THIS STUDY

You have the right to be informed of the progress of the research study and of its final results. During the time that you are participating in the study, you will be informed of any new findings which might affect your willingness to continue.

CONTACT PERSONS

The physician in charge of this study is *(give name, telephone number of PI)*. If you need more information about this study before you decide to join, or at any other time, you may wish to contact him/her. In the event that you do decide to participate, he/she should also be called if there are severe side effects from the treatment.

PATIENT INFORMED CONSENT FOR CLINICAL RESEARCH

TITLE: 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

Tamoxifen vs.
Ovarian Function Suppression + Tamoxifen vs.
Ovarian Function Suppression + Exemestane

STATEMENT OF PHYSICIAN OBTAINING INFORMED CONSENT

I have fully explained this clinical research study to the patient _____. In my judgment, and that of the patient, there was sufficient access to information, including risks and benefits, to make an informed decision.

Collection of tissue sample: It is planned that a sample of tissue obtained at the time of your surgery for breast cancer will be sent to a central laboratory or institute for pathology review, and at a later stage for use in research projects to investigate biologic properties of breast cancer as described above. Please indicate your choice in regards to the use of the sample of your breast cancer:

☐ I grant advance authorization for possible future new studies on my stored tissue specimens, with the understanding that their confidential nature will be fully protected and that a prior approval of an appropriate ethics committee will be obtained.

☐ I would like to be asked to consent to any such future study.

☐ I refuse consent to storage and further research on my tissue specimens except for the needs of the present study.

DATE: _____

PHYSICIAN'S SIGNATURE: _____

PHYSICIAN'S NAME: _____

PATIENT'S STATEMENT

I have read the description of the clinical research study or have had it translated into language I understand. I have also talked it over with the doctor to my satisfaction. I understand that my participation is voluntary. I know enough about the purpose, methods, risks and benefits of the

research study to judge that I want to take part in it. I understand that I may freely stop being part of this study at any time. I have received a copy of this consent form and of the patient information sheet to keep for myself.
DATE: _____ [Date must be written by the patient]

PATIENT'S SIGNATURE: _____

PATIENT'S NAME: _____

PATIENT'S DATE OF BIRTH: _____

WITNESS' SIGNATURE (if applicable): _____

WITNESS' NAME (if applicable): _____

PLEASE KEEP A COPY OF THE SIGNED INFORMED CONSENT. DO NOT SEND THE SIGNED INFORMED CONSENT FORM TO THE IBCSG.

Patient ID number assigned at randomization _____

IBCSG Trials 24-02, 25-02, 26-02/BIG 2-02, 3-02, 4-02

Appendix II: NCI Common Toxicity Criteria, Version 2

[available from the internet at: http://ctep.info.nih.gov/reporting/ctc.html.**]**

IBCSG Trials 24-02, 25-02, 26-02/BIG 2-02, 3-02, 4-02 Appendix III: Guidelines for the Immunocytochemical Evaluation of Hormone Receptor Status and Quality Assurance

1 Tissue samples

Sections from a representative formalin-fixed paraffin-embedded block of the tumor should be immunostained. Immunostaining of frozen tissue samples is not recommended.

Ideally, the blocks should be taken from the periphery of the tumor and include a small component of nonneoplastic breast tissue (to serve as an internal control for immunostaining).
The choice of the block best suitable for the immunocytochemical investigation should also be based on the following characteristics:

- Be representative of the invasive component of the tumor (even in cases with extensive or predominant intraductal component) and of the dominant histologic type of the tumor (in case of mixed carcinomas).
- Good preservation of the tissue morphology (avoid use of the permanent paraffin block of previously frozen tissue for intraoperative diagnosis or other purposes).
- Lack of extensive necrosis or fibrosis.

In case of *multifocal or multicentric tumors*, only one block needs to be immunostained.

2 Immunocytochemical staining

Several different monoclonal antibodies to estrogen and progesterone receptors are commercially available and are suitable for immunostaining of formalin-fixed paraffin-embedded tissue sections with consistent results.

It is recommended to pretreat the tissue sections with an antigen retrieval solution (e.g. citrate buffer) under microwave irradiation or other suitable heating devices (pressure cooker, autoclave, etc.), according to the expertise and the facilities of the different laboratories.

Different detection systems may be used according to the laboratory routine, based on peroxidase or alkaline phosphatase as reporter molecules. Immunofluorescence techniques are not recommended.

3 Evaluation of the results

It is recommended to evaluate the results according to the following procedure:

3.1 Check for expected immunostaining of nonneoplastic breast tissue:

- Intense nuclear staining of at least a minor percentage of luminal epithelial non-myoepithelial cells, and
- Lack of immunoreactivity of stromal and inflammatory (if any) cells

3.2 Evaluate the staining pattern of the neoplastic component at low/intermediate magnification (100-250x), taking into account any significant heterogeneity of staining in different parts of the invasive tumor.

Do not consider staining of the intraductal (or in situ) component.

3.3 At higher magnification (HPF=400x), check for a definitely nuclear localization of the immunostaining:

Do not consider as specific any membrane or cytoplasmic staining. This unspecific staining may appear on occasion (especially when apocrine or squamous metaplasia is present) and it does not interfere with the specific nuclear staining of the hormone-responsive neoplastic cells.

3.4 In case of tumors with **homogeneous** staining throughout, randomly select at least 10 HPFs (comprising a minimum of 2,000 invasive tumor cells) and count the number of cells showing nuclear immunostaining (irrespective of the staining intensity) over the total number of neoplastic cells.

Record the results as an overall percentage of cells showing nuclear immunostaining on the IBCSG Hormone Receptor Form F.

3.5 In case of tumors with significant staining ***heterogeneity***, select the 10 HPFs in order to mirror the degree of staining heterogeneity. For example, if only 20% of the invasive tumor area shows diffuse nuclear staining and the remaining tumor has only occasional (or none) immunoreactive cells, count only 2 HPFs in the former area and 8 HPFs in the latter.

3.6 For many IBCSG trials hormone receptor positive is defined as a value of 10% or higher immunoreactive neoplastic cells. Accordingly, ***if your evaluation of a given case is 10%*** or very close to this value, ***repeat*** the assessment of the results at least once on additional 10 HPFs, in order to check for consistency.

4 Quality assurance and external quality assessment

Quality assurance is essential in clinical laboratories for the provision of precise and accurate analyzes to support optimal patient care and to monitor participant competence in clinical trials. Quality assurance improves test reliability minimizing variability arising from biological or analytical sources, inherent in all quantitative measurements of qualitative examinations.

Overall, quality assurance seeks to guarantee the right result from the right test, at the right time, on the right specimen from the right patient, interpreted using the right reference data. There are three main components:

Quality Assurance (QA) encompasses all measures taken to ensure the reliability of investigations, starting from test selection, through obtaining a satisfactory sample from the right patient, analyzing it and recording the result promptly and correctly, to appropriate interpretation and reporting to the appropriate clinician for action, with all procedures being documented for reference.

Internal Quality Control (IQC) assesses, in real time, whether the performance of an individual laboratory or testing site is sufficiently similar to the previous performance for results to be used; it controls reproducibility or precision, and facilitates continuity of patient care over time. Most IQC procedures employ analysis of a control material and compare the results with predetermined limits of acceptability - unsatisfactory sets of results may thereby be suppressed.

External Quality Assessment (EQA). QA and IQC are systems that look within a particular testing site. EQA by contrast looks at differences among different sites testing the same analyte, so there can be continuity of testing over geography. This usually involves the analysis of identical specimens at many laboratories, and the comparison of results with those of other sites and a "correct" answer; the process is necessarily retrospective. The overriding need is for comparability of results, which requires good IQC practices and the complementary discipline of EQA.

4.1 External quality assessment

All IBCSG participating laboratories should participate in an external quality assessment program. One such program is the UK NEQAS, which provides a network of educational schemes unmatched in its comprehensiveness and quality throughout the world. To enroll in this program, contact Barry Gusterson at the Central Pathology Office (tel: +44 141 211 2233, fax: +44 141 337 2494, email: bag5f@clinmed.gla.ac.uk).

While IQC controls the precision of investigations, EQA should be providing an assessment of their accuracy (lack of bias) with respect to other test sites. This is done periodically and retrospectively, hence use of the term "assessment" rather than "control".

Though individual laboratory performance is frequently the main consideration, EQA also provides assessment of:

- *the overall standard of performance (state of the art)*
- *the relative performance of analytical procedures (method principle, reagents, instruments)*
- *the specimens distributed*

These are important in that EQA can provide information through pilot surveys and schemes, on intra-laboratory concordance and on whether establishing a regular EQA scheme is likely to help stimulate any needed improvement. Similarly, EQA may indicate analytical procedures showing excellent performance characteristics which can be recommended, and also identify unsatisfactory procedures which should be discouraged. The assessment of materials provides a continuing check on the reliability of the scheme and its specimens.

Experience has indicated a number of fundamental criteria required for effective EQA design. EQA can only document the need for, stimulate and monitor improvement: the improvements themselves come from effective quality assurance and IQC procedures within the individual participating laboratories.

These criteria are:

- ***Sufficient recent data, achieved through:***
  - *frequent distributions*
  - *rapid feedback of initial performance information following analysis*
- ***Effective communication of performance data, through:***
  - *structured, informative and intelligible reports*
  - *a cumulative scoring system*
- ***An appropriate basis for assessment, including:***
  - *stable, homogeneous specimens which where practicable resemble clinical specimens*
  - *reliable valid target values*

Though the evidence is necessarily circumstantial, schemes satisfying these criteria are associated with improved between-laboratory comparability, both overall and in individual participating laboratories. Full and regular participation in appropriate external quality assessment schemes is therefore established as a necessary and integral part of the rational provision of reliable clinical laboratory services. **All of the above applies to measurements in the setting of clinical trials and in particular when a measurement is used as an entry criterion.**

IBCSG Trials 24-02, 25-02, 26-02/BIG Trials 2-02, 3-02, 4-02 Appendix IV: Pathology Guidelines

1 Pathologists and central review

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 is responsible for ensuring that the Pathology Form is compete and accurate, and that the pathology materials are properly collected and submitted. The central review pathologist will review the submitted specimens and complete the Central Pathology Review (CPR) form.

2 Collecting and submitting materials

The following items are required for all randomized patients:

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

The tissue blocks may be returned to the participating center upon request.

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

2.1 Pathology Form (P)

2.1.1 Maximum diameter and ductal carcinoma *in situ*

All lesions should be measured in the fresh or fixed state and on the histological preparation. If the two measurements are discrepant, that obtained from histological examination should be recorded where tumors are small enough to be visualized in cross-section. This may give a small underestimation in the size due to shrinkage of the tissue in processing. It is considered, however, that the slight but consistent underestimation in the size of all tumors is preferable to the larger and less predictable errors that may result from measuring poorly delineated tumors macroscopically. Clearly, sufficient blocks should be taken from the periphery of larger tumors to allow accurate estimates of their size to be made from combined histological and macroscopic examination. The largest dimension should be recorded to the nearest millimeter.

With the increasing use of conservation surgery for breast cancer, the identification of histological features associated with an increased risk of local recurrence is clearly important. The Boston group defines extensive intraductal carcinoma (EIC) as that comprising more than 25% of the main invasive tumor mass extending beyond it into surrounding breast tissue or a tumor which shows foci of invasion, but is predominantly of intraduct type. A recent EORTC consensus meeting concluded that "the principal risk factor for local relapse after breast conserving treatment is large residual burden, and the main source of this burden is an extensive *in situ* component which is found adjacent to 10-15% of all invasive breast carcinomas" (1). Holland reported locally recurrent carcinoma after a maximum of 7 years (mean 3.7) at a rate of 13% with EIC and 3.7% without (2). A significant proportion of such cases relapse as invasive carcinoma. These findings suggest that part of the routine histological assessment of breast tumors should include information about the nature of the intraduct component.

It is recommended that pathologists take blocks from macroscopically normal tissue between an excised tumor and excision margins in all three planes of section.

For invasive carcinomas, only the invasive component needs to be recorded. The largest dimension, to the nearest millimeter, is recorded in each case. Foci of lymphatic and blood vessel invasion are not included in the whole tumor measurement.

2.1.2 Histological type, please attempt to place the type in one of the designated categories.

2.1.3 Grade

Grading should be according to the Bloom, Richardson, Elston (B.R.E.) method (3) which has been shown to be more accurate for statistical analysis. Please try to use it. The following instructions are provided to assist you. Please refer to the original publication and to the NHSBCS booklet (4) for detailed examples. As histopathologists often have difficulties with the grading scheme of Bloom and Richardson; the modified Elston version only includes true mitotic figures and not "hyperchromatic figures".

The method has been recently adopted by the Royal College of Pathologists Working Group for the National Health Service Screening Programme in the UK. The use of this grading system is also supported by D Page (Vanderbilt University, US) as the best system for grading. It is also being supported by the European Union which is funding a teaching CD for pathologists which will incorporate this grading scheme as the standard. The method involves assessment of three components of tumor morphology; tubule formation, nuclear pleomorphism and frequency of mitoses. We ask you to enter each of the three scores individually and then add them together for a total score.

Tubule Formation
Score

1. majority of tumor (greater than 75%)
2. moderate amount (10-75%)
3. little or none (less than 10%)

Nuclear pleomorphism
Score

1. nuclei small, with little increase in size in comparison with normal breast epithelial cells, regular outlines, uniform nuclear chromatic, little variation in size.
2. cells larger than normal with open vesicular nuclei, visible nucleoli and moderate variability in both size and shape.
3. vesicular nuclei, often with prominent nucleoli, exhibiting marked variation in size and shape, occasionally with very large and bizarre forms.

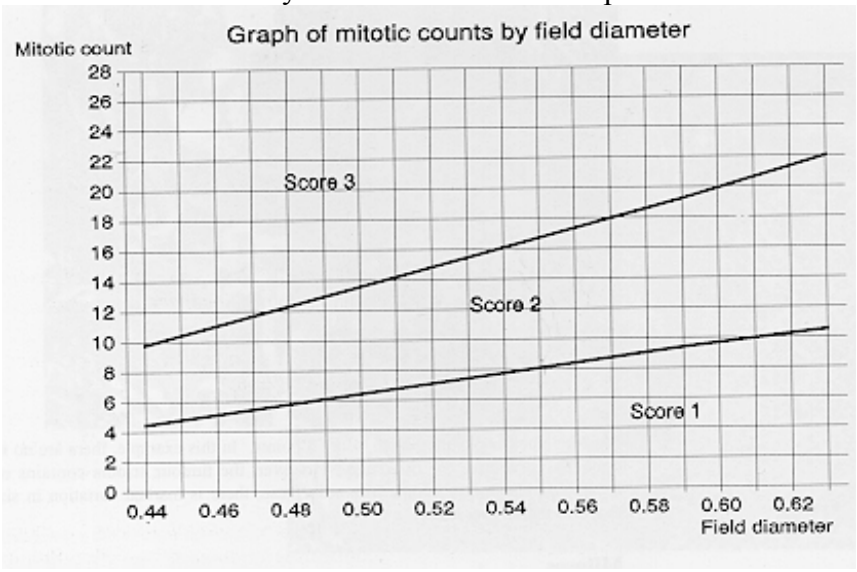
Mitoses
The score depends on the number of mitoses per 10 high power fields assessed at the tumor periphery. The size of a high power field is very variable and hence it is necessary to standardize the mitotic count using the graph in the figure. In order to determine the mitotic count for an individual microscope, the following procedure should be adopted:

1. measure the field diameter of the microscope with a graticule.
2. plot this value on the horizontal axis of the graph.
3. draw a vertical line at this value.
4. read off the value **a** on the vertical axis where the line intersects the lower bold line.
5. read off the value **b** on the vertical axis where the line intersects the upper bold line.
6. the count is then:

Score	Count
1	0 to **a**
2	between **a**+1 and **b**
3	>**b**

For example, for a field diameter of 0.48 **a**=6, **b**=12 and therefore
Score 1 = 0-6 mitoses / 10hpf
Score 2 = 7-12 mitoses / 10hpf
Score 3 = >12 mitoses / 10hpf

This needs to be done only once for each microscope.



Overall Grade

The scores for tubule formation, nuclear pleomorphism and mitoses are then added together and assigned to grades as below:

Grade 1 = score 3-5
Grade 2 = score 6-7
Grade 3 = score 8-9

It is recommended that grading is not restricted to invasive carcinoma NOS but is undertaken on all histological subtypes. There are two major reasons for this recommendation:

1. There are occasionally problems in deciding whether to classify a tumor as NST or some other type.
2. There may be significant variation within certain subtypes, e.g. invasive lobular carcinoma.

It must be clearly stated if a grading system other than that described above is used.
Occasionally, if there is insufficient material or poor fixation, it may not be possible to use the B.R.E. method accurately. In those cases:

Grade 1 -- well differentiated
Grade 2 -- for moderately differentiated
Grade 3 -- for poorly differentiated

is acceptable. Note this simple grading does not correlate with the Bloom, Richardson, Elston grade. If you have difficulty in using the Elston grading scheme, which is now being applied in many centers, please send details of the difficulty with examples and Central Review will advise.

IF WE DO NOT USE UNIFORM CRITERIA, THE RESULTS ARE MEANINGLESS.

Grading Ductal Carcinoma *in situ*
Ductal carcinoma *in situ* (DCIS) is defined as a proliferation of epithelial cells with cytological features of malignancy within parenchymal structures of the breast and is distinguished from invasive carcinoma by the absence of stromal invasion across the basement membrane.

DCIS varies in cell type, growth pattern and extent of disease and may thus represent a group or spectrum of related *in situ* neoplastic processes. Classification has traditionally been according to growth pattern but has been carried out with little enthusiasm given a perceived lack of clinical relevance. More recently, evidence has emerged that lesions composed of cells of high nuclear grade are more aggressive. There is currently no generally accepted method of classifying DCIS but distinction between common histological subtypes is of value for correlating pathological and radiological appearances, improving diagnostic consistency, assessing the likelihood of invasion and determining the probability of recurrence after local excision. Despite the name, most DCIS is generally considered to arise from the terminal duct lobular units. The nuclear grading system adopted below is derived from that employed by Holland *et. al.* (5)

High Nuclear Grade DCIS

This is composed of cells with pleomorphic, irregularly-spaced and usually large nuclei exhibiting marked variation in size, irregular nuclear contours, coarse chromatin and prominent nucleoli. Mitoses are frequently present and abnormal forms may be seen.

High nuclear grade DCIS may exhibit several different growth patterns. It is often *solid* with central, *comedo*-type necrosis which frequently contains deposits of amorphous calcification. This is the easiest pattern to recognize. Sometimes a *solid* proliferation of malignant cells fills the duct without necrosis but this is relatively rare and is usually confined to nipple ducts in cases presenting with Paget's disease. High nuclear grade DCIS may also exhibit *micropapillary* and *cribriform* patterns frequently associated with central comedo-like necrosis. Unlike low nuclear grade DCIS, there is rarely any polarization of cells covering the micropapillae lining the intercellular spaces.

Low Nuclear Grade DCIS

This is composed of monomorphic, evenly-spaced cells with roughly spherical, centrally-placed nuclei and inconspicuous nucleoli. The nuclei are usually, but not invariably, small. Mitoses are few and there is rarely individual cell necrosis.

The cells are generally arranged in *micropapillary* and *cribriform* patterns, which are frequently present within the same lesion, although the latter is more common and tends to predominate. There is usually polarization of cells covering the micropapillae or lining the intercellular lumina. Less frequently, low nuclear grade DCIS has *solid* growth pattern. When terminal duct lobular units are involved, the process can be very difficult to distinguish from lobular carcinoma *in situ*. Features in favor of DCIS are greater cellular cohesion and lack of intracytoplasmic lumina. Occasionally, however, there may be combination of both processes.

Intermediate Nuclear Grade DCIS

Some cases of DCIS cannot be assigned easily to the high or low nuclear grade categories. The nuclei show mild to moderate pleomorphism which is less than that seen in high grade DCIS but they lack the monotony of the small cell type. The nucleo cytoplasmic ratio is often high and one or two nucleoli may be identified.

The growth pattern may be *solid, cribriform, or micropapillary* and the cells usually exhibit some degree of polarization covering papillary processes or lining intercellular lumina although this is not as marked as in low nuclear grade DCIS.

Mixed Types

A proportion of cases of DCIS exhibit features of more than one histological sub-type. One of the advantages of classifying DCIS according to nuclear grade is that, although variations of growth pattern are frequent, there is usually a dominant cell type and the lesion is fairly easily classified into one of the above main groups.

Rarely, cells of different nuclear grade may be seen within a single-lesion. This should be recorded *but the case should be classified according to the highest nuclear grade observed*.

2.1.4 Excision margins

The distance from the nearest resection margin should be recorded and checked from the histological sections. Other margins can be reported if required. This normally refers to the infiltrative component but, if associated ductal carcinoma *in situ* extends nearer to the margin than the infiltrative component, then enter its distance from the margin and state in the appropriate section in the P form.

There are many ways to mark the planes of surgical excision of biopsies. No single method is ideal, each having advantages and disadvantages. Practical advice and comments are contained in reviews listed at the end of this appendix (6,7,8). These should be consulted to determine the method most appropriate to local circumstances. Some biopsies are submitted fresh, others in the fixed state. The requirement for fresh tissues of material for biochemical analysis may be adversely affected by the marking paints.

India ink is widely used but is slow to dry and thus has the tendency to penetrate the planes of the tissue close to the site of its application. In consequence, some regard it as an unreliable marker of the external plane of surgical excision. Nevertheless, preliminary drying of the specimen or coating with alcohol can obviate this problem. Non-aqueous solvents like acetone and ethanol have been tried and allow the ink to dry more quickly. The specimen should not, of course, be sliced until the ink is dry.

Another recommended method is to coat the specimen with warm gelatin. Instead of relying upon the evaporation of a solvent, the use of gelatin depends on the setting of the gel. This is facilitated by preliminary chilling of the tissue. Fixation of the coated specimen apparently increases polymerization in the gel, thus rendering it still more durable. The well-known typists' aid "Tippex" has also been tried but, unfortunately, is densely radio-opaque on account of its titanium content. The dye Alcian blue and inorganic pigments are fast drying and the latter can be used for differential color marking. Commercially available pigment markers have been recommended which also have the advantage of being able to identify different planes for clearance.

The evaluation of surgical margins of biopsies is to be encouraged given the provisions stated above. Except in cases where the margin passes directly through a focus of cancer, the findings should, however, be interpreted with circumspection. The histopathology report should comment on the closest margin giving distance in mm, and specifying whether any involvement is by invasive or non-invasive cancer. The information should be related to orientation markers if given.

2.1.5 Vessel invasion includes both lymphatic and blood vessels.
The presence of unequivocal tumor in vessel spaces should be recorded. If there is doubt about diagnosing vessel invasion, please choose the **no** box. The difficulty in identifying small vessels as blood or lymphatic precludes accurate recording of their type and specification of lymphatic or venous invasion is not required. Ideally, a clear rim of endothelium should be identified around the tumor before vessel invasion is recorded. The use of immunostaining for endothelial markers may be helpful in confirming vessel invasion in difficult cases but is not recommended on a routine basis. Morphological features which may be helpful when diagnosing vessel invasion are:

1. clumps of tumor in spaces outside the main tumor mass are more likely to indicate vessel invasion.
2. nests of tumor separated from the stroma by shrinkage artifact usually conform better to the shape of the space in which they lie.
3. the proximity of larger veins and arteries helps in the diagnosis of lymphatic invasion.
4. the presence within the space of erythrocytes and/or thrombus.

2.1.6 HER2/NEU Record the HER2/neu expression.

2.1.7 Markers Record if any of the markers were done. If sub-studies of a given marker are planned cases can be identified.

2.1.8 Axillary nodal involvement All lymph nodes should be examined histologically. The use of immunohistology is most appropriate in cases where there is doubt about the presence of small metastases. The clinical relevance of metastases detected solely by this means remains controversial.

2.1.9 Sentinel node biopsy information should be recorded if such a biopsy was performed. The sentinel node must be examined serially and completely in frozen sections or after formalin fixation and paraffin embedding. The node must be bisected along its major axis (or sliced at 2-3 mm intervals if thicker than 0.7-0.8 cm) and both moieties (or all slices) must be embedded. Special attention must be paid to preserve the integrity of the node capsule. Serial sections must be cut at 50-150 micron intervals until the complete examination of the node. Please consider that approximately 10% of the micrometastases seen with 50-micron cutting levels will be missed with cutting levels of 150-micron.

Immunochemistry for cytokeratins may help in the identification of micrometastases, but this is not considered mandatory. It is suggested to perform immunocytochemical stainings only to ascertain the nature of suspicious cells seen in H&E sections. The assessment of the size of the sentinel node metastases is correlated with the likelihood of additional metastases to nonsentinel axillary nodes. It is recommended to measure the largest size of the metastases in the plane of the sections and to calculate their thickness according to the number of contiguous sections involved and to the cutting intervals (i.e., if a metastasis is present in three contiguous 5-micron sections at 100-micron interval, calculate the thickness adding the 100 micron before the first involved section, the 200 micron between the 3 involved section, the 100 micron after the last involved section and the 15 micron representing the thickness of the 3 sections = 100+200+100+15=415 micron. Record on the P form the maximum size, which may be either the largest diameter in the plane of the sections or the calculated thickness of the metastases.

2.2 <u>The Pathology Report</u> should be a copy of all relevant clinic/hospital pathology reports. The patient's initials, specimen number, and randomization number should be clearly written on the report. The Report should be submitted to the Coordinating Center.

2.3 <u>Pathologic material</u> Two paraffin blocks, one tumor and one normal tissue, and representative H & E slides must be submitted to the Coordinating Center. All material must be labeled with the patient's randomization number.

Institutions will submit paraffin blocks to the Coordinating Center, who will forward them to the Central Pathology Laboratory. Whenever indicated, the Central Lab will use the tissue array technology (see below) to obtain a small amount of material from the block. The tissue array will be logged and stored, and the paraffin blocks will be returned to the participating center upon request. The Group anticipates that returning the blocks to the institutions within a short time will increase the feasibility of full compliance with tissue collection.

Tissue array technology was designed as a method for analyzing changes involved in the development and progression of cancers at both the molecular and the protein level. This

technique is unique in its ability to simultaneously analyze large numbers of human tumors with minimal consumption of rare archival specimens. Tissue arrays are made up of 0.6mm cores from tumor biopsies of different tumor blocks, precisely arrayed in a single paraffin block (9).

Advantages of tissue arrays have been demonstrated in two recent publications (10, 11) and include:

- Negligible damage to donor blocks
- 600 different tumors can be arrayed in a single block
- Simultaneous screening of large number of biopsies
- In clinical trials, simultaneous testing and targeting of new diagnostic or prognostic markers
- Significant reduction in staining and microscopy time
- Reduction in the consumption of reagents.

Tissue arrays are suitable for use in IHC, FISH, PCR and RT-PCR, and cores can be used for DNA and RNA extraction. It is estimated that the amount of DNA extracted from a 0.6mm core is sufficient for 50 PCR runs.

2.4 Submitting material

Fax the Pathology (P) Form and the Pathology Report to an IBCSG DataFax number. Full instructions on submitting forms will be distributed to each center and are available on the IBCSG website (www.ibcsg.org). The website also lists fax numbers available for faxing reports and forms.

Slides and blocks should be mailed to:
IBCSG Coordinating Center
Effingerstrasse 40
CH-3008 BERN, Switzerland

All reports, slides, and blocks must be marked with the IBCSG patient ID number. Slides should be sent in customized slide boxes. They should be packed with tissue paper to prevent any movement. If slides move around when the box is shaken, they have not been packed sufficiently.

3 Fixative

3.1 Standard procedure

Aqueous solution of formaldehyde 4% (10% formalin) isotonic and neutral.

Adequate dissection of the specimen must be accomplished before fixation, as this fixative penetrates slowly (1 mm/hour).

NB: For those using immunohistochemistry for ER and/or PgR determination, please cut tumor into 2 mm slices and fix immediately after surgery.

Whenever possible, at least one section of the primary tumor should be allowed to fix in a large volume of formalin for at least 24 hours before processing.

3.2 Frozen tissue

Whenever possible a sample of primary tumor (0.5gm) and a sample of non-tumorous breast should be snap frozen without prior fixation and stored at -70˚ or in liquid nitrogen.

4 Sampling

4.1 Primary tumor

Sufficient blocks should be taken to enable complete histological assessment. Ideally one should include the maximum tumor dimension.

At least one block of grossly non-cancerous breast tissue should be submitted from each quadrant in each case and its source designated in the protocol.

Other lesions found in any of the breast quadrants should be noted in the protocol and submitted for microscopic examination with appropriate identification.

At least one central section of the nipple should be submitted. If vascular invasion is present, a representative slide should be submitted.

4.2 Lymph nodes

Care should be taken during excision and handling of lymph nodes, as compression of tissue during the procedure can result in distortion. Forceps should be applied only to the surrounding tissue and not to the node. The node should be removed intact rather than in fragments. Ideally, the node should be sectioned in the mid-line of long axis from cortex to medulla.

5 Embedding and sectioning

Embed in paraffin or paraplast.

6 Staining and mounting

Routine staining using hematoxilin eosin method is the accepted standard. Routine mounting on glass slides covered with glass slips is the accepted standard.

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Acknowledgement

We acknowledge the use of text and figures from Pathology Reporting in Breast Cancer Screening (Second Edition) (4).

APPENDIX V
QUALITY-OF-LIFE PROTOCOL
Suppression of Ovarian Function Trial (SOFT)
IBCSG Trial 24-02; BIG 2-02

1. Introduction

Breast cancer patients receiving adjuvant endocrine treatment are faced with menopausal symptoms [1, 2]. These symptoms have an important impact on patients' daily life, not only on physical but also on emotional well-being [3,4]. For example, vasomotor symptoms are frequent [5, 6] and may be associated with sleeping difficulties and feelings of depression [7]. Quality-of-life (QL) evaluation including menopausal symptoms is therefore an essential objective in the IBCSG Trial 24-02.

The two objectives of QL assessment in this protocol are: (i) to compare treatments in regard to QL; (ii) to compare QL in this trial to that in other adjuvant breast cancer trials.

These objectives will be addressed using the same basic approach to QL assessment that the IBCSG has used since 1986 [8, 9]. It has been shown to be feasible for international breast cancer clinical trials [10, 11]. Previous methodological and clinical investigations were mainly related to chemo- and chemo-endocrine effects. An example relevant to the IBCSG Trial 24-02 is the analysis of the indicator for *hot flushes* in node-negative postmenopausal patients with operable breast cancer (IBCSG Trial IX) [9]. This indicator showed a high discriminative capacity between patients on chemotherapy and those on tamoxifen within the first three months.

Using the same approach to QL assessment will allow us to make comparisons across IBCSG trials, using the extensive QL database, which will be available from other trials.

2. Objectives

QL will be described in regard to intermediate- and long-term sequelae of treatment and disease, and the treatments will be compared in regard to QL. Specifically, the hypotheses to be investigated are

2.1. Primary hypotheses

2.1.1 Patients receiving tamoxifen plus ovarian function suppression will report more menopausal symptoms than those with tamoxifen only (see section 8.).

2.1.2 Patients receiving tamoxifen plus ovarian function suppression will report more sexual impairment than those with tamoxifen only (see section 8.).

2.1.3 Patients receiving exemestane plus ovarian function suppression will report more menopausal symptoms than those with tamoxifen plus ovarian function suppression (see section 8.).

2.1.4 Patients receiving exemestane plus ovarian function suppression will report more sexual impairment than those with tamoxifen plus ovarian function suppression (see section 8.).

These hypotheses will be tested by comparing the treatment groups using serial measurements of QL indicators over time (see 5.1). The indicator for *hot flushes* included in the IBCSG QL Core Form is selected as primary endpoint for the first and third hypotheses. The indicator for *loss of sexual interest* included in the trial-specific QL module is selected as primary endpoint for the second and fourth hypotheses.

2.2. Secondary hypotheses

2.2.1 The differences between treatments will persist over the whole treatment period (see 8.).

2.2.2 Those patients who report more severe menopausal symptoms during the first 6 months on endocrine therapy will also report delayed adaptation in other QL indicators both during and beyond that time (see 8.).

Physical well-being, mood and coping will be used to describe patients' adaptation over time [10]. The findings of this trial will be compared to that in other IBCSG adjuvant breast cancer trials.

Further exploratory analyses will address (i) the relationships among the QL measures (e.g., the impact of menopausal symptoms on global QL indicators, especially on overall treatment burden, physical well-being, coping and mood); (ii) bio-psychosocial interactions (e.g., the impact of initial prognostic factors on QL) [12].

3. Patient Selection

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 will be determined at the activation of the trial for each participating cooperative group.

Recruitment of 1872 patients will maximize the opportunity to detect clinically relevant treatment effects on QL.

4. Study Design

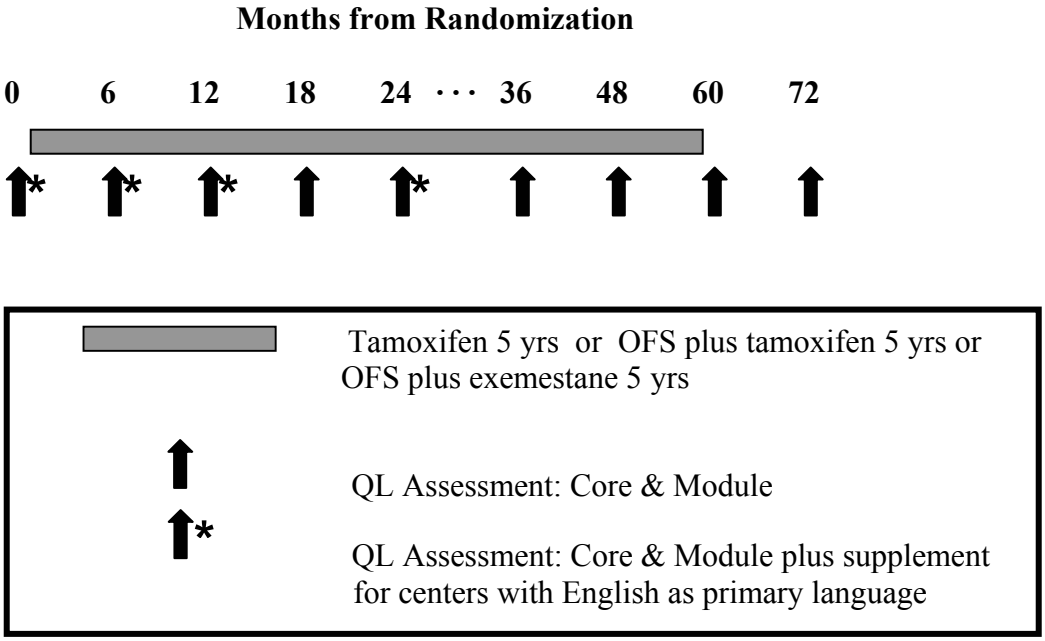
As in the other IBCSG trials with QL, a longitudinal design is used, including a baseline assessment, assessments to evaluate intermediate and long-term effects, and assessments following treatment failure to evaluate the impact of relapse. To the extent feasible, the assessment time schedule is compatible to that of the other trials to keep it as simple as possible and to allow comparisons across trials.

Patients are asked to complete a QL core form plus a trial-specific module

- at baseline, prior to randomization
- every 6 months during the first and second year,
- and annually in years 3 to 6.

All patients, regardless of disease status, are to be assessed on the same schedule. A detailed data collection schedule is displayed in *Figure 1*.

Figure 1: Quality of Life Assessment Time Points



To eliminate any differential anticipatory effects on baseline scores and to help insure compliance with the protocol requirements, a QL Core Form plus Module must be completed prior to randomization (i.e., it is an eligibility requirement for IBCSG participating centers).

5. Quality-of-Life Measures

5.1 Patient rated Quality of Life

The QL assessment consists of the *IBCSG QL Core Form* and a trial specific *module*.

The QL Core Form was developed in 1986 [8], and was subsequently revised for IBCSG Trials 10-93 through 14-93 [9], which started on May 1, 1993. The revised form is designed to address the endpoints in adjuvant trials more specifically while still keeping the questionnaire simple and short. It includes global linear analogue self-assessment (LASA) indicators for physical well-being, mood [13], coping (PACIS) [14], perceived social support and subjective health estimation (SHE) [15]. The indicators for physical well-being, mood and coping were confirmed to be responsive to cytotoxic side effects, mental distress and psychosocial dysfunction in patients with early breast cancer [16]. They are suitable to describe patients' adaptation over time. Validation studies are summarized elsewhere [9].

In addition, LASA indicators specific to symptoms of nausea and vomiting, tiredness, *hot flushes*, and restrictions in arm movement are included, covering possible QL effects of all of the treatment modalities involved in these trials (surgery, chemo-, endocrine and radiation therapy).

For the IBCSG Trial 24-02, a one-page module for endocrine symptoms will be used in addition to the QL Core form. Besides non-experimental studies, the selection of symptoms was based on two recent breast cancer prevention trials which compared the effects of tamoxifen with those of placebo [5, 6]. All symptoms are assessed in the LASA response format. In addition, one global indicator is included for overall treatment burden ("Overall, how much are you bothered by any treatment related difficulties?"). This indicator has been validated regarding side-effects of anti-emetic and cytotoxic therapies [17] and is expected to be similarly responsive to endocrine symptoms.

An expanded three-page IBCSG Trial 24-02 module will be used for participating centers having English as the primary language. The first page will be the same as the module completed at all participating centers in the study. The second and third page will contain additional questions from the Center for Epidemiologic Studies-Depression Scale (CES-D) [18] and the Medical Outcomes Study (MOS) sexual problems measures [19]. These questionnaires have been used frequently for US Intergroup studies. The CES-D and the MOS are included to provide cross-validation between responses to selected IBCSG core and module questions and these comprehensive measures. These questionnaires will also be used as common QL reference data for the IBCSG and CALGB trial. Their assessment is restricted to baseline, months 6, 12 and 24.

In clinical trials, the distinction between indicators of specific symptoms and global indicators sensitive to treatment as well as disease-related problems in the broadest sense is very useful. In the global indicators, the score reflects a patient's *subjective*, intuitive choice and weighting of different aspects, summarized in a single response. Specific disease and treatment-related indicators can be used to examine the changing impact of symptoms on overall measures over time and in different situations. This can be done within a treatment group (e.g., for patients receiving tamoxifen plus ovarian function suppression, how much of the variation in the coping measure can be explained by the major menopausal symptoms over the first year) or to explain differences in the global measures among treatment groups (e.g., does *hot flushes* explain differences in physical well-being among the randomized treatments at 12 months).

The conceptual basis of the IBCSG approach to QL assessment, along with a description of methodological issues, clinical findings and planned steps for further development, have been summarized elsewhere [9].

5.2 Sociodemographics and Co-morbidity

As in the other IBCSG QL trials, sociodemographic data and co-morbidity are part of the standard study documentation.

6. Timing Requirements, Data Collection and Local Data Management

6.1 Timing requirements

Assessment time points are determined by the interval from date of randomization, and coincide with the required clinical follow-up time points. The QL assessment time points are illustrated in Figure 1.

The schedule of QL assessment must be followed as closely as possible. The QL form has to be filled in always *prior to* diagnostic procedures. If exact timing is not possible, assessment should be done as close as possible to the required date.

For methodological reasons, the required schedule has to be followed exactly, with neither more nor fewer assessments. Shortly after randomization, the IBCSG operations office sends the local investigator a *schedule of the dates* of required QL assessments. This list should be put into each patient's chart to aid in the correct timing of the QL assessment.

6.2 Data Collection and Local Data Management

Within the first 6 years, every study patient is to fill in both the QL Core Form and the trial specific module at each scheduled assessment time point, as described in Figure 1; no form selection is acceptable.

If the patient does not complete the required QL Forms, then a Missing QL Assessment Form **must** be submitted for that assessment time point to provide the reason why the assessment was not completed.

The QL forms are to be filled in at the clinic. If the patient is being followed elsewhere, arrangements are to be made with the clinic or physician to have the patient fill in the forms as required. If, for administrative reasons, the form has not been presented to the patient, it may be filled in at home and mailed.

For the first assessment, the QL forms have to be explained to the patient, with particular emphasis on making sure the patient understands both LASA format (used in all questionnaires) and categorical response format (used only in supplemental questionnaires for centers with English as the primary language). For later assessments, the patient should be instructed to seek help only if she has problems in understanding any of the items in the form.

All questions on the QL Core Form and the QL Module should be answered. The forms should be checked after completion and, if necessary, the patients should be asked to fill in missing answers. Patients may wish to leave some questions unanswered if they make them feel very uncomfortable. They should be encouraged to answer all items, however, especially those concerning menopausal symptoms, as they represent a primary objective of the QL study.

Detailed instructions for the QL assessment are given in the *IBCSG QL Manual*. Copies are available from the IBCSG Coordinating Center in Bern.

7. Central Data Management

Computerized data quality control measures will be used to monitor the submission rates of the QL forms and the timing of assessment as required by the study protocol. Institutions will receive feedback on their performance and specific problems on a regular basis.

8. Statistical Considerations

8.1 Sample Size Calculations

This phase III randomized clinical trial is designed to compare differences in QL between patients who receive five years of tamoxifen and those who receive five years of ovarian function suppression (OFS) plus five years of tamoxifen. In addition, differences between OFS plus tamoxifen and OFS plus exemestane will be assessed. These two pairwise comparisons will each be assessed separately with no adjustment for multiple comparisons. According to investigator choice, patients can either receive no adjuvant chemotherapy or receive adjuvant chemotherapy and remain premenopausal and be randomized following completion of chemotherapy. The randomization is stratified according to chemotherapy use. QL will be described in regard to intermediate and long-term sequelae of treatment and disease. We will test the above hypotheses by comparing the treatment groups using serial measurements of QL indicators over time.

Many QL indicators are collected, but the indicators *hot flushes* and *loss of sexual interest* are selected to determine sample size. The indicator for *hot flushes* included in the IBCSG QL Core Form is the primary endpoint used to test whether patients receiving tamoxifen with ovarian function suppression will report more menopausal symptoms than those receiving tamoxifen alone. This measure will also be considered primary for the OFS plus tamoxifen versus OFS plus exemestane comparison. We will calculate the QL sample size to reflect both short and long term effects. First, to reflect the short-term effects we will base the QL sample size on the mean treatment difference of the change in *hot flush* scores from baseline to 6 months. Next, to reflect the long-term effects we will use the mean treatment difference of the change in *hot flush* scores from baseline to 24 months. Both sample size calculations were based on a two-sided 0.05 level test and respective standard deviations from IBCSG Trial IX were used to compute the 2 sample sizes.

To address the short-term effects, the common standard deviation, calculated from the pooled estimator of the variance of the change in *hot flush* scores from IBCSG Trial IX of Arm E (Tamoxifen) and Arm F (CMF -> Tamoxifen), was 35.1. 304 assessable patients per arm (608 total) are needed to achieve an 80% statistical power to detect a mean treatment difference in a change in *hot flush* score of 8 units on the original scale. In IBCSG Trial IX, 66% of the eligible patients filled out the indicator for *hot flushes* at baseline and 6 months post randomization. If we assume a similar compliance rate in Trial 24-02 we would need a total of 921 patients randomized to two-arms to detect an 8-unit difference in treatment means of the change in *hot flush* scores from baseline to 6 months with 80% power. Thus, 1382 patients are required for the three-arm trial.

Table 1 illustrates the total number of patients **enrolled in two arms** needed to detect a range of given treatment differences of the change in *hot flush* scores from baseline to 6 months with 80% power

Table 1

Δ*	Total Assessed	Total Needed Assuming 66% Compliance
10	390	591
9	480	727
8	608	921
7	792	1200

*****Mean treatment difference of the change in *hot flush* score from baseline to 6 month

To address the long-term effects, the pooled standard deviation from IBCSG Trial IX between the two treatment arms was 34.2. In order to detect an 8-unit mean treatment difference of the change in *hot flush* score from baseline to month 24 with 80% power we will need 288 assessable patients per treatment arm (576 total). Sixty percent of patients enrolled in IBCSG Trial IX responded to the *hot flush* indicator at baseline and at month 24. If we assume a 60% compliance rate in Trial 24-02, then we would need a total of 960 patients randomized to two-arms to detect an 8-unit mean treatment difference with 80% power. Thus, 1440 patients are required for the three-arm trial.

Table 2 shows the total number of patients **enrolled in two arms** needed to detect a range of given treatment differences of the change in *hot flush* scores from baseline to month 24 with 80% power.

Table 2

Δ*	Total Assessed	Total Needed Assuming 60% Compliance
10	370	617
9	456	760
8	576	960
7	752	1253

*****Mean treatment difference of the change in *hot flush* score from baseline to 24 months

The indicator for *loss of sexual interest* included in the trial-specific QL Module is the primary endpoint for testing whether patients receiving tamoxifen plus ovarian function suppression will report more sexual impairment than those receiving tamoxifen alone. This endpoint will also be assessed for the OFS plus tamoxifen versus OFS plus exemestane comparison. The use of the QL Module for IBCSG Trial 15-95 was the first time an indicator for the *loss of sexual interest* was collected in an IBCSG trial. Trial 15-95 had two treatment arms: Arm A (standard dose EC/AC x 4 -> CMFx3 -> Tamoxifen) and Arm B (high dose ECx3 -> Tamoxifen). With regard to addressing the short-term effects, these QL data have matured and a common standard

deviation of 35.6 was observed from calculating the mean treatment difference of the change in *loss of sexual interest* from baseline to 6 months. To detect a mean treatment difference of 8 units on the original scale with 80% power, 312 assessable patients are required in each group (624 total).

In Trial 15-95, 50% of the patients answered the *loss of sexual interest* question at baseline and at month 6. Assuming a 50% compliance rate in Trial 24-02, we would need a total of 1248 patients randomized in two arms to detect a mean difference of 8 units with 80% power. Thus, 1872 patients are required for the three-arm trial.

Table 3 shows the total number of patients **enrolled in two arms** needed to detect a given range of treatment differences with 80% power.

Table 3

Δ*	**Total Assessed**	**Total Needed Assuming 50% Compliance**
10	400	800
9	494	988
8	624	1248
7	814	1628

*****Mean treatment difference of the change in *loss of sexual interest* score from baseline to 6 months

Although IBCSG 24-02 and IBCSG 25-02 include slightly different patient populations and treatment programs, both studies include comparisons of OFS plus tamoxifen versus OFS plus exemestane. We, therefore, intend to perform an analysis of the primary hypotheses of this QL study combining the information from both trials. This will enhance the power to detect QL differences between the two treatment groups.

8.2 Statistical Analysis

The primary analyses will be based on treatment differences at each QL assessment time point. Wilcoxon Rank Sum tests will be used to test for statistical significance. In addition, longitudinal data analysis techniques will be used to examine QL change over time. The longitudinal model accommodates informative censoring (dropout due to events that also affect QL such as relapse or death) and adjusts for data missing at random [20-22]. We will be modeling jointly the QL measure and time-to-event, such as overall survival. The survival component of the model acts as a "missing data mechanism". Intermittent missingness (missing data that occurs before the patient's time-to-event) is considered ignorable in this model (missing at random).

We will be collecting information on reasons why the patient did not fill out the QL assessment form. This information will be used to impute QL scores for intermittent data not missing at random. A sensitivity analysis will be done in parallel with various imputation techniques to validate the effect that imputing values has on the parameter estimates. A SAS macro has been made available to estimate these longitudinal models of informatively censored data.

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IBCSG Trials IBCSG 24-02/ BIG 2-02, IBCSG25-02/BIG 3-02, IBCSG26-02/BIG 4-02
Appendix VI: Authorization Log

Principal Investigator: _____ Group Number: _____

Job Title: _____ Center No: _____

Study Personnel, whose specimen signatures and initials appear below, are authorized to perform the following study tasks indicated by codes "A" to "I", on my behalf within the dates indicated. I confirm that they are qualified and appropriately informed about the trial.

A* = finally determine eligibility	D = make CRF entries/corrections	G = _____
B* = obtain informed consent	E* = sign CRFs	H = _____
C = perform key trial measurements	F = dispense medication	I = _____

*** Functions marked with an asterisk are considered the sole responsibility of the Principal Investigator, but may be delegated to Co-investigators. Codes G, H, and I may be used to specify other tasks or any of the above functions in which study personnel assist the investigator.**

Principal Investigator

Printed Name	Signature	Initials	Date
_____	_____	_____	_____

Participating Center personnel (Please use BLOCK CAPITALS)	Authorization code(s) (see above)	Signature	Initials	Date Authorized From/To + Principal Inv.'s Initials
Name: _____ Job Title: _____ Function:				From: _____ To: _____ Init: _____
Name: _____ Job Title: _____ Function:				From: _____ To: _____ Init: _____
Name: _____ Job Title: _____ Function:				From: _____ To: _____ Init: _____
Name: _____ Job Title: _____ Function:				From: _____ To: _____ Init: _____
Name: _____ Job Title: _____ Function:				From: _____ To: _____ Init: _____
Name: _____ Job Title: _____ Function:				From: _____ To: _____ Init: _____

IBCSG Trials 24-02, 25-02, 26-02/BIG Trials 2-02, 3-02, 4-02 Appendix VII: Participating Group Specific Logistical Information for [*insert the name of the Group*]

Appendix VII contains 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. This Appendix was developed and is maintained by the [*insert the name of the coordinating center or the operations office of the Group*]. The following information can be found in this appendix.

1 Group specific contact information ……. VII-1

2 Randomization procedures …… VII-2

3 Drug supply information ……... VII-3

4 Serious adverse event reporting procedures ……..…….. VII-4

5 Data submission and query resolution procedures ……. VII-5

6 Participation in the quality-of-life (QL) study …… VII-6

7 Pathology specimen submission procedures …… VII-7

8 Country/Group specific regulations and procedures ……. VII-8

Each Group should complete the following sections to provide the logistical information that is required to conduct the trial for their Group members. [This is a template that can be modified to satisfy the needs of your Group if so desired.]

Email a copy of the original Appendix VII that is created for your Group as well as any subsequent revised Appendix VII to the IBCSG Coordinating Center at STP@ibcsg.org so that we can maintain accurate and current records.

1 Group specific contact information

[This section includes information on group specific contact information, study participants, etc.]

2 Randomization procedures

[This section includes instructions on how to enroll patients to the study.]

3 Data submission and query resolution procedures

[This section includes instructions on how to submit CRFs. Instructions concerning how to submit responses to queries are also given.]

4 Serious adverse event reporting procedures

[This section describes how to report serious adverse events.]

5 Drug supply information

[This section describes how to obtain study drug supplies that are provided free of charge by the protocol - specifically, exemestane and triptorelin.]

6 Pathology specimen submission procedure

[This section includes instructions on where and how to submit the protocol required pathology tissues and slides.]

7 Country/Group specific regulations and procedures

[This section includes any other country/group specific regulations or procedures that the Group Coordinating Center/Operations Office considers useful to communicate to facilitate local conduct of this global clinical trial.]

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.

Protocol Amendment 2 Signature Page

IBCSG 24-02 / BIG 2-02

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

Protocol Amendment 1 Signature Page

IBCSG 24-02 / BIG 2-02

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

IBCSG 24-02 / BIG 2-02

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

(Signature on file) 17Apr03

Date

Principal Investigator Protocol Signature Page
Amendment 2

IBCSG 24-02 / BIG 2-02

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

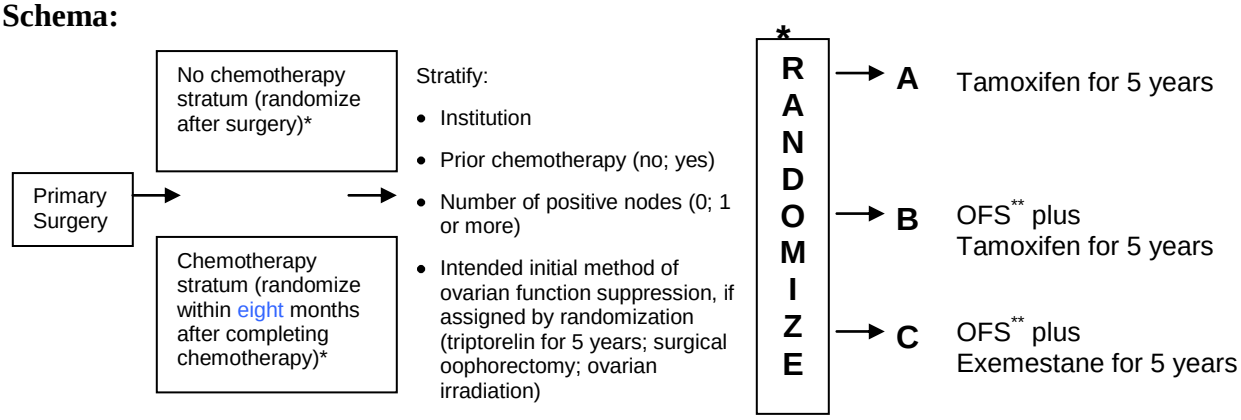
Patient Population: Premenopausal women (estradiol (E_2) levels in the premenopausal range) with histologically proven, resected breast cancer with ER and/or PgR positive tumors who have received either no chemotherapy or remain premenopausal following completion of adjuvant and/or neoadjuvant chemotherapy.

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:



* 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 ≥ 2 months if an anthracycline was included (e.g. 4 cycles of EC or AC) or ≥ 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).

TABLE OF CONTENTS

Section			Page
1	**Introduction**		12
2	**Trial objectives**		16
3	**Patient selection**		16
	3.1	Criteria for patient eligibility	16
	3.2	Criteria for patient ineligibility	18
4	**Randomization and stratification**		20
	4.1	Randomization timing	20
	4.2	Registration procedures	20
	4.3	Randomization help desk	21
	4.4	Randomized groups	22
4.5	Stratification		22
5	**Treatment details**		23
	5.1	Trial treatments	23
	5.2	Side effects of study drugs	25
	5.3	Concomitant treatments	26
	5.4	Study drug supply	27
6	**End points and definitions of treatment failure**		28
	6.1	Trial end points	28
	6.2	Diagnosis of treatment failure	28
7	**Study parameters**		32
	7.1	Table of study parameters	32
	7.2	Adverse event reporting	34
	7.3	Serious Adverse Event (SAE) reporting	35
	7.4	Exposure in utero reporting	37
8	**Data submission**		37
	8.1	Case report forms schedule	38
	8.2	Data management	40
	8.3	Investigators' file	40
	8.4	Authorization log	41
	8.5	Patient identification log	41

9 Statistical considerations 41
9.1 Study design, objectives, and stratification 42
9.2 Data analyses 42
9.3 Sample size considerations 42
9.4 Interim monitoring 45
9.5 Data and safety monitoring committee 45

10 Quality of life (see Appendix V) 45

11 Additional protocol-specific parameters 46
11.1 Hormone receptors 46
11.2 Pathology and pathology material banking 46
11.3 Family history 48

12 Regulatory approval procedures and patient informed consent 48
12.1 Ethical Review Board/Ethics Committee 48
12.2 Regulatory approval procedures 48
12.3 Requirements for Center Activation 48
12.4 Protection of human subjects 48
12.5 Informed consent procedures 49
12.6 Quality assurance 50

13 Administrative considerations 50
13.1 Insurance 50

14 References 51

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

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 $\geq$ 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 recurrence-free 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 anthracycline-treated 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 months if an anthracycline was included (e.g. 4 cycles of EC or AC) or ≥ 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.

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 non-hormonal 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 non-significant 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. Six-month 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 (non-breast) 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	1[A]	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
Estradiol[B]	x															
Adverse Events (AE)[C]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Late AEs[D]																x
Laboratory tests																
Hematology[E]	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Blood chemistry[F]	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-ray[H] (PA and lateral views) or chest CT	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Bone scan[I]	y	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Abdominal US, CT or liver scan[J]	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Gynecological exam[K]	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Bone mineral densitometry[L]	y				y		y		y		y		y		y	
CRFs[M]																
Quality of Life[N]	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 24-QLC, 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-SAE-A	Serious Adverse Event Form (Section A)	DataFax within 24 hours when SAE occurs, see Section 7.3.
Form 24-SAE-B	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:

- 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, node-positive disease who received chemotherapy plus tamoxifen. Premenopausal women with ER-positive, 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 ER-positive 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

INTERNATIONAL BREAST CANCER STUDY GROUP

IBCSG Trial 24-02
BIG Trial 2-02

Suppression of Ovarian Function Trial (SOFT)

Amendment 1

Reasons for Amendment:
The protocol has been revised for the following reasons:

1. To modify the eligibility and other sections to include patients with bilateral breast cancer
2. To increase the eligibility timeframe after chemotherapy from 6 months to eight months
3. To modify/clarify eligibility requirements including:
    a. Defining a premenopausal group that does not require estradiol testing
    b. Clarifying definitions of surgical margins
    c. Defining eligible prior malignancies
4. To clarify timing of randomization with respect to surgery, radiotherapy, and chemotherapy
5. To clarify that trastuzumab is allowed prior to and/or concurrent with protocol treatment
6. To include new findings about exemestane efficacy and side effects in postmenopausal women
7. To add details of treatment administration
8. To clarify pathology requirements and central review
9. To correct the statement on patient insurance
10. To update regulatory approval procedures
11. To update contact details
12. To add revised and additional CRFs
    a. Form A (revised)
    b. Form B (revised)
    c. Forms C, F, P, R (revised)
    d. Form OFS (revised)
    e. Form TE (revised)
    f. Form E (revised)
    g. Form CCM (revised)
    h. Form RF (new)
    i. Forms BC, BF, BP, BR (new)

Revised documents include:

1. A working protocol incorporating the changes from Amendment 1 (highlighting all changes in blue)
2. Revised Appendices I, III, IV
3. New Appendix VIII (IBCSG Guidelines for Publication and Presentations)
4. Revised CRFs

This document contains changes to the IBCSG Trial 24-02/BIG Trial 2-02 protocol and appendices made in Amendment 1. Specific text additions are highlighted and in **bold.**

Section	Prior version	New Version
Title Page	N/A	**EudraCT number: 2004-000166-13**
Contact Information		Updated all contacts
Throughout document		Global change: Pharmacia to **Pfizer**
Throughout document		Global change: Beaufour Ipsen to **Ipsen**
Protocol Summary and Schema	**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 6 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 6 months after the final dose of 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.
Protocol Summary and Schema	Chemotherapy stratum (randomize within six months after completing chemotherapy)*	Chemotherapy stratum (randomize within **eight** months after completing chemotherapy)*
Treatment Schedules	**Chemotherapy:** Patients in the chemotherapy stratum must have completed adjuvant (and/or neoadjuvant) chemotherapy prior to randomization. A planned duration of ≥ 2 months if an anthracycline was included (e.g. 4 cycles of EC or AC) or ≥ 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 6 months prior to randomization.	**Chemotherapy:** Patients in the chemotherapy stratum must have completed adjuvant (and/or neoadjuvant) chemotherapy prior to randomization. A planned duration of ≥ 2 months if an anthracycline was included (e.g. 4 cycles of EC or AC) or ≥ 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	Triptorelin (GnRH analogue) 3.75 mg by 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.	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.
Table of Contents	N/A	Section 12 updated Added Appendix VIII

Section	Prior version	New Version
1.3 Second paragraph	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 first results of the ATAC trial (anastrozole, tamoxifen and combination) in 9366 postmenopausal women with operable breast cancer were recently published. Among the 84% of patients with steroid hormone receptor positive disease, the hazard ratio for disease recurrence comparing anastrozole with tamoxifen was 0.78 (p=0.005) [26].	**(First paragraph remains unchanged)** 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].** **Remaining paragraphs in this section remain unchanged.**
Section 3.1.1	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.	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**

Section	Prior version	New Version
	• Patients who received prior adjuvant and/or neoadjuvant chemotherapy should be randomized after completing chemotherapy and within 6 months of the final dose of chemotherapy as soon as premenopausal status is confirmed; such patients should have estradiol (E_2) in the premenopausal range between 2 weeks and 6 months after completing chemotherapy. Patients with temporary chemotherapy-induced amenorrhea who regain premenopausal status within six months of the final dose of chemotherapy are eligible. [Attention: under tamoxifen or aromatase inhibitors, even without evidence of menses, some women 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].	**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 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.**
Section 3.1.3	Patients must have hormone receptor positive tumors. 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.	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.

Section	Prior version	New Version
Sections 3.1.5	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. Radiation therapy to the conserved breast is required.	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.**
Section 3.1.6	A3.1.6 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 positive axillary nodes require axillary dissection, except for patients with microscopically positive (pN1mi: micrometastasis > 0.2mm, none > 2.0mm) axillary sentinel nodes who are randomized in a clinical trial evaluating microscopically positive lymph nodes.	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.**
Section 3.2.2d	3.2.2d Patients with positive final margins (referring to only DCIS and invasive cancer, not LCIS).	3.2.2**c** 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.**
Section 3.2.2e	3.2.2e Patients with clinically detectable residual axillary disease.	3.2.2**d** Patients with clinically detectable residual axillary disease.
Section 3.2.3	3.2.3 Patients with a history of prior ipsilateral or contralateral invasive breast cancer.	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).**
Section 3.2.4	3.2.4 Patients with previous or	3.2.4 Patients with previous or concomitant

Section	Prior version	New Version
	concomitant malignancy EXCEPT adequately treated: • basal or squamous cell carcinoma of the skin • *in situ* carcinoma of the cervix or bladder, • contra- or ipsilateral *in situ* breast carcinoma.	**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:** o **stage I papillary thyroid cancer** o **stage Ia carcinoma of the cervix** o **stage Ia or b endometrioid endometrial cancer** o **borderline or stage I ovarian cancer**
3.2.6	3.2.6 Patients who have had a bilateral oophorectomy or ovarian irradiation or are planning oophorectomy within 5 years.	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.**
Section 3.2.8, Table in Section 7	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.	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 6 months after their breast cancer diagnosis.	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).**
Section 3.2.12	3.2.12 Patients with psychiatric, addictive, or any disorder, which compromises ability to give informed consent for participation in this study.	3.2.12 Patients with psychiatric, addictive, or any disorder **that would prevent compliance with protocol requirements.**
Section 4.1	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	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

Section	Prior version	New Version
	adjuvant/neoadjuvant chemotherapy should be randomized between 2 weeks and 6 months after the last dose of chemotherapy, as soon as premenopausal status is confirmed, as described in Section 3.1.1.	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.**
Section 4.2.3	Complete baseline Quality of Life (QL) Core form. (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.	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.
Section 4.2.6	When randomization is complete, fill in Confirmation of Registration Form (A) and fax Form A, and Form QL to an IBCSG DataFax number. This completed Form A is considered the essential document for regulatory purposes. It should be filed at your institution.	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.
Section 4.3	FSTRF Randomization Help Desk Frontier Science & Technology Research Foundation (FSTRF) 4033 Maple RD, Amherst, NY 14226 USA Phone: +1 716 834-0900 ext 301 Fax: +1 716 834 8432 Email: bc.helpdesk@fstrf.org	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
Section 4.5.4	Intended initial method of ovarian function suppression, if assigned by randomization • Triptorelin for 5 years • Surgical oophorectomy • Ovarian irradiation	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
Section 5.1.1	5.1.1 Triptorelin (GnRH analogue) 3.75 mg by injection every 28 days for 5 years, 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). Triptorelin will be supplied free of charge for patients randomized to ovarian function suppression in this study.	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

Section	Prior version	New Version
	In case of intolerance to or unavailability of 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.	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.
Section 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, FSH and LH. If biochemistry shows that radiation was not successful in achieving ovarian function suppression, then this should be achieved by alternate means.	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.
Section 5.1.5	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. Exemestane should begin 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	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

Section	Prior version	New Version
	analogue is discontinued) is not an effective treatment.] Exemestane will be provided free of charge.	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.
Section 5.1.6	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.	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.** **(Remainder of section is unchanged)**
Section 5.1.7	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 months if an anthracycline was included (e.g. 4 cycles of EC or AC) or ≥ 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 6 months prior to randomization.	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 months if an anthracycline was included (e.g. 4 cycles of EC or AC) or ≥ 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.

Section	Prior version	New Version
Section 5.2.3	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.	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 that 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 non-significant excess of myocardial infarctions was noted in those treated with exemestane compared with tamoxifen in the population (mean age 64 years).**
Sections 5.3.4, 5.3.5	5.3.4 Patients should be advised that a low risk of pregnancy remains despite GnRH analogue therapy [22]. 5.3.5 Patients will not receive other investigational agents while on study except as described in Section 5.3.3.	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.
Section 5.4	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	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

Section	Prior version	New Version
	or useless drugs should be sent back to the supplier for destruction. Any study drug returned by patients at study completion may not be reused and should be destroyed or returned as above.	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.
Section 6.2.1	Local failure is defined as a tumor recurrence in any soft tissues of the ipsilateral conserved breast or the chest wall, mastectomy scar, and/or skin. Acceptable for recurrence in 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.	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.
Section 6.2.2	Regional failure is defined as a tumor recurrence in the ipsilateral axillary lymph nodes, extranodal soft tissue of the ipsilateral axilla, ipsilateral internal mammary lymph nodes, and/or ipsilateral supraclavicular lymph nodes. Acceptable: positive cytology or histology or evidence of new lesions by CT or MRI without a benign etiology. Suspicious: a visible or palpable lesion.	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.
Section 6.2.3	6.2.3 Contralateral breast failure Acceptable: positive cytology or histology. Suspicious: a visible or palpable lesion, suspicious mammogram, ultrasound, or MRI. Appearance of DCIS or LCIS in the contralateral breast is not considered an event for DFS.	6.2.3 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**

Section	Prior version	New Version
		cannot be defined.
Section 6.2.4.7	6.2.4.7 Distant lymph nodes, not including ipsilateral supraclavicular lymph nodes Acceptable: positive cytology or histology, or enlarged lymph nodes in CT or MRI, or progressive disease by physical exam without an obvious benign etiology. Suspicious: evidence of enlarged lymph nodes by physical exam.	6.2.4.7 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.**
Section 7.1 Table	N/A	Footnote added: ***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.**
Section 7.1 Table	Chest-X-ray[H] (PA and lateral views)	Chest-X-ray[H] (PA and lateral views) **or chest CT**
Section 7.1 Table	Form F | x | and at disease relapse	Form F | x | and at disease relapse **(Form RF)**
Section 7.1 Table	N/A	**Forms BC, BF, BP and BR** | **Submit for patients with synchronous bilateral breast cancer as required per protocol.**
Legend to Table 7.1 B	B. Estradiol must be in the premenopausal range within 12 weeks of surgery or within 6 months after the final dose of chemotherapy, whichever is later (Section 3.1.1).	**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**

Section	Prior version	New Version
		treatments during the 6 months prior to randomization.
Legend to Table 7.1 H	H. A chest X-ray 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.	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.
Legend to Table Section 7.1 L	L. Bone densitometry by DEXA is recommended within one year prior to randomization and then yearly for 5 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.	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.
Section 7.2	1 = Grade 1 Mild 2 = Grade 2 Moderate 3 = Grade 3 Severe 4 = Grade 4 Life-threatening 5 = Grade 5 Lethal	1 = Grade 1 Mild 2 = Grade 2 Moderate 3 = Grade 3 Severe 4 = Grade 4 Life-threatening 5 = Grade 5 **Fatal**
Section 7.3.3	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 about all SAEs related to study medication (per	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

Section	Prior version	New Version
	either investigator or IBCSG medical review) within 24 hours of receipt at the IBCSG Coordinating Center. • The IBCSG Coordinating Center will record the SAE and prepare a summary report of all SAEs received at the end of each month. Principal Investigators will receive the summary report on a monthly basis, and these reports can be found on the IBCSG web site (www.ibcsg.org). The duplicate copy of the Serious Adverse Event Form, and the fax confirmation sheet must be kept with the case report forms at the participating center.	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).
Section 8.1	N/A	**Form 24 RF** **Relapse Hormone Receptor Form** **DataFax if a hormone receptor analysis was done at relapse.**
Section 8.1	N/A	*** 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)**
Section 8.1.2	N/A	**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:** • **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.**

Section	Prior version	New Version
Section 8.2	Deleted	Subsequent sections renumbered
Section 8.4	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 • 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	**8.3** 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 • 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**
Section 9.2	The three primary treatment comparisons 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 three arms. Cox proportional hazards regression models will be used to investigate whether the three treatment comparisons are modified by adjustments for various	The three primary treatment comparisons 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 three arms. Cox proportional hazards regression models will be used to investigate whether the three treatment comparisons are modified by adjustments for various covariates. To guarantee the overall alpha level of at most

Section	Prior version	New Version
	covariates. To guarantee the overall alpha level of at most 0.05 for all three tests, each of the pairwise hypotheses will be tested at the two-sided 0.0167 level. 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, and ER/PgR subgroup. These analyses will be considered as secondary and descriptive. The following additional secondary outcomes will be assessed: overall survival, systemic disease-free survival, quality of life, sites of first recurrence, late side effects of early menopause, causes of death without recurrence, incidence of second (non-breast) malignancies.	0.05 for all three tests, each of the pairwise hypotheses will be tested at the two-sided 0.0167 level. 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, systemic disease-free survival, quality of life, sites of first recurrence, late side effects of early menopause, causes of death without recurrence, incidence of second (non-breast) malignancies.
Section 11.1.1	11.1.1 Hormone receptor determination Immunohistochemical measurements of estrogen receptor (ER) and progesterone receptor (PgR) 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 ER-positive and/or PgR-positive tumors are eligible. The following items are required for all patients: 1. Completed Hormone Receptor Form 2. Steroid Hormone Receptor Report	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 ER-positive 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**

Section	Prior version	New Version
Section 11.2.1	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	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** **(Remainder of section is unchanged)**
Section 11.2.2	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 Coordinating Center Office in Bern (IBCSG Coordinating Center, Effingerstrasse 40, CH-3008 Bern). The	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 Coordinating Center Office in Bern (IBCSG Coordinating Center, Effingerstrasse 40, CH-3008 Bern). The Australia-New Zealand Group will maintain a

Section	Prior version	New Version
	Australia-New Zealand Group will maintain a tumor bank within Australia. The H&E section is sent to Prof. Gusterson's laboratory in Glasgow for central pathology review, and then returned to Bern for storage. Central pathology review reports will be available to institution pathologists who wish to see them. The blocks will be available for prospective and retrospective studies approved by the Biological Protocols Working Group and by the IBCSG Ethical Committee.	tumor bank within Australia. The H&E section is sent for central pathology review, and 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 expression 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.
Section 12	**12 Ethics committee review and patient informed consent** **12.1 Ethical Review Board /Ethics** All protocols and the patient informed consent forms must have the approval of a properly constituted committee or committees responsible for approving clinical trials. The ERB/IRB written, signed approval letter/form must contain approval of the designated investigator, the institution, the protocol (identifying protocol title and version number), and of the patient informed consent template, as well as the composition of the Ethical Committee (names of members) that approved such documents. Documentation of ethical committee approval should be sent to the IBCSG Coordinating Center prior to enrollment of the first patient. The IBCSG Ethical Committee also reviews the protocol annually. **12.2 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	**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**

Section	Prior version	New Version
	all of the other items listed in Section 12.3. Additional institution-specific sections should be added to Appendix I as described in Section 12.3. The medical record must be available for review by the IBCSG audit team as described in Section 12.4. Serious adverse event (SAE) reports are distributed monthly. In addition they are available on the IBCSG website (www.ibcsg.org). **12.3 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/17-c_e.html) 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.	**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

Section	Prior version	New Version
		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. **Section 12.6 has been renumbered, but is otherwise unchanged.**
Section 13.1	**13.1 Insurance** The IBCSG through the SIAK/SAKK has a Public and Products Liability Insurance. All persons, acting on behalf of the Named Insured, are covered as Additional Insured. The scope of coverage is Comprehensive Swiss Form. This insurance does not cover any liability resulting from medical malpractice. Specifically the negligence in the application of the protocol and/or treatment of the patients is excluded. The IBCSG insurance does NOT cover patients from the United States of America or from Canada. Each group will be responsible for obtaining proper insurance coverage.	**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.**
References	N/A	**46. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, Hoctin-Boes G, Houghton J, Locker GY, Tobias JS, ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005;365(9453):60-62.** **47. Coombes RC, Hall E, Gibson LJ, et al; Intergroup Exemestane Study. A**

Section	Prior version	New Version
		randomized trial of exemestane after 2 to 3 years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004;350;101-1092. **48. Coombes RC, Hall E, Snowdon CF, et al; A randomized trial in postmenopausal patients with early breast cancer who remain disease-free after 2 to 3 years of tamoxifen: updated survival analysis. 27th Annual San Antonio Breast Cancer Symposium; December 8-11, 2004; San Antonio, TX (oral presentation). Breast Cancer Res Treat Vol 88 suppl 1, 2004 pS7.** **49. Thurlimann BJ, Thurlimann BJ, Keshaviah A, Mouridsen H, Mauriac L, Forbes JF, Paridaens R, Castiglione-Gertsch M, Gelber RD, Smith I, Goldhirsch A. BIG 1-98: Randomized double-blind phase III study to evaluate letrozole vs. tamoxifen as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. Proc Am Soc Clin Oncol 2005;23(16S):6s (suppl, abstr 511).**
Appendices List	N/A	**VIII. IBCSG Guidelines for Publication and Presentations**
APPENDIX 1 Risks and discomforts	While on the study, you are at risk for side effects, as discussed below. You should discuss these with your doctor. There may also be other side effects that we cannot predict. Other drugs may be given to make some of these side effects less serious and uncomfortable. Many side effects go away shortly after the drugs are stopped, but in some cases side effects can be serious, long lasting or permanent. There may also be unexpected risks (risks not known about).	While on the study, you are at risk for side effects, as discussed below. You should discuss these with your doctor. There may also be other side effects that we cannot predict. Other drugs may be given to make some of these side effects less serious and uncomfortable. Many side effects go away shortly after the drugs are stopped, but in some cases side effects can be serious, long lasting or permanent. There may also be unexpected risks (risks not known about). The following has been moved from the end of this section to after the first paragraph: **Your physician will be checking you closely to see if any of the side effects are occurring. Physical exam, routine blood tests and other tests (depending on the choice of therapy) will be done to monitor the effects of treatment.** **Your physician may prescribe medication to keep these side effects under control. Schedules and dosages may be also altered to**

Section	Prior version	New Version
		reduce their frequency and intensity. **You should report any side effect or symptom that you experience to your physician. Moreover, it is important that you tell your physician about additional medication that you take during or after the treatment.** **Your physician may also decide to stop the treatment early in case of thromboembolic events, vaginal bleeding, abnormal lab values or any other serious toxicity.**
Exemestane	The most common side effects are hot flushes, nausea, increased sweating, fatigue, hair thinning, dizziness and skin rash. Exemestane may result in loss of bone mineral density (which can lead to broken bones).	The most common side effects of exemestane are hot flushes, sweating, nausea, fatigue, **and flu-like symptoms (aches and pains). Skin rash and hair thinning occur less commonly. Furthermore headaches, insomnia, depression, dizziness, diarrhea, visual disturbances, blood clots and high blood pressure have been observed while taking exemestane.** Exemestane may result in loss of bone mineral density (which can lead to broken bones).
Insurance	IBCSG has a public and products liability insurance. All persons, acting on behalf of the named insured, are covered as additional insured. The scope of coverage is comprehensive Swiss form. This insurance does not cover any liability resulting out of medical malpractice; especially the negligence in the application of the respective protocol and/or treatment of the patients is excluded.IBCSG has a public and products liability insurance. All persons, acting on behalf of the named insured, are covered as additional insured. The scope of coverage is comprehensive Swiss form. This insurance does not cover any liability resulting out of medical malpractice; especially the negligence in the application of the respective protocol and/or treatment of the patients is excluded.	**[As this paragraph has to be adapted for each country according to local insurance requirements, please contact the IBCSG Coordinating Center to receive the appropriate and locally approved Insurance Paragraph.]**

Section	Prior version	New Version
CONFIDENTI-ALITY	Medical records of patients are maintained under strict confidentiality as required by law. Confidentiality will be maintained during and after your participation in the study. Data collected during the study will be stored and analyzed by computer. It will be stored for a prolonged period (over 15 years). If at any time you wish to withdraw from the study and have the data relating to your case destroyed, please notify the IBCSG directly or through your doctor by submitting a written statement. Data will be analyzed exclusively for the purposes of research in breast cancer. Neither your name nor anything that could identify you will be used in any reports or publications that result from this study. During their required reviews, representatives of IBCSG, the health authorities, the pharmaceutical company representatives or subcontractors (Pharmacia/Pfizer Oncology) and the local ethics committee may have access to medical records that contain your identity. This will be done only under the formal agreement that confidentiality will be respected in all cases.	Medical records of patients are maintained under strict confidentiality as required by law. Confidentiality will be maintained during and after your participation in the study. Data collected during the study will be stored and analyzed by computer. It will be stored for a prolonged period (over 15 years). **If at any time you wish to withdraw from the study you may do so. In that case, we would continue to store the data already collected, and with your agreement, we would like to continue to collect basic information about your health status in the future. If however, you wish to withdraw from the study and do not want data relating to you personally to be stored, then the data already collected about your health will be 'anonymised' (That means, it cannot be linked to you in any way), and no further data will be collected. Please notify the IBCSG through your doctor by submitting a written statement.** Data will be analyzed exclusively for the purposes of research in breast cancer. Neither your name nor anything that could identify you will be used in any reports or publications that result from this study. During their required reviews, representatives of IBCSG, the health authorities, the pharmaceutical company representatives (Pfizer Oncology) or subcontractors and the local ethics committee may have access to medical records that contain your identity. This will be done only under the formal agreement that confidentiality will be respected in all cases.
Collection of Biological Material	N/A	**The pathology review at a central laboratory or institute is a requirement for this study. Testing of genes which may be inherited in your family is not part of the pathology review of this study.**
Appendix III Hormone Receptor	4.1 External quality assessment All IBCSG participating laboratories should participate in an external quality assessment program. One such program is the UK NEQAS, which provides a network of educational schemes unmatched in its comprehensiveness and quality throughout the world. To enroll in this program, contact Barry Gusterson at the Central Pathology Office (tel: +44 141 211 2233, fax: +44 141 337 2494, email: bag5f@clinmed.gla.ac.uk).	4.1 External quality assessment All IBCSG participating laboratories should participate in an external quality assessment program. One such program is the UK NEQAS, which provides a network of educational schemes unmatched in its comprehensiveness and quality throughout the world. To enroll in this program, contact the Central Pathology Office. **(See page 3 of the protocol for contact information)** **(Remainder of section unchanged)**
Appendix IV	1 Pathologists and central review	1 Pathologists and central review

Section	Prior version	New Version
Pathology Section 1	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 is responsible for ensuring that the Pathology Form is compete and accurate, and that the pathology materials are properly collected and submitted. The central review pathologist will review the submitted specimens and complete the Central Pathology Review (CPR) form.	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 is responsible for ensuring that the Pathology Form is compete and accurate, and that the pathology materials are properly collected and submitted. The central review pathologist will review the submitted specimens and complete the Central Pathology Review (CPR) form. **Central Pathology review will include histopathological parameters (tumor type and grade, occurrence of peritumoral vascular invasion), hormone receptors (estrogen and progesterone receptors), HER2 expressions 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.**
Appendix IV Pathology Section 2	N/A	**In addition, for patients with bilateral breast cancer, the following items are required for the second breast/side**: **1. Completed Pathology Form BP** **2. Pathology Report** **3. Tumor block** **4. Representative H & E section of the above block** **(Remainder of section unchanged)**
Appendix IV Pathology Section 2.3 Pathologic Material	**Pathologic material** Two paraffin blocks, one tumor and one normal tissue, and representative H & E slides must be submitted to the Coordinating Center. All material must be labeled with the patient's randomization number. Institutions will submit paraffin blocks to the Coordinating Center, who will forward them to the Central Pathology Laboratory. Whenever indicated, the Central Lab will use the tissue array technology (see below) to obtain a small amount of material from the block. The tissue array will be logged and stored, and the paraffin blocks will be returned to the participating center upon request. The Group anticipates that returning the blocks to the institutions within a short time will increase the feasibility of full compliance with tissue collection.	**Pathologic material** Two paraffin blocks, one tumor and one normal tissue, and representative H & E slides must be submitted to the Coordinating Center. All material must be labeled with the patient's randomization number. **IBCSG wants to be ready with a suitable tissue bank for application of the newer assays which are most likely to be available in the very near future. In particular, IBCSG expects that novel predictive parameters will be identified by gene expression profiling. This will open at least one of the following possibilities:** **1. the application of gene expression profiling to paraffin embedded material** **2. the identification of specific mRNAs which could be detectable by molecular biology assays (RT-PCR, in situ hybridization, etc) in paraffin-embedded tissue** **3. the identification of protein molecules detectable by immunohistochemistry.**

Section	Prior version	New Version
		These assays will most likely require a comparison between neoplastic and normal tissue, and this is why IBCSG is banking two sets of samples per patient. In many cases (but not all) normal tissue may be found around the invasive tumors. If we will apply extractive techniques, then avoiding contamination of the normal sample by neoplastic cells will be mandatory, and this will be difficult to achieve if both components are in the same block. Institutions will submit paraffin blocks to the Coordinating Center, who will forward them to the Central Pathology Laboratory. Whenever indicated, the Central Lab will use the tissue array technology (see below) to obtain a small amount of material from the block. The tissue array will be logged and stored, and the paraffin blocks will be returned to the participating center upon request. The Group anticipates that returning the blocks to the institutions within a short time will increase the feasibility of full compliance with tissue collection.
Appendix IV Pathology 2.4 Submitting Material	Slides and blocks should be mailed to: IBCSG Coordinating Center Effingerstrasse 40 CH-3008 BERN, Switzerland All reports, slides, and blocks must be marked with the IBCSG patient ID number. Slides should be sent in customized slide boxes. They should be packed with tissue paper to prevent any movement. If slides move around when the box is shaken, they have not been packed sufficiently.	Slides and blocks should be mailed to: IBCSG Coordinating Center **Pathology Coordinating Office** Effingerstrasse 40 CH-3008 BERN, Switzerland **with a COPY of the Pathology Form and a COPY of the pathology report of the local pathologist.** All reports, slides, and blocks must be marked with the IBCSG patient ID number. Slides should be sent in customized slide boxes. They should be packed with tissue paper to prevent any movement. If slides move around when the box is shaken, they have not been packed sufficiently. **Blocks and slides can be shipped to the IBCSG Coordinating Center via regular mail. Overnight or express delivery services are not necessary**.
Appendix VIII IBCSG Guidelines for Publication and Presentations	N/A	**New Appendix added**

INTERNATIONAL BREAST CANCER STUDY GROUP

IBCSG Trial 24-02
BIG Trial 2-02

Suppression of Ovarian Function Trial (SOFT)

Amendment 2

Reasons for Amendment:
The protocol has been revised for the following reasons:

1. To modify the statistical analysis plan. Accrual has been completed with 3066 patients enrolled. It is not possible to increase the sample size. Patients are doing much better than originally anticipated. The estimated event rate is 2% per year as opposed to 8% per year in the original protocol. Consequently, the original event-driven analysis plan would require an additional 13 years of follow up (end of 2023) before providing the first report of results. The Steering Committee, with the endorsement from the Data Safety and Monitoring Committee, therefore decided to implement a time-driven analysis plan with a cut-off defined for the fall of 2013 at a median follow up of approximately 5 years.
2. To include breast cancer-free interval (BCFI) and distant recurrence-free interval (DRFI) as secondary endpoints replacing systemic disease free survival. The BCFI and DRFI endpoints are consistent with the Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials proposed by Hudis et al. J Clin Oncol 25:2127-2131, 2007.
3. To collect additional targeted adverse event information on glucose intolerance (diabetes) and anti-diabetic concomitant medications. Increased risk of diabetes has been suggested by epidemiologic studies in men being treated with GnRH agonists for prostate cancer. Diabetes has been added to the case report forms as a targeted adverse event.

Revised documents include:
1. A working protocol incorporating the changes from Amendment 2 (highlighting all changes in green)
2. Appendix IV (Pathology)
3. Revised Adverse Event (24-AE) Form

This document contains changes to the IBCSG Trial 24-02/BIG Trial 2-02 protocol and appendices made in Amendment 2. Specific text additions are highlighted and in **bold.**

Section	Prior version	New Version
Contact Information		Updated contact information
Protocol Summary and Schema	**Sample Size:** 3000 patients (600 per year for 5 years with 1.9 years of additional follow-up)	**Sample Size:** 3000 patients
2.1 Primary objectives	2.1.2 To compare OFS plus exemestane vs. tamoxifen alone 2.1.3 To compare OFS plus exemestane vs. OFS plus tamoxifen	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)**
2.3.2	Systemic disease-free survival	**Replaced with:** **Breast cancer-free interval and distant recurrence-free interval**
4.3 Randomization help desk		Updated contact information
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 non-hormonal contraception should therefore be discussed.	**First three paragraphs remain unchanged.** **The following paragraph is added at the end:** **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**

Section	Prior version	New Version
		will prospectively capture adverse event information specifically on hyperglycemia and glucose intolerance (diabetes) and the use of anti-diabetic drugs as concomitant medications.
6.1.2	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.	Replaced the first two paragraphs with the following: **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.**
Legend to 7.1	N/A	Inserted in section C • **Glucose Intolerance (Diabetes) and/or anti-diabetes treatment** • **Hyperglycemia**
8.3 Investigator's file	N/A	Inserted in list of documentation: • **Health Authority Approval** • **Correspondence with Health Authority**
9.2 Data analyses	The three primary treatment comparisons 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 three arms. Cox proportional hazards regression models will be used to investigate whether the three treatment comparisons are modified by adjustments for various covariates. To guarantee the overall alpha level of at most 0.05 for all three tests, each of the pairwise hypotheses will be tested at the two-sided 0.0167 level. Other factors will be used to characterize the patients enrolled in the study and to provide descriptive statistics of outcomes	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

Section	Prior version	New Version
	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, systemic disease-free survival, quality of life, sites of first recurrence, late side effects of early menopause, causes of death without recurrence, incidence of second (non-breast) malignancies.	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 – *inserted here* 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, node-positive disease who received chemotherapy plus tamoxifen. Premenopausal women with ER-positive,	**Replaced the first five paragraphs of Section 9.3 and Tables 9.1 and 9.2 with the highlighted text below:** **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**

Section	Prior version	New Version
	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. – *inserted here* 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	**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.** **Revised the last paragraph in Section 9.3 and added a sentence as shown 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;

Section	Prior version	New Version
	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. 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%, 98%, and 99%, 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.	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 **63%, 84%, and 95%**, respectively, assuming that both SOFT and TEXT **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].	**Replaced by:** **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	The study will be presented for review by the IBCSG Data and Safety Monitoring	**Deleted third sentence, new version reads:**

Section	Prior version	New Version
Monitoring Committee (DSMC)	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.	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. 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.
11.2.1 Pathology requirements	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.	**Revised last two paragraphs:** The tissue blocks, particularly in case of small tumors, may be returned to the participating center upon request. All reports, slides, and blocks must be marked with the randomization number The **IBCSG** 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 Coordinating Center Office in Bern (**IBCSG Coordinating Center, Effingerstrasse 40, CH-3008 Bern**). The Australia-New Zealand Group will maintain a tumor bank within Australia. The H&E section is sent for central pathology review,. 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	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** (**IBCSG Central Pathology Office, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy**. The Australia-New Zealand Group will maintain a tumor bank within Australia. **Immunohistochemistry characterization is done as part of**—central pathology review**, and the respective sections are stored in the central repository thereafter.** Central pathology review reports will be available to institution pathologists who wish to see them. Central pathology review will include

Section	Prior version	New Version
	invasion), hormone receptors (estrogen and progesterone receptors), HER2 expression 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.	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.
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.	**Removed "Coordinating Center" from 2nd last sentence.** 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 prior to enrollment of the first patient. The IBCSG Ethics Committee also approves the protocol and reviews it annually.
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.	**Removed "Coordinating Center" from last sentence.** 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. Logistics for transmitting regulatory documents and ethics and health authority approvals for participating groups are described in Appendix VII.
References	41. EaSt 2000 (Early Stopping) statistical software package. Cytel Corporation, Cambridge, MA, USA, 2000.	**Deleted**

Section	Prior version	New Version
	42. O'Brien PC, Fleming TR: A multiple testing procedure for clinical trials. Biometrics 35:549-556, 1979.	
Appendix IV Pathology	N/A	General updates

INTERNATIONAL BREAST CANCER STUDY GROUP

IBCSG 25-02
BIG 3-02

Tamoxifen and Exemestane Trial (TEXT)

A Phase III Trial Evaluating the Role of Exemestane Plus GnRH Analogue as Adjuvant Therapy for Premenopausal Women with Endocrine Responsive Breast Cancer

ovarian function suppression + tamoxifen versus
ovarian function suppression + exemestane

Coordinating Group: International Breast Cancer Study Group (IBCSG)

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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Protocol Signature Page

IBCSG 25-02 / BIG 3-02

Tamoxifen and Exemestane Trial (**TEXT**).

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

Signature on file

_____ _____

Date

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

Signature on file

_____ _____

Date

Principal Investigator and Co-investigator Protocol Signature Page

IBCSG 25-02 / BIG 3-02

Tamoxifen and Exemestane Trial (TEXT).

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Name of Principal Investigator:_____

Signature:

_____ _____

Date

Name of Co-investigator:_____

Signature:

_____ _____

Date

Name of Co-investigator:_____

Signature:

_____ _____

Date

Name of Co-investigator:_____

Signature:

_____ _____

Date

Name of Co-investigator:_____

Signature:

_____ _____

Date

Protocol Summary and Schema

Tamoxifen and Exemestane Trial (TEXT)

A Phase III Trial Evaluating the Role of Exemestane Plus GnRH Analogue as Adjuvant Therapy for Premenopausal Women with Endocrine Responsive Breast Cancer

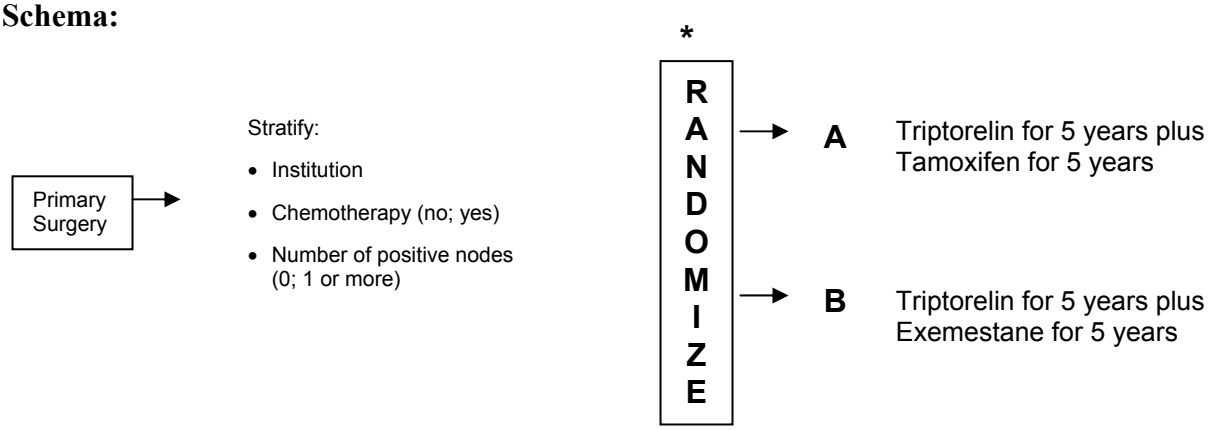
Patient Population: Premenopausal women with histologically proven, resected breast cancer with ER and/or PgR positive tumors.

Entry: Patients should be randomized within 12 weeks after surgery prior to commencing any adjuvant systemic therapy.

Stratification Factors:
-Institution
-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)

Sample Size: 1845 patients (410 per year for 4.5 years with 2.4 years of additional follow-up)

Schema:



* Randomization prior to receiving any adjuvant systemic therapy

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 should commence chemotherapy after randomization at the same time as GnRH analogue. A planned duration of ≥ 2 months if an anthracycline is included (e.g. 4 cycles of EC or AC) or ≥ 4 months if no anthracycline is given (e.g. 6 cycles of CMF) is recommended. If an anthracycline is used, an epirubicin-containing regimen is recommended.

Adjuvant Endocrine Therapy:

Triptorelin: Triptorelin (GnRH analogue) 3.75 mg by 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.

Tamoxifen: Tamoxifen 20 mg orally daily until 5 years from date of randomization, unless relapse or intolerance should occur earlier. Tamoxifen should start after adjuvant chemotherapy has been completed or at least six weeks after the initiation of GnRH analogue, whichever is later.

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 start after adjuvant chemotherapy has been completed or at least six weeks after the initiation of GnRH analogue, whichever is later.

TABLE OF CONTENTS

Section			Page
1	Introduction		10
2	Trial objectives		13
3	Patient selection		14
	3.1	Criteria for patient eligibility	14
	3.2	Criteria for patient ineligibility	15
4	Randomization and stratification		16
	4.1	Randomization timing	16
	4.2	Registration procedures	17
	4.3	Randomization help desk	17
	4.4	Randomized groups	18
	4.5	Stratification	18
5	Treatment details		19
	5.1	Trial treatments	19
	5.2	Side effects of study drugs	20
	5.3	Concomitant treatments	21
	5.4	Study drug supply	22
6	End points and definitions of treatment failure		22
	6.1	Trial end points	22
	6.2	Diagnosis of treatment failure	23
7	Study parameters		26
	7.1	Table of study parameters	26
	7.2	Adverse event reporting	28
	7.3	Serious Adverse Event (SAE) reporting	29
	7.4	Exposure in utero reporting	31
8	Data submission		31
	8.1	Case report forms schedule	31
	8.2	Pathology materials submission	33
	8.3	Data management	33
	8.4	Investigators' file	33
	8.5	Authorization log	34
	8.6	Patient identification log	34

9 Statistical considerations 34
9.1 Study design, objectives, and stratification 34
9.2 Data analyses 35
9.3 Sample size considerations 35
9.4 Interim monitoring 37
9.5 Data and safety monitoring committee 37

10 Quality of life (see Appendix V.) 37

11 Additional protocol-specific parameters 37
11.1 Hormone receptors 37
11.2 Pathology and pathology material banking 38
11.3 Family history 39

12 Ethics committee review and patient informed consent 39
12.1 Ethical Review Board/Ethics 39
12.2 Protection of human subjects 39
12.3 Informed consent procedures 40
12.4 Quality assurance 41

13 Administrative considerations 41
13.1 Insurance 41

14 References 42

Appendices

I. Requirements for Informed Consent
II. NCI Common Toxicity Criteria, Version 2 [available from the internet at: http://ctep.info.nih.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

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

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. There is some evidence that GnRH analogues may have a direct beneficial effect on tumor cell death, for breast cancer and other cancers [22-25]. A trial conducted by the ECOG in postmenopausal patients (based on some anecdotal information [26]) confirmed some efficacy of GnRH analogue for the ER+ cohort, but no significant effect was observed for the ER- cohort [27]. Although it is clear that the effect of GnRH analogues, when given alone, is mainly through the indirect inhibition of endocrine ovarian function, antitumor efficacy via other mechanisms is not entirely elucidated. Furthermore, the combination of GnRH analogue and chemotherapy might also be useful to protect ovarian function from definitive cytotoxic-related damage. This might be advantageous especially for young women who choose to preserve fertility [28]. Therefore, use of GnRH analogue for five years is the method of choice to achieve ovarian function suppression in this clinical trial.

There are case studies of failure of ovarian function suppression under GnRH analogue [29]. 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 [30].

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 [31,32], and trials comparing aromatase inhibitors to tamoxifen for postmenopausal women in the adjuvant setting are awaiting maturity. The first results of the ATAC trial (anastrozole, tamoxifen and combination) in 9366 postmenopausal women with operable breast cancer were recently published. Among the 84% of patients with steroid hormone receptor positive disease, the hazard ratio for disease recurrence comparing anastrozole with tamoxifen was 0.78 (p=0.005) [33].

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 [34]. 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 [35,36]. 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 [37].

Either the combination of a GnRH analogue with tamoxifen or the combination of a GnRH analogue with an aromatase inhibitor (exemestane) has the potential to improve survival in premenopausal women with endocrine responsive tumors over that seen with tamoxifen alone. This trial is designed to assess the role of GnRH analogue plus exemestane compared with GnRH analogue plus tamoxifen. 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 [38]. 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 [39]. A pre-clinical trial by Goss et al. [40] 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 long-term use of GnRH analogue) plus exemestane compared with GnRH analogue plus tamoxifen for premenopausal women with steroid hormone receptor positive early invasive breast cancer. Patients may either receive no chemotherapy or commence chemotherapy at the same time that GnRH analogue is initiated.

2.1 To compare GnRH analogue plus exemestane vs. GnRH analogue plus tamoxifen

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
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) following surgery]. Patients should be randomized within 12 weeks after definitive surgery.

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. 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) with radiotherapy planned. The local pathologist must document negative margins of resection in the pathology report. Radiation therapy to the conserved breast is required.

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 positive axillary nodes require axillary dissection, except for patients with microscopically positive (pN1mi: micrometastasis ≤ 2mm) axillary sentinel nodes who are randomized in a clinical trial evaluating microscopically positive lymph 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.

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 bilateral invasive breast cancer.

3.2.2d Patients with positive final margins (referring to only DCIS and invasive cancer, not LCIS).

3.2.2e Patients with clinically detectable residual axillary disease.

3.2.3 Patients with a history of prior ipsilateral or contralateral invasive breast cancer.

3.2.4 Patients with previous or concomitant malignancy EXCEPT adequately treated:
basal or squamous cell carcinoma of the skin
in situ carcinoma of the cervix or bladder,
contra- or ipsilateral *in situ* breast carcinoma.

3.2.5 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.

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.

3.2.9 Patients who received any neoadjuvant or adjuvant endocrine therapy after their breast cancer diagnosis.

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.

3.2.11 Patients who received any prior neoadjuvant or adjuvant chemotherapy.

3.2.12 Patients with psychiatric, addictive, or any disorder, which compromises ability to give informed consent for participation in this study.

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 adjuvant systemic therapy, either GnRH analogue if no chemotherapy given or GnRH analogue plus chemotherapy if chemotherapy is given.

4.2 Registration procedures

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

4.2.1 Verify eligibility.

4.2.2 Obtain signed informed consent.

4.2.3 Complete baseline Quality of Life (QL) Core form (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 Form QL 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). Do not mail Form A.

4.3 Randomization help desk

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

Business Hours: 7:30-18:00 US Eastern Time
FSTRF Randomization Help Desk
Frontier Science & Technology Research Foundation (FSTRF)
4033 Maple RD, Amherst, NY 14226 USA
Phone: +1 716 834 0900 ext. 301
Fax: +1 716 834 8432
Email: bc.helpdesk@fstrf.org

4.4 Randomized groups

Randomization (1:1) to 2 groups:

4.4.1 Triptorelin (GnRH analogue) for 5 years plus tamoxifen for 5 years.

4.4.2 Triptorelin (GnRH analogue) for 5 years plus exemestane for 5 years.

4.5 Stratification

4.5.1 Institution.

4.5.2 Adjuvant/neoadjuvant chemotherapy [the decision to use adjuvant chemotherapy may be made by previous randomization in the PERCHE trial or by investigator/patient choice]
- 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.

5 Treatment details

5.1 Trial treatments

5.1.1 Chemotherapy Patients in the chemotherapy stratum should commence chemotherapy after randomization at the same time as GnRH analogue. A planned duration of ≥ 2 months if an anthracycline is included (e.g. 4 cycles of EC or AC) or ≥ 4 months if no anthracycline is given (e.g. 6 cycles of CMF) is recommended. If an anthracycline is used, an epirubicin-containing regimen is recommended.

5.1.2 Triptorelin (GnRH analogue) 3.75 mg by injection every 28 days for 5 years, 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). Triptorelin will be supplied free of charge. Bilateral surgical oophorectomy or bilateral ovarian irradiation (with biochemical confirmation of cessation of ovarian function) is allowed after at least six months of triptorelin (GnRH analogue).

In case of intolerance to or unavailability of 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 [29]. In such cases ovarian function suppression should be achieved by other means providing patient accepts an alternative method.

5.1.3 Tamoxifen 20 mg orally daily until 5 years from date of randomization, unless relapse or intolerance should occur prior to 5 years. Tamoxifen should start after adjuvant chemotherapy has been completed or at least six weeks after the initiation of GnRH analogue, whichever is later.

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. Exemestane should start after adjuvant chemotherapy has been completed or at least six weeks after the initiation of GnRH analogue, whichever is later. [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.] 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.

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 [41,42].

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 anthracycline-treated 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 [43]. 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 [44]. 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.

5.2 Side effects of study drugs

5.2.1 Chemotherapy: Side effects of chemotherapy will vary according to the regimen used.

5.2.2 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 during pregnancy and lactation. Cases of pregnancy have occurred in women receiving regular injections of GnRH analogue [29]. The role of non-hormonal contraception should therefore be discussed.

5.2.3 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.

5.2.4 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.

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 [45]. 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) [46].

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 should be advised that a low risk of pregnancy remains despite GnRH analogue therapy [29].

5.3.5 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 Pharmacia. Triptorelin will be provided by Pharmacia in North and South America and by Beaufour 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 Beaufour 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 Pharmacia 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, Beaufour Ipsen and Pharmacia 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. Six-month 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 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.

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 events.

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 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.

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

6.2.3 **Contralateral breast failure**

Acceptable: positive cytology or histology.
Suspicious: a visible or palpable lesion, suspicious mammogram, ultrasound, or MRI.

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

6.2.4 **Distant failure**

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

6.2.4.1 <u>Bone marrow</u>

Acceptable: positive cytology, aspiration or biopsy.
Suspicious: unexplained depression of peripheral blood counts and/or a leucoerythroblastic blood picture.

6.2.4.2 <u>Lung</u>

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 <u>Pleura</u>

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

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

Suspicious: evidence of enlarged lymph nodes by physical exam.

6.2.4.8 Other sites

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

Suspicious: clinical and radiological evidence of a tumor.

6.2.5 **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 (non-breast) 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	1 A	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
Estradiol[B]	x															
Adverse Events (AE)[C]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Late AEs[D]																x
Laboratory tests																
Hematology[E]	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Blood chemistry[F]	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-ray[H] (PA and lateral views)	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Bone scan[I]	y	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Abdominal US, CT or liver scan[J]	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Gynecological exam[K]	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Bone mineral densitometry[L]	y				y		y		y		y		y		y	
CRFs[M]																
Quality of Life[N]	x		x		x	x	x		x		x		x		x	
Forms B,C,H,F,P	x															
Form F	x	and at disease relapse														
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 CT, R, SAE, EIU, GYN	as needed per protocol															

x = mandatory
y = recommended
v = if medically indicated

Legend to Table 7.1

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

B. Estradiol following surgery is needed to confirm premenopausal status at study entry.

C. Adverse events should be graded using the NCI CTC version 2 (Appendix II). The following list gives targeted adverse events that should be recorded on the CRF at any time:
- Vaginal dryness/dyspareunia (pain or discomfort with intercourse) and/or treatment to alleviate
- Urinary incontinence
- Decreased libido (sexual interest)
- Vasomotor menopausal symptoms (hot flushes, night sweats) and/or treatment to alleviate
- Bone mineral densitometry
- Bone fracture or document osteoporosis and/or treatment to prevent/alleviate
- Musculoskeletal symptoms (myalgia, arthralgia (joint pain), stiffness not including bone fractures) and/or treatment to alleviate
- Depression
- Hypertension
- Cardiac ischemia/infarction
- Thrombosis and/or embolism
- CNS cerebrovascular ischemia
- Insomnia
- Fatigue
- Nausea
- Allergic reaction and/or hypersensitivity
- Injection site reaction
- Other Grade 3 or higher adverse events
- Use of antidepressants and primary reason for use
- Gynecologic surgery/procedures excluding PAP smears and procedures related to diagnosis of cervical carcinoma *in situ*
- Hyperplasia of the endometrium

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. For patients receiving chemotherapy, hematology is also required on day 1 of each cycle.

F. Blood chemistry (includes liver function tests with alkaline phosphatase) must be done within 2 months prior to randomization and whenever medically indicated. For patients receiving chemotherapy, blood chemistry is also required on day 1 of each cycle.

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 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 5 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 25-02 Data Management Manual.

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

Patients on chemotherapy will be seen on day 1 of each cycle. A complete blood count should be performed at that time. 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 Toxicity Criteria (CTC). The CTC should be labeled: CTC Version 2.0. The CTC 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	Lethal

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

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

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 25-EU) 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 Pharmacia 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 Pharmacia 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—TEXT

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 25/26-QLC, 25/26-QLM, 25/26-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 25-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.

8.1 Case report forms schedule--TEXT (continued on next page)

8.1 Case report forms schedule--TEXT (continued from previous page)

BASELINE FORMS		
Form 25/26-B	Clinical Form	DataFax within 1 month of randomization.
Form 25/26-C	Surgery Form	DataFax within 1 month of randomization.
Form 25/26-H	Prior Treatment History Form	DataFax within 1 month of randomization.
Form 25/26-F	Hormone Receptor Form	DataFax within 1 month of randomization with the hormone receptor report and again if a hormone receptor analysis was done at recurrence.
Form 25/26-P	Pathology Form	DataFax within 1 month of randomization with a copy of the original path report.
Form 25/26-AE	Adverse Event Form	Complete prior to starting protocol treatment (tamoxifen, exemestane, triptorelin) and DataFax within 1 month of randomization. This form is also required at follow-up (see instructions below.)
Form 25/26-CCM	Concomitant Medications Form	Complete prior to starting protocol treatment (tamoxifen, exemestane, triptorelin) and DataFax within 1 month of randomization. This form is also required at follow-up (see instructions below.)
FOLLOW-UP FORMS		
Form 25/26-E	Follow-Up Form	DataFax every 3 months in Year 1, every 6 months during Years 2-6, and yearly thereafter.
Form 25/26-OFS	Ovarian Function Suppression Form	DataFax at each follow-up period until completion of OFS.
Form 25/26-TE	Tamoxifen/Exemestane Form	DataFax at each follow-up period until the completion of tamoxifen and/or exemestane.
Form 25/26-AE	Adverse Event Form	DataFax at each follow-up period during protocol therapy (tamoxifen, exemestane, triptorelin), and with Form 25/26-E at 6 and 12 months after the last dose of protocol therapy. This form is also required at baseline.
Form 25/26-CCM	Concomitant Medications Form	DataFax at each follow-up period during protocol therapy (tamoxifen, exemestane, triptorelin), and with Form 25/26-E at 6 and 12 months after the last dose of protocol therapy. This form is also required at baseline.
Forms 25/26-QLC, 25/26-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 25/26-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 25/26-MQL	Missed QL Form	DataFax if scheduled QL Core, Module and/or Supplement Form(s) is/are not obtained.
EVENT-DRIVEN FORMS		
Form 25/26-R	Radiotherapy Form	DataFax after completion of radiotherapy, or if radiotherapy was planned but not given.
Form 25/26-CT	Chemotherapy Form	Data Fax after completion of chemotherapy, or if chemotherapy was planned but not given.
Form 25/26-SAE-A	Serious Adverse Event Form (Section A)	DataFax within 24 hours when SAE occurs, see Section 7.3.
Form 25/26-SAE-B	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 25/26-EIU	Exposure in Utero Form	DataFax if patient becomes pregnant during protocol therapy (tamoxifen, exemestane, triptorelin), and when pregnancy outcome is known.
Form 25/26-GYN	Gynecologic Procedures Form	Use to report gynecologic surgery, procedures and/or diagnostic imaging (excluding PAP smears and procedures related to diagnosis of cervical carcinoma in situ). DataFax with the next scheduled Form 25/26-E.

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.

8.2 Pathology materials submission

The following material must be sent to the IBCSG Coordinating Center within three months of randomization: 1 tumor tissue block, 1 normal tissue block, 1 representative H&E slide from each of the blocks (see Appendix IV). 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. See Section 11 for more information.

8.3 Data management

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

8.4 Investigators' file

Each 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
- 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

8.5 Authorization log

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

8.6 Patient identification log

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

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

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

9 Statistical considerations

9.1 Study design, objectives, and stratification

This study is a multi-national, Phase III, randomized clinical trial designed to evaluate five years of GnRH analogue plus tamoxifen versus five years of GnRH analogue plus exemestane. The trial is designed to answer the following question for premenopausal patients with hormone-receptor positive breast cancer:

Do results differ between GnRH analogue plus tamoxifen for five years and GnRH analogue plus exemestane for five years?

The randomization will be stratified according to participating institution, use of adjuvant/neoadjuvant chemotherapy (no; yes), and number of positive axillary and/or internal mammary lymph nodes (0 – including pN0(sn), pN0(i+)(sn) and pNx; 1 or more – including pN1mi). In addition to the overall study population, treatment comparisons will be performed separately according to chemotherapy and nodal status strata.

9.2 Data analyses

Primary treatment comparisons 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 alpha level of 0.05. Kaplan-Meier estimates of the DFS distributions will be calculated for each of the two arms. Cox proportional hazards regression models will be used to investigate whether the treatment comparison is modified by adjustments for various covariates.

Other factors will be used to characterize the patients enrolled in the study and to provide descriptive statistics of outcomes according to subgroups of the population. These factors include age at randomization, type and schedule of chemotherapy, type of surgery, use of post mastectomy radiation, tumor size, tumor grade, hormone receptor proportion score, and ER/PgR subgroup. These analyses will be considered as secondary and descriptive.

The following additional secondary outcomes will be assessed: overall survival, systemic disease-free survival, 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

Because all women will receive GnRH analogue, the patients enrolled in this protocol are likely to be younger premenopausal women. We will assume that most of the women enrolled in the trial will receive chemotherapy together with GnRH analogue. 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].

Premenopausal women with ER-positive, 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). If we assume that a little over 60% of the cases enrolled in this trial will be node-positive, the 5-year DFS with chemotherapy alone is estimated at 51%. A 40% reduction in risk of relapse by adding tamoxifen [3] and a hypothesized 25% additional risk reduction associated with GnRH analogue puts the estimated baseline risk for the GnRH analogue plus tamoxifen control group at 74.1%.

The treatment comparison will be based on a logrank test with an overall two-sided level of 0.05. Table 9.1 shows the operating characteristics of three alternative designs that would allow the detection of 20%, 25%, and 30% reduction in hazard by using exemestane instead of tamoxifen.

Table 9.1. Operating characteristics for the GnRH analogue plus exemestane versus GnRH analogue plus tamoxifen comparison.

Reduction in hazard	20%	**25%**	30%
GnRH analogue + tamoxifen 5-yr DFS	74.1%	**74.1%**	74.1%
GnRH analogue + exemestane 5-yr DFS	78.6%	**79.8%**	81.0%
Two-sided alpha level	.05	**.05**	.05
Required number of events*	653	**396**	260
Power	.80	**.80**	.80
Accrual rate (pts/year)	410	**410**	410
Total accrual time (yrs)	4.5	**4.5**	4.5
Sample size	1845	**1845**	1845
Total Study duration with 4 interim + 1 final analyses (yrs)*	10.4	**6.9**	5.3

* Under the alternative hypothesis with 4 interim analyses and 1 final analysis [47].

For planning purposes, we will target a 25% reduction in hazard. This will require recruitment of **1845 patients** (410 patients per year for 4.5 years with 2.4 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. Approximately 9% were less than 35 years of age and about 25% were less than 40. Thus, we anticipate approximately 40 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.

We prospectively plan to combine the data available for the TEXT study with the arms comparing exemestane plus ovarian function suppression (OFS) versus tamoxifen plus OFS in the complementary Suppression of Ovarian Function Trial (SOFT: IBCSG 24-02). We note that TEXT and SOFT differ with respect to patient selection and treatment for women who receive chemotherapy; TEXT enrolls patients following surgery and uses concurrent GnRH analogue and chemotherapy, while SOFT enrolls patients who remain premenopausal following chemotherapy and initiates OFS (GnRH analogue, surgical oophorectomy or ovarian irradiation) following the completion of 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 comparison (at the 0.05 level) to detect a 20%, 25%, or 30% reduction in hazard with OFS + exemestane versus OFS + tamoxifen would be at least 88%, 98%, and 99%, respectively, assuming that both SOFT and TEXT recruit as planned and the combined analysis is performed 6.9 years from the opening of the two studies.

9.4 Interim monitoring

A group sequential design with four interim analyses and one final analysis will be used [47]. The target number of events for the final analysis is 396, and interim analyses will be planned after 99 (25%), 158 (40%), 237 (60%), and 317 (80%) events have been observed. We anticipate that this monitoring scheme will provide annual formal analyses from the time that 99 events have been observed. At each interim analysis and at the final analysis, testing will be performed using the O'Brien-Fleming boundaries (3.969, 3.297, 2.659, 2.284, 2.036) [48].

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 99th 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) 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 ER-positive and/or PgR-positive tumors are eligible.

The following items are required for all patients:

1. Completed Hormone Receptor Form
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

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 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 Coordinating Center Office in Bern (**IBCSG Coordinating Center, Effingerstrasse 40, CH-3008 Bern**). The Australia-New Zealand Group will maintain a tumor bank within Australia. The H&E section is sent to Prof. Gusterson's laboratory in Glasgow for central pathology review, and then returned to Bern for storage. Central pathology review reports will be available to institution pathologists who wish to see them. 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 [49] and second primaries [50]. In addition, research is ongoing to determine whether genetically-associated breast cancer responds differently to treatment [51].

12 Ethics committee review and patient informed consent

12.1 Ethical Review Board/Ethics

All protocols and the patient informed consent forms must have the approval of a properly constituted committee or committees responsible for approving clinical trials. The ERB/IRB written, signed approval letter/form must contain approval of the designated investigator, the institution, the protocol (identifying protocol title and version number), and of the patient informed consent template, as well as the composition of the Ethical Committee (names of members) that approved such documents. Documentation of ethical committee approval should be sent to the IBCSG Coordinating Center prior to enrollment of the first patient. The IBCSG Ethical Committee also reviews the protocol annually.

12.2 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 12.3. Additional institution-specific sections should be added to Appendix I as described in Section 12.3.

The medical record must be available for review by the IBCSG audit team as described in Section 12.4.

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

12.3 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/17-c_e.html) 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.

12.4 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

The IBCSG through the SIAK/SAKK has a Public and Products Liability Insurance. All persons, acting on behalf of the Named Insured, are covered as Additional Insured. The scope of coverage is Comprehensive Swiss Form.

This insurance does not cover any liability resulting from medical malpractice. Specifically the negligence in the application of the protocol and/or treatment of the patients is excluded.

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

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Appendices

I. Requirements for Informed Consent
II. NCI Common Toxicity Criteria, Version 2 [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

IBCSG Trial 25-02 (TEXT) /BIG Trial 3-02

Appendix I

IBCSG PATIENT INFORMATION AND INFORMED CONSENT

1) This 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.

2) This template can be edited to incorporate information specific to your institution and the final version should receive the Institutional Review Board/ Local Ethical Committee approval in advance of use.

3) Following the ICH-GCP guidelines, the Informed Consent should contain information about the following items:
   a) The trial involves research
   b) Purpose of the trial
   c) Trial treatment (s) and the probability of random assignment
   d) The subject's responsibilities
   e) The aspects of the trial that are experimental
   f) Risks
   g) Benefits
   h) Alternative treatments available
   i) Compensation/Expenses
   j) Subject's participation is voluntary/right to withdraw
   k) Confidentiality
   l) Information about course of the trial
   m) Circumstance under which trial may be terminated
   n) Contact persons for further information or in case of injury
   o) The approximate number of subjects involved in the trial
   p) Duration of subject's participation in the trial

4) This 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.

5) In order to assist in the preparation of your customized version, an electronic file in Word will be distributed via e-mail to all Principal Investigators or IBCSG members may download it from the IBCSG web site (www.ibcsg.org).

PATIENT INFORMATION SHEET AND INFORMED CONSENT APPENDIX I

IBCSG PATIENT INFORMATION SHEET FOR CLINICAL RESEARCH

You are being asked to participate in a clinical research study. The doctors at different centers of the International Breast Cancer Study Group (IBCSG) throughout the world study the nature of breast cancer and attempt to develop improved methods of diagnosis and treatment. This is called clinical research. In order to decide whether or not you should agree to be part of this research study you should understand enough about its risks and benefits to make an informed judgment. This process is known as Informed Consent.

This Patient Information Sheet gives detailed information about the research study which your doctor has already discussed with you. Once you understand the study, if you wish to participate, you will be asked to sign the Patient Informed Consent. You will have a copy of this document and of the Patient Informed Consent to keep as a record.

PROPOSAL FOR A NEW CLINICAL RESEARCH STUDY

The clinical research study being proposed to you is:

Tamoxifen and Exemestane Trial (TEXT)

A Phase III Trial Evaluating the Role of Exemestane Plus GnRH Analogue as Adjuvant Therapy for Premenopausal Women with Endocrine Responsive Breast Cancer

PURPOSE OF THE RESEARCH STUDY

You have been diagnosed with a type of breast cancer that is known to respond to hormonal treatment in the majority of patients, because it expresses hormone receptors. The disease has been confined to the breast, possibly to lymph nodes under the axilla, but there is no evidence of spread elsewhere in your body. Standard local therapy consists of surgery with or without radiation therapy. In addition, standard therapy involves hormonal therapy which is known, in patients with breast cancer similar to yours, to decrease the chance of the cancer reappearing in your body at a later date. Standard hormonal treatment includes an estrogen modulator called tamoxifen. More recently, another family of hormonal drugs called aromatase inhibitors, to which the drug exemestane (Aromasin®) belongs, has shown initial promising results in post-menopausal women. It is still unclear whether tamoxifen or an aromatase inhibitor is the best preventive treatment for post-menopausal breast cancer patients. Aromatase inhibitors are not efficient on their own in premenopausal women as high levels of estrogens are present. In addition, premenopausal patients also benefit from suppression of the ovaries to simulate menopause. This ovarian function

suppression can be achieved by either radiation therapy, surgical resection of the ovaries or by a class of drugs, known as the GnRH analogues, given as monthly injections for five years. The addition of aromatase inhibitors will further decrease the level of circulating estrogen. Chemotherapy has also been shown to lower the risk of recurrence in premenopausal patients with breast cancer, independent of whether the cancer is sensitive to hormone therapy or not, and could be added to your treatment plan.

This study will compare the effectiveness of exemestane with tamoxifen, both given orally for 5 years. All patients will also receive monthly GnRH analogue (triptorelin) injections to suppress ovarian function for 5 years. The hormonal treatment could be stopped earlier in case of evidence of disease recurrence. Chemotherapy, if needed, will be given at the beginning, concomitantly to the start of the monthly injections.

DESCRIPTION OF THE CLINICAL RESEARCH STUDY

Patients will be assigned randomly (similar to the toss of a coin) to receive the current standard therapy with tamoxifen and the monthly injection of triptorelin or the combination of exemestane and the same monthly injection. Your doctor will choose the type of chemotherapy, if deemed necessary. This study will permit the estimation of the effects of the treatment on the patients' likelihood of recurrence and death from breast cancer and on their quality of life. A total of 1845 patients are expected to be enrolled in this study over a period of four years at many centers around the world.

Your participation in this research trial is entirely voluntary and you will be given sufficient time to decide whether or not you wish to participate.

TREATMENT

It is not clear at this time which combination of hormonal treatment will be better for you. For this reason, the treatment offered to you will be chosen by a method called randomization. Randomization is a method similar to the "flip of a coin"; the chances of you receiving either of the treatments are approximately equal. In consequence, neither you nor your doctor will choose a treatment for you, but at random (by chance), you will be assigned to receive one of the following treatment programs:

Arm A: Triptorelin and tamoxifen for 5 years

Arm B: Triptorelin and exemestane for 5 years

Tamoxifen is taken in tablet form by mouth each day. Exemestane is taken as a tablet by mouth each day.

The drug given as a monthly injection to suppress the ovaries on this study is triptorelin and its use in early stage breast cancer is experimental. The injections will be given intramuscularly. With triptorelin, the ovaries may start working again when injections are stopped. In rare circumstances your physician may suggest a different drug for injection (goserelin), but it will not be provided by the study.

If necessary, your doctor will also choose an appropriate chemotherapy regimen. The duration of chemotherapy is between 3 and 6 months depending on the choice of therapy.

You will have a full medical history and physical examination taken at the time you enter the study and every 3 months for the first year, every 6 months for the second to sixth year, and once a year thereafter. You will also have blood tests (about one tablespoon). A mammogram and a chest x-ray will be done at the time you enter the study if they have not already been done in the past 12 months. Your doctor may suggest other tests, such as a bone scan.

Bilateral mammogram or mammography of the contralateral breast is also recommended at yearly intervals or according to national standards or hospital specific requirements.

Bone densitometry is recommended yearly for 6 years. Your doctor may recommend a medication if your bone mineral density is adversely affected.

For patients receiving chemotherapy, lab tests will be done regularly during treatment and before each cycle.

You will be followed regularly by your medical doctor, during study treatment, but also thereafter for the remainder of your life.

At specified intervals during the study, you will be asked to fill out questionnaires that ask you how well you feel and what side effects you are having from the treatment. You will be given Quality of Life Questionnaires before you begin the study, every 6 months during the first and second years and once a year during years 3 to 6. If, for any reason, a question makes you fell very uncomfortable, you may leave the question unanswered. However, we would like to encourage you to answer all of the questions because your answers may help us better understand how the treatment influences the quality of patients' everyday life.

You will receive the hormone treatment (tamoxifen or exemestane) for 5 years unless there is evidence of disease recurrence. However you will continue to be followed on this study for the remainder of your life to determine if your cancer ever comes back.

If during the course of the study, information becomes available to clearly identify that one of the treatment options is better, you will be informed and further treatment will be discussed.

As described in detail below, hormone treatments produce some side effects. It is important that you tell your physician about additional medication that you take during or after treatment. Your physician will recommend medications to help with these side effects. For women with vaginal dryness and/or dyspareunia (pain with intercourse) vaginal moisturizers and lubricants may be used. If these do not help the symptoms, local vaginal estrogens may be considered. If you have troublesome hot flushes your doctor might recommend a serotonin reuptake inhibitor medication. Because any of the treatments in this study may increase the risk of osteoporosis, adequate calcium intake or supplements and weight bearing exercise may be recommended. Women who have evidence of bone density loss (osteoporosis) may be recommended to have specific treatments for osteoporosis, such as alendronate (Fosamax).

RISKS AND DISCOMFORTS

While on the study, you are at risk for side effects, as discussed below. You should discuss these with your doctor. There also may be other side effects that we cannot predict. Other drugs may be given to make some of these side effects less serious and uncomfortable. Many side effects go away shortly after the drugs are stopped, but in some cases side effects can be serious, long lasting or permanent. There may also be unexpected risks (risks not known about).

You should report any side effect or symptom that you experience to your physician.

Triptorelin or gosereline injections (GnRH analogue):
The most common side effects include the usual symptoms experienced during menopause. These side effects are hot flushes, stopping of menstrual periods, inability to have children, decrease in sex drive, and vaginal dryness and/or dyspareunia (painful intercourse). Infertility and other menopausal side effects may be reversible after ceasing the injections. Less frequent side effects are headache, tiredness, mood changes, sleep disturbance, nausea, back or joint pain, local irritation where the shots are given and slight rise in cholesterol. Loss of bone mineral density (osteoporosis) may occur and may lead to broken bones. Rare side effects include skin rash, allergic reactions, changes in blood pressure and elevated liver blood tests. Anaphylactic shock, a very severe allergic reaction that can cause death, is very rare but has occurred.

Tamoxifen:
The most common side effects are hot flushes, night sweating, vaginal discharge or dryness, fluid retention, irregular periods, vulvar itching and nausea. Tamoxifen may be associated with loss of bone mineral density in pre-menopausal women while it decreases bone mineral density loss in the menopausal state. Rare side effects of tamoxifen include retaining fluid, skin rash, and hair thinning. An infrequent side effect is abnormal occurrence of thromboembolic events. A blood clot in the leg can cause serious problems, including death, if it travels to the lungs. If you have had a history of a

thromboembolic event you might not be suitable to take part in this study. Women taking tamoxifen may be at a slightly higher risk for getting cataracts or rarely other eye problems. Tamoxifen can raise sensitivity to blood thinners such as coumadin.

Tamoxifen may cause changes in the lining of the uterus (endometrium). In addition, for every 1000 patients who take tamoxifen each year, 1-2 patients have developed cancer of the uterine lining (endometrial cancer), and even fewer have developed a cancer of the uterine muscle (uterine sarcoma). There may be also an increased risk of polyps and hyperplasia. In the event of abnormal vaginal bleeding or pelvic pain, you should have a gynecological examination.

Exemestane:
The most common side effects are hot flushes, nausea, increased sweating, fatigue, hair thinning, dizziness and skin rash. Exemestane may result in loss of bone mineral density (which can lead to broken bones).

Chemotherapy:
The expected side effects of chemotherapy depend on the treatment chosen by your doctor. In general, chemotherapy may cause a transient increase in your risk of infection and of bleeding; some chemotherapy regimens may also cause transitory nausea and vomiting as well as reversible hair thinning or hair loss. Your doctor will offer you a detailed explanation of specific risks related to the combination of chemotherapy drugs he/she has chosen for you.

Reproductive risks (all treatments):
Treatment under this study may involve unforeseeable risks to an unborn child if a woman should become pregnant during the course of this study treatment. In general, if your ovaries are suppressed, you will not be able to become pregnant, but you cannot be certain about that. For this reason, women are advised to use effective non-hormonal contraception during participation in this study. Hormonal contraception of any type is not allowed while on this study. You should not breast feed while taking study treatment. You should not participate in this study if you are pregnant or wish to become pregnant within the next 5 years.

Your physician will be checking you closely to see if any of the side effects are occurring. Physical exam, routine blood tests and other tests (depending on the choice of therapy) will be done to monitor the effects of treatment.

Your doctor will prescribe medication to keep these side effects under control. Schedules and dosages may be also altered to reduce their frequency and intensity.

Your physician may also decide to stop the treatment early in case of thromboembolic event, vaginal bleeding, abnormal blood counts (white blood

cells, red blood cells, platelets, neutrophils), impaired functioning of the kidneys or liver, severe gastrointestinal symptoms or any other serious toxicity.

This clinical research protocol has been approved by (*please insert name of local Ethical Committee that has approved the protocol*). This committee is responsible for making sure that research with patients is appropriate and that, in your community, the patient's rights and welfare are protected.

BENEFITS

The ultimate goal of conducting clinical research studies in breast cancer patients is to better understand the behavior of breast cancer and to find better ways of treatment. We hope that the treatment under this clinical research study will be of benefit to you and/or that it will help others, although we cannot guarantee this. The aim of this study is to define the best combined hormone treatment in premenopausal women with hormone sensitive breast cancer.

ALTERNATIVE TREATMENTS

Instead of being in this study, your doctor may recommend that you receive hormonal therapy with tamoxifen for five years plus or minus a GnRH analogue with or without chemotherapy.

EXPENSES

You will receive no payment for taking part in this study. Exemestane and triptorelin will be supplied to you on this study free of charge if you are randomized to a treatment using one of those drugs. All other expenses, including the cost of tamoxifen, chemotherapy, surgery or radiation and routine standard examinations will be handled similarly as if you were receiving standard treatment and not participating in a clinical trial.

INSURANCE

IBCSG has a public and products liability insurance. All persons, acting on behalf of the named insured, are covered as additional insured. The scope of coverage is comprehensive Swiss form. This insurance does not cover any liability resulting out of medical malpractice; especially the negligence in the application of the respective protocol and/or treatment of the patients is excluded.

CONFIDENTIALITY

Medical records of patients are maintained under strict confidentiality as required by law. Confidentiality will be maintained during and after your participation in the study. Data collected during the study will be stored and analyzed by computer. It will be stored for a prolonged period (over 15 years). If at any time you wish to withdraw from the study and have the data relating to your case destroyed,

please notify the IBCSG directly or through your doctor by submitting a written statement. Data will be analyzed exclusively for the purposes of research in breast cancer. Neither your name nor anything that could identify you will be used in any reports or publications that result from this study. During their required reviews, representatives of IBCSG, the health authorities, the pharmaceutical company representatives or subcontractors (Pharmacia/Pfizer Oncology) and the local ethics committee may have access to medical records that contain your identity. This will be done only under the formal agreement that confidentiality will be respected in all cases.

COLLECTION OF BIOLOGICAL MATERIAL

If you participate in this study, it is planned that a sample of tissue obtained at the time of your surgery for breast cancer will be sent to a central laboratory or institute for pathology review, and at a later stage for use in research projects to investigate biologic properties of breast cancer. Samples may be collected and stored at the IBCSG Coordinating Center. The use of the material for research will be under the supervision of the Scientific Committee of the IBCSG and will be submitted to the appropriate Ethical Committees.

You may decide to grant advance authorization for possible future new studies on your stored tissue specimens, with the understanding that their confidential nature will be fully protected and that a prior approval of an appropriate ethics committee will be obtained. Alternatively, you will be asked to consent to any such future study. On the other hand, you have the right to refuse consent to storage and further research on your tissue specimens except for the needs of the present study.

There will be no advantage or disadvantage to you as a result of such studies, and you will not incur additional cost as a result of obtaining the above-mentioned samples.

VOLUNTARY PARTICIPATION/RIGHT TO REFUSE OR WITHDRAW

The choice to enter, or not to enter, this study is yours. You are free to make a decision after you have fully understood what the doctor has explained, what you have read about the research study and other possible forms of care. If you begin the study, you will have the right to withdraw at any time without giving any reason. This will not affect in any way your future medical assistance. However, if you decide to stop participating in the study, we encourage you to talk your doctor first. If you should withdraw from study treatment, you will be offered other available care which suits your needs and medical condition.

In this case, we request your agreement to periodically contact you or your treating physician to provide basic information about your medical status. If instead you chose to withdraw from both treatment and follow-up, you may be asked to have a last examination before you withdraw.

TERMINATION OF THE STUDY

You might stop receiving study treatment without your consent for the following reasons:

a) If your breast cancer recurs.

b) If the doctors treating you detect side effects that they consider dangerous for you.

c) If you refuse to have the treatments or follow-up examinations and tests needed to determine whether the treatment is safe and effective.

d) If you become pregnant.

e) If the early analyses of trial data show a significant potential benefit or harm for one of the two arms.

NEW INFORMATION ARISING FROM THIS STUDY

You have the right to be informed of the progress of the research study and of its final results. During the time that you are participating in the study, you will be informed of any new findings which might affect your willingness to continue.

CONTACT PERSONS

The physician in charge of this study is (*give name, telephone number of PI*). If you need more information about this study before you decide to join, or at any other time, you may wish to contact him/her. In the event that you do decide to participate, he/she should also be called if there are severe side effects from the treatment.

PATIENT INFORMED CONSENT FOR CLINICAL RESEARCH

TITLE: Tamoxifen and Exemestane Trial (TEXT)

A Phase III Trial Evaluating the Role of Exemestane Plus GnRH Analogue as Adjuvant Therapy for Premenopausal Women with Endocrine Responsive Breast Cancer Tamoxifen and Exemestane Trial

Ovarian Function Suppression + Tamoxifen vs. Ovarian Function Suppression + Exemestane

STATEMENT OF PHYSICIAN OBTAINING INFORMED CONSENT

I have fully explained this clinical research study to the patient _____. In my judgment, and that of the patient, there was sufficient access to information, including risks and benefits, to make an informed decision.

Collection of tissue sample: It is planned that a sample of tissue obtained at the time of your surgery for breast cancer will be sent to a central laboratory or institute for pathology review, and at a later stage for use in research projects to investigate biologic properties of breast cancer as described above. Please indicate your choice in regards to the use of the sample of your breast cancer:

☐ I grant advance authorization for possible future new studies on my stored tissue specimens, with the understanding that their confidential nature will be fully protected and that a prior approval of an appropriate ethics committee will be obtained.

☐ I would like to be asked to consent to any such future study.

☐ I refuse consent to storage and further research on my tissue specimens except for the needs of the present study.

DATE: _____

PHYSICIAN'S SIGNATURE: _____

PHYSICIAN'S NAME: _____

PATIENT'S STATEMENT

I have read the description of the clinical research study or have had it translated into language I understand. I have also talked it over with the doctor to my satisfaction. I understand that my participation is voluntary. I know enough about the purpose, methods, risks and benefits of the research study to judge that I want to take part in it. I understand that I may

freely stop being part of this study at any time. I have received a copy of this consent form and of the patient information sheet to keep for myself.
DATE: _____ [Date must be written by the patient]

PATIENT'S SIGNATURE: _____

PATIENT'S NAME: _____

PATIENT'S DATE OF BIRTH: _____

WITNESS' SIGNATURE (if applicable): _____

WITNESS' NAME (if applicable): _____

PLEASE KEEP A COPY OF THE SIGNED INFORMED CONSENT. DO NOT SEND THE SIGNED INFORMED CONSENT FORM TO THE IBCSG.

Patient ID number assigned at randomization _____

IBCSG Trials 24-02, 25-02, 26-02/BIG 2-02, 3-02, 4-02

Appendix II: NCI Common Toxicity Criteria, Version 2

[available from the internet at: http://ctep.info.nih.gov/reporting/ctc.html.**]**

IBCSG Trials 24-02, 25-02, 26-02/BIG 2-02, 3-02, 4-02 Appendix III: Guidelines for the Immunocytochemical Evaluation of Hormone Receptor Status and Quality Assurance

1 Tissue samples

Sections from a representative formalin-fixed paraffin-embedded block of the tumor should be immunostained. Immunostaining of frozen tissue samples is not recommended.

Ideally, the blocks should be taken from the periphery of the tumor and include a small component of nonneoplastic breast tissue (to serve as an internal control for immunostaining).
The choice of the block best suitable for the immunocytochemical investigation should also be based on the following characteristics:

- Be representative of the invasive component of the tumor (even in cases with extensive or predominant intraductal component) and of the dominant histologic type of the tumor (in case of mixed carcinomas).
- Good preservation of the tissue morphology (avoid use of the permanent paraffin block of previously frozen tissue for intraoperative diagnosis or other purposes).
- Lack of extensive necrosis or fibrosis.

In case of *multifocal or multicentric tumors*, only one block needs to be immunostained.

2 Immunocytochemical staining

Several different monoclonal antibodies to estrogen and progesterone receptors are commercially available and are suitable for immunostaining of formalin-fixed paraffin-embedded tissue sections with consistent results.

It is recommended to pretreat the tissue sections with an antigen retrieval solution (e.g. citrate buffer) under microwave irradiation or other suitable heating devices (pressure cooker, autoclave, etc.), according to the expertise and the facilities of the different laboratories.

Different detection systems may be used according to the laboratory routine, based on peroxidase or alkaline phosphatase as reporter molecules. Immunofluorescence techniques are not recommended.

3 Evaluation of the results

It is recommended to evaluate the results according to the following procedure:

3.1 Check for expected immunostaining of nonneoplastic breast tissue:

- Intense nuclear staining of at least a minor percentage of luminal epithelial non-myoepithelial cells, and
- Lack of immunoreactivity of stromal and inflammatory (if any) cells

3.2 Evaluate the staining pattern of the neoplastic component at low/intermediate magnification (100-250x), taking into account any significant heterogeneity of staining in different parts of the invasive tumor.

Do not consider staining of the intraductal (or in situ) component.

3.3 At higher magnification (HPF=400x), check for a definitely nuclear localization of the immunostaining:

Do not consider as specific any membrane or cytoplasmic staining. This unspecific staining may appear on occasion (especially when apocrine or squamous metaplasia is present) and it does not interfere with the specific nuclear staining of the hormone-responsive neoplastic cells.

3.4 In case of tumors with **homogeneous** staining throughout, randomly select at least 10 HPFs (comprising a minimum of 2,000 invasive tumor cells) and count the number of cells showing nuclear immunostaining (irrespective of the staining intensity) over the total number of neoplastic cells.

Record the results as an overall percentage of cells showing nuclear immunostaining on the IBCSG Hormone Receptor Form F.

3.5 In case of tumors with significant staining ***heterogeneity***, select the 10 HPFs in order to mirror the degree of staining heterogeneity. For example, if only 20% of the invasive tumor area shows diffuse nuclear staining and the remaining tumor has only occasional (or none) immunoreactive cells, count only 2 HPFs in the former area and 8 HPFs in the latter.

3.6 For many IBCSG trials hormone receptor positive is defined as a value of 10% or higher immunoreactive neoplastic cells. Accordingly, ***if your evaluation of a given case is 10%*** or very close to this value, ***repeat*** the assessment of the results at least once on additional 10 HPFs, in order to check for consistency.

4 Quality assurance and external quality assessment

Quality assurance is essential in clinical laboratories for the provision of precise and accurate analyzes to support optimal patient care and to monitor participant competence in clinical trials. Quality assurance improves test reliability minimizing variability arising from biological or analytical sources, inherent in all quantitative measurements of qualitative examinations.

Overall, quality assurance seeks to guarantee the right result from the right test, at the right time, on the right specimen from the right patient, interpreted using the right reference data. There are three main components:

Quality Assurance (QA) encompasses all measures taken to ensure the reliability of investigations, starting from test selection, through obtaining a satisfactory sample from the right patient, analyzing it and recording the result promptly and correctly, to appropriate interpretation and reporting to the appropriate clinician for action, with all procedures being documented for reference.

Internal Quality Control (IQC) assesses, in real time, whether the performance of an individual laboratory or testing site is sufficiently similar to the previous performance for results to be used; it controls reproducibility or precision, and facilitates continuity of patient care over time. Most IQC procedures employ analysis of a control material and compare the results with predetermined limits of acceptability - unsatisfactory sets of results may thereby be suppressed.

External Quality Assessment (EQA). QA and IQC are systems that look within a particular testing site. EQA by contrast looks at differences among different sites testing the same analyte, so there can be continuity of testing over geography. This usually involves the analysis of identical specimens at many laboratories, and the comparison of results with those of other sites and a "correct" answer; the process is necessarily retrospective. The overriding need is for comparability of results, which requires good IQC practices and the complementary discipline of EQA.

4.1 External quality assessment

All IBCSG participating laboratories should participate in an external quality assessment program. One such program is the UK NEQAS, which provides a network of educational schemes unmatched in its comprehensiveness and quality throughout the world. To enroll in this program, contact Barry Gusterson at the Central Pathology Office (tel: +44 141 211 2233, fax: +44 141 337 2494, email: bag5f@clinmed.gla.ac.uk).

While IQC controls the precision of investigations, EQA should be providing an assessment of their accuracy (lack of bias) with respect to other test sites. This is done periodically and retrospectively, hence use of the term "assessment" rather than "control".

Though individual laboratory performance is frequently the main consideration, EQA also provides assessment of:

- *the overall standard of performance (state of the art)*
- *the relative performance of analytical procedures (method principle, reagents, instruments)*
- *the specimens distributed*

These are important in that EQA can provide information through pilot surveys and schemes, on intra-laboratory concordance and on whether establishing a regular EQA scheme is likely to help stimulate any needed improvement. Similarly, EQA may indicate analytical procedures showing excellent performance characteristics which can be recommended, and also identify unsatisfactory procedures which should be discouraged. The assessment of materials provides a continuing check on the reliability of the scheme and its specimens.

Experience has indicated a number of fundamental criteria required for effective EQA design. EQA can only document the need for, stimulate and monitor improvement: the improvements themselves come from effective quality assurance and IQC procedures within the individual participating laboratories.

These criteria are:

- ***Sufficient recent data, achieved through:***
  - *frequent distributions*
  - *rapid feedback of initial performance information following analysis*
- ***Effective communication of performance data, through:***
  - *structured, informative and intelligible reports*
  - *a cumulative scoring system*
- ***An appropriate basis for assessment, including:***
  - *stable, homogeneous specimens which where practicable resemble clinical specimens*
  - *reliable valid target values*

Though the evidence is necessarily circumstantial, schemes satisfying these criteria are associated with improved between-laboratory comparability, both overall and in individual participating laboratories. Full and regular participation in appropriate external quality assessment schemes is therefore established as a necessary and integral part of the rational provision of reliable clinical laboratory services. **All of the above applies to measurements in the setting of clinical trials and in particular when a measurement is used as an entry criterion.**

IBCSG Trials 24-02, 25-02, 26-02/BIG Trials 2-02, 3-02, 4-02 Appendix IV: Pathology Guidelines

1 Pathologists and central review

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 is responsible for ensuring that the Pathology Form is compete and accurate, and that the pathology materials are properly collected and submitted. The central review pathologist will review the submitted specimens and complete the Central Pathology Review (CPR) form.

2 Collecting and submitting materials

The following items are required for all randomized patients:

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

The tissue blocks may be returned to the participating center upon request.

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

2.1 Pathology Form (P)

2.1.1 Maximum diameter and ductal carcinoma *in situ*

All lesions should be measured in the fresh or fixed state and on the histological preparation. If the two measurements are discrepant, that obtained from histological examination should be recorded where tumors are small enough to be visualized in cross-section. This may give a small underestimation in the size due to shrinkage of the tissue in processing. It is considered, however, that the slight but consistent underestimation in the size of all tumors is preferable to the larger and less predictable errors that may result from measuring poorly delineated tumors macroscopically. Clearly, sufficient blocks should be taken from the periphery of larger tumors to allow accurate estimates of their size to be made from combined histological and macroscopic examination. The largest dimension should be recorded to the nearest millimeter.

With the increasing use of conservation surgery for breast cancer, the identification of histological features associated with an increased risk of local recurrence is clearly important. The Boston group defines extensive intraductal carcinoma (EIC) as that comprising more than 25% of the main invasive tumor mass extending beyond it into surrounding breast tissue or a tumor which shows foci of invasion, but is predominantly of intraduct type. A recent EORTC consensus meeting concluded that "the principal risk factor for local relapse after breast conserving treatment is large residual burden, and the main source of this burden is an extensive *in situ* component which is found adjacent to 10-15% of all invasive breast carcinomas" (1). Holland reported locally recurrent carcinoma after a maximum of 7 years (mean 3.7) at a rate of 13% with EIC and 3.7% without (2). A significant proportion of such cases relapse as invasive carcinoma. These findings suggest that part of the routine histological assessment of breast tumors should include information about the nature of the intraduct component.

It is recommended that pathologists take blocks from macroscopically normal tissue between an excised tumor and excision margins in all three planes of section.

For invasive carcinomas, only the invasive component needs to be recorded. The largest dimension, to the nearest millimeter, is recorded in each case. Foci of lymphatic and blood vessel invasion are not included in the whole tumor measurement.

2.1.2 Histological type, please attempt to place the type in one of the designated categories.

2.1.3 Grade

Grading should be according to the Bloom, Richardson, Elston (B.R.E.) method (3) which has been shown to be more accurate for statistical analysis. Please try to use it. The following instructions are provided to assist you. Please refer to the original publication and to the NHSBCS booklet (4) for detailed examples. As histopathologists often have difficulties with the grading scheme of Bloom and Richardson; the modified Elston version only includes true mitotic figures and not "hyperchromatic figures".

The method has been recently adopted by the Royal College of Pathologists Working Group for the National Health Service Screening Programme in the UK. The use of this grading system is also supported by D Page (Vanderbilt University, US) as the best system for grading. It is also being supported by the European Union which is funding a teaching CD for pathologists which will incorporate this grading scheme as the standard. The method involves assessment of three components of tumor morphology; tubule formation, nuclear pleomorphism and frequency of mitoses. We ask you to enter each of the three scores individually and then add them together for a total score.

Tubule Formation
Score

1. majority of tumor (greater than 75%)
2. moderate amount (10-75%)
3. little or none (less than 10%)

Nuclear pleomorphism
Score

1. nuclei small, with little increase in size in comparison with normal breast epithelial cells, regular outlines, uniform nuclear chromatic, little variation in size.
2. cells larger than normal with open vesicular nuclei, visible nucleoli and moderate variability in both size and shape.
3. vesicular nuclei, often with prominent nucleoli, exhibiting marked variation in size and shape, occasionally with very large and bizarre forms.

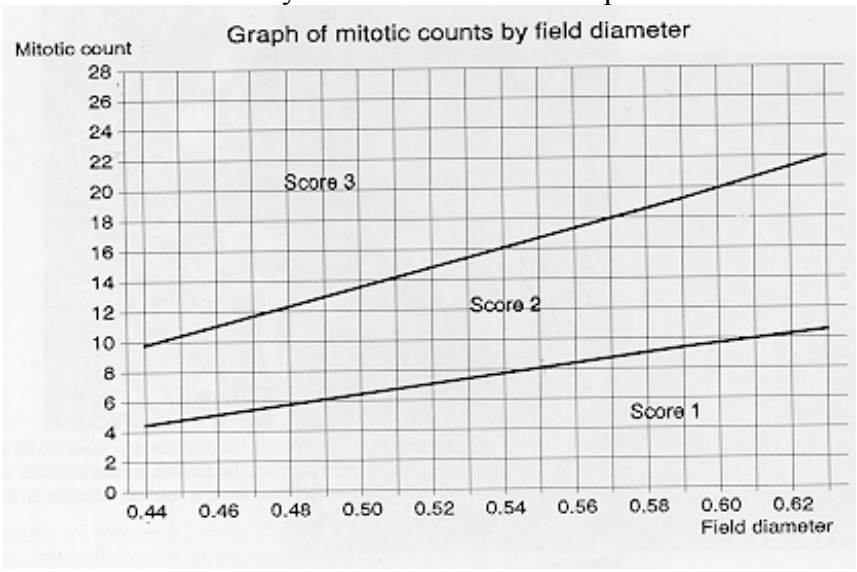
Mitoses
The score depends on the number of mitoses per 10 high power fields assessed at the tumor periphery. The size of a high power field is very variable and hence it is necessary to standardize the mitotic count using the graph in the figure. In order to determine the mitotic count for an individual microscope, the following procedure should be adopted:

1. measure the field diameter of the microscope with a graticule.
2. plot this value on the horizontal axis of the graph.
3. draw a vertical line at this value.
4. read off the value **a** on the vertical axis where the line intersects the lower bold line.
5. read off the value **b** on the vertical axis where the line intersects the upper bold line.
6. the count is then:

Score	Count
1	0 to **a**
2	between **a**+1 and **b**
3	>**b**

For example, for a field diameter of 0.48 **a**=6, **b**=12 and therefore
Score 1 = 0-6 mitoses / 10hpf
Score 2 = 7-12 mitoses / 10hpf
Score 3 = >12 mitoses / 10hpf

This needs to be done only once for each microscope.



Overall Grade

The scores for tubule formation, nuclear pleomorphism and mitoses are then added together and assigned to grades as below:

Grade 1 = score 3-5
Grade 2 = score 6-7
Grade 3 = score 8-9

It is recommended that grading is not restricted to invasive carcinoma NOS but is undertaken on all histological subtypes. There are two major reasons for this recommendation:

1. There are occasionally problems in deciding whether to classify a tumor as NST or some other type.
2. There may be significant variation within certain subtypes, e.g. invasive lobular carcinoma.

It must be clearly stated if a grading system other than that described above is used.
Occasionally, if there is insufficient material or poor fixation, it may not be possible to use the B.R.E. method accurately. In those cases:

Grade 1 -- well differentiated
Grade 2 -- for moderately differentiated
Grade 3 -- for poorly differentiated

is acceptable. Note this simple grading does not correlate with the Bloom, Richardson, Elston grade. If you have difficulty in using the Elston grading scheme, which is now being applied in many centers, please send details of the difficulty with examples and Central Review will advise.

IF WE DO NOT USE UNIFORM CRITERIA, THE RESULTS ARE MEANINGLESS.

Grading Ductal Carcinoma *in situ*
Ductal carcinoma *in situ* (DCIS) is defined as a proliferation of epithelial cells with cytological features of malignancy within parenchymal structures of the breast and is distinguished from invasive carcinoma by the absence of stromal invasion across the basement membrane.

DCIS varies in cell type, growth pattern and extent of disease and may thus represent a group or spectrum of related *in situ* neoplastic processes. Classification has traditionally been according to growth pattern but has been carried out with little enthusiasm given a perceived lack of clinical relevance. More recently, evidence has emerged that lesions composed of cells of high nuclear grade are more aggressive. There is currently no generally accepted method of classifying DCIS but distinction between common histological subtypes is of value for correlating pathological and radiological appearances, improving diagnostic consistency, assessing the likelihood of invasion and determining the probability of recurrence after local excision. Despite the name, most DCIS is generally considered to arise from the terminal duct lobular units. The nuclear grading system adopted below is derived from that employed by Holland *et. al.* (5)

High Nuclear Grade DCIS

This is composed of cells with pleomorphic, irregularly-spaced and usually large nuclei exhibiting marked variation in size, irregular nuclear contours, coarse chromatin and prominent nucleoli. Mitoses are frequently present and abnormal forms may be seen.

High nuclear grade DCIS may exhibit several different growth patterns. It is often *solid* with central, *comedo*-type necrosis which frequently contains deposits of amorphous calcification. This is the easiest pattern to recognize. Sometimes a *solid* proliferation of malignant cells fills the duct without necrosis but this is relatively rare and is usually confined to nipple ducts in cases presenting with Paget's disease. High nuclear grade DCIS may also exhibit *micropapillary* and *cribriform* patterns frequently associated with central comedo-like necrosis. Unlike low nuclear grade DCIS, there is rarely any polarization of cells covering the micropapillae lining the intercellular spaces.

Low Nuclear Grade DCIS

This is composed of monomorphic, evenly-spaced cells with roughly spherical, centrally-placed nuclei and inconspicuous nucleoli. The nuclei are usually, but not invariably, small. Mitoses are few and there is rarely individual cell necrosis.

The cells are generally arranged in *micropapillary* and *cribriform* patterns, which are frequently present within the same lesion, although the latter is more common and tends to predominate. There is usually polarization of cells covering the micropapillae or lining the intercellular lumina. Less frequently, low nuclear grade DCIS has *solid* growth pattern. When terminal duct lobular units are involved, the process can be very difficult to distinguish from lobular carcinoma *in situ*. Features in favor of DCIS are greater cellular cohesion and lack of intracytoplasmic lumina. Occasionally, however, there may be combination of both processes.

Intermediate Nuclear Grade DCIS

Some cases of DCIS cannot be assigned easily to the high or low nuclear grade categories. The nuclei show mild to moderate pleomorphism which is less than that seen in high grade DCIS but they lack the monotony of the small cell type. The nucleo cytoplasmic ratio is often high and one or two nucleoli may be identified.

The growth pattern may be *solid, cribriform, or micropapillary* and the cells usually exhibit some degree of polarization covering papillary processes or lining intercellular lumina although this is not as marked as in low nuclear grade DCIS.

Mixed Types

A proportion of cases of DCIS exhibit features of more than one histological sub-type. One of the advantages of classifying DCIS according to nuclear grade is that, although variations of growth pattern are frequent, there is usually a dominant cell type and the lesion is fairly easily classified into one of the above main groups.

Rarely, cells of different nuclear grade may be seen within a single-lesion. This should be recorded *but the case should be classified according to the highest nuclear grade observed*.

2.1.4 Excision margins

The distance from the nearest resection margin should be recorded and checked from the histological sections. Other margins can be reported if required. This normally refers to the infiltrative component but, if associated ductal carcinoma *in situ* extends nearer to the margin than the infiltrative component, then enter its distance from the margin and state in the appropriate section in the P form.

There are many ways to mark the planes of surgical excision of biopsies. No single method is ideal, each having advantages and disadvantages. Practical advice and comments are contained in reviews listed at the end of this appendix (6,7,8). These should be consulted to determine the method most appropriate to local circumstances. Some biopsies are submitted fresh, others in the fixed state. The requirement for fresh tissues of material for biochemical analysis may be adversely affected by the marking paints.

India ink is widely used but is slow to dry and thus has the tendency to penetrate the planes of the tissue close to the site of its application. In consequence, some regard it as an unreliable marker of the external plane of surgical excision. Nevertheless, preliminary drying of the specimen or coating with alcohol can obviate this problem. Non-aqueous solvents like acetone and ethanol have been tried and allow the ink to dry more quickly. The specimen should not, of course, be sliced until the ink is dry.

Another recommended method is to coat the specimen with warm gelatin. Instead of relying upon the evaporation of a solvent, the use of gelatin depends on the setting of the gel. This is facilitated by preliminary chilling of the tissue. Fixation of the coated specimen apparently increases polymerization in the gel, thus rendering it still more durable. The well-known typists' aid "Tippex" has also been tried but, unfortunately, is densely radio-opaque on account of its titanium content. The dye Alcian blue and inorganic pigments are fast drying and the latter can be used for differential color marking. Commercially available pigment markers have been recommended which also have the advantage of being able to identify different planes for clearance.

The evaluation of surgical margins of biopsies is to be encouraged given the provisions stated above. Except in cases where the margin passes directly through a focus of cancer, the findings should, however, be interpreted with circumspection. The histopathology report should comment on the closest margin giving distance in mm, and specifying whether any involvement is by invasive or non-invasive cancer. The information should be related to orientation markers if given.

2.1.5 Vessel invasion includes both lymphatic and blood vessels.
The presence of unequivocal tumor in vessel spaces should be recorded. If there is doubt about diagnosing vessel invasion, please choose the **no** box. The difficulty in identifying small vessels as blood or lymphatic precludes accurate recording of their type and specification of lymphatic or venous invasion is not required. Ideally, a clear rim of endothelium should be identified around the tumor before vessel invasion is recorded. The use of immunostaining for endothelial markers may be helpful in confirming vessel invasion in difficult cases but is not recommended on a routine basis. Morphological features which may be helpful when diagnosing vessel invasion are:

1. clumps of tumor in spaces outside the main tumor mass are more likely to indicate vessel invasion.
2. nests of tumor separated from the stroma by shrinkage artifact usually conform better to the shape of the space in which they lie.
3. the proximity of larger veins and arteries helps in the diagnosis of lymphatic invasion.
4. the presence within the space of erythrocytes and/or thrombus.

2.1.6 HER2/NEU Record the HER2/neu expression.

2.1.7 Markers Record if any of the markers were done. If sub-studies of a given marker are planned cases can be identified.

2.1.8 Axillary nodal involvement All lymph nodes should be examined histologically. The use of immunohistology is most appropriate in cases where there is doubt about the presence of small metastases. The clinical relevance of metastases detected solely by this means remains controversial.

2.1.9 Sentinel node biopsy information should be recorded if such a biopsy was performed. The sentinel node must be examined serially and completely in frozen sections or after formalin fixation and paraffin embedding. The node must be bisected along its major axis (or sliced at 2-3 mm intervals if thicker than 0.7-0.8 cm) and both moieties (or all slices) must be embedded. Special attention must be paid to preserve the integrity of the node capsule. Serial sections must be cut at 50-150 micron intervals until the complete examination of the node. Please consider that approximately 10% of the micrometastases seen with 50-micron cutting levels will be missed with cutting levels of 150-micron.

Immunochemistry for cytokeratins may help in the identification of micrometastases, but this is not considered mandatory. It is suggested to perform immunocytochemical stainings only to ascertain the nature of suspicious cells seen in H&E sections. The assessment of the size of the sentinel node metastases is correlated with the likelihood of additional metastases to nonsentinel axillary nodes. It is recommended to measure the largest size of the metastases in the plane of the sections and to calculate their thickness according to the number of contiguous sections involved and to the cutting intervals (i.e., if a metastasis is present in three contiguous 5-micron sections at 100-micron interval, calculate the thickness adding the 100 micron before the first involved section, the 200 micron between the 3 involved section, the 100 micron after the last involved section and the 15 micron representing the thickness of the 3 sections = 100+200+100+15=415 micron. Record on the P form the maximum size, which may be either the largest diameter in the plane of the sections or the calculated thickness of the metastases.

2.2 <u>The Pathology Report</u> should be a copy of all relevant clinic/hospital pathology reports. The patient's initials, specimen number, and randomization number should be clearly written on the report. The Report should be submitted to the Coordinating Center.

2.3 <u>Pathologic material</u> Two paraffin blocks, one tumor and one normal tissue, and representative H & E slides must be submitted to the Coordinating Center. All material must be labeled with the patient's randomization number.

Institutions will submit paraffin blocks to the Coordinating Center, who will forward them to the Central Pathology Laboratory. Whenever indicated, the Central Lab will use the tissue array technology (see below) to obtain a small amount of material from the block. The tissue array will be logged and stored, and the paraffin blocks will be returned to the participating center upon request. The Group anticipates that returning the blocks to the institutions within a short time will increase the feasibility of full compliance with tissue collection.

Tissue array technology was designed as a method for analyzing changes involved in the development and progression of cancers at both the molecular and the protein level. This

technique is unique in its ability to simultaneously analyze large numbers of human tumors with minimal consumption of rare archival specimens. Tissue arrays are made up of 0.6mm cores from tumor biopsies of different tumor blocks, precisely arrayed in a single paraffin block (9).

Advantages of tissue arrays have been demonstrated in two recent publications (10, 11) and include:

- Negligible damage to donor blocks
- 600 different tumors can be arrayed in a single block
- Simultaneous screening of large number of biopsies
- In clinical trials, simultaneous testing and targeting of new diagnostic or prognostic markers
- Significant reduction in staining and microscopy time
- Reduction in the consumption of reagents.

Tissue arrays are suitable for use in IHC, FISH, PCR and RT-PCR, and cores can be used for DNA and RNA extraction. It is estimated that the amount of DNA extracted from a 0.6mm core is sufficient for 50 PCR runs.

2.4 Submitting material

Fax the Pathology (P) Form and the Pathology Report to an IBCSG DataFax number. Full instructions on submitting forms will be distributed to each center and are available on the IBCSG website (www.ibcsg.org). The website also lists fax numbers available for faxing reports and forms.

Slides and blocks should be mailed to:
IBCSG Coordinating Center
Effingerstrasse 40
CH-3008 BERN, Switzerland

All reports, slides, and blocks must be marked with the IBCSG patient ID number. Slides should be sent in customized slide boxes. They should be packed with tissue paper to prevent any movement. If slides move around when the box is shaken, they have not been packed sufficiently.

3 Fixative

3.1 Standard procedure

Aqueous solution of formaldehyde 4% (10% formalin) isotonic and neutral.

Adequate dissection of the specimen must be accomplished before fixation, as this fixative penetrates slowly (1 mm/hour).

NB: For those using immunohistochemistry for ER and/or PgR determination, please cut tumor into 2 mm slices and fix immediately after surgery.

Whenever possible, at least one section of the primary tumor should be allowed to fix in a large volume of formalin for at least 24 hours before processing.

3.2 Frozen tissue

Whenever possible a sample of primary tumor (0.5gm) and a sample of non-tumorous breast should be snap frozen without prior fixation and stored at -70˚ or in liquid nitrogen.

4 Sampling

4.1 Primary tumor

Sufficient blocks should be taken to enable complete histological assessment. Ideally one should include the maximum tumor dimension.

At least one block of grossly non-cancerous breast tissue should be submitted from each quadrant in each case and its source designated in the protocol.

Other lesions found in any of the breast quadrants should be noted in the protocol and submitted for microscopic examination with appropriate identification.

At least one central section of the nipple should be submitted. If vascular invasion is present, a representative slide should be submitted.

4.2 Lymph nodes

Care should be taken during excision and handling of lymph nodes, as compression of tissue during the procedure can result in distortion. Forceps should be applied only to the surrounding tissue and not to the node. The node should be removed intact rather than in fragments. Ideally, the node should be sectioned in the mid-line of long axis from cortex to medulla.

5 Embedding and sectioning

Embed in paraffin or paraplast.

6 Staining and mounting

Routine staining using hematoxilin eosin method is the accepted standard. Routine mounting on glass slides covered with glass slips is the accepted standard.

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Acknowledgement

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APPENDIX V
QUALITY-OF-LIFE PROTOCOL
Tamoxifen and Exemestane Trial (TEXT)
IBCSG Trial 25-02; BIG 3-02

1. Introduction

Breast cancer patients receiving adjuvant endocrine treatment are faced with menopausal symptoms [1, 2]. These symptoms have an important impact on patients' daily life, not only on physical but also on emotional well-being [3,4]. For example, vasomotor symptoms are frequent [5, 6] and may be associated with sleeping difficulties and feelings of depression [7]. Quality-of-life (QL) evaluation including menopausal symptoms is therefore an essential objective in the IBCSG Trial 25-02.

The two objectives of QL assessment in this protocol are: (i) to compare treatments in regard to QL; (ii) to compare QL in this trial to that in other adjuvant breast cancer trials.

These objectives will be addressed using the same basic approach to QL assessment that the IBCSG has used since 1986 [8, 9]. It has been shown to be feasible for international breast cancer clinical trials [10, 11]. Previous methodological and clinical investigations were mainly related to chemo- and chemo-endocrine effects. An example relevant to the IBCSG Trial 25-02 is the analysis of the indicator for *hot flushes* in node-negative postmenopausal patients with operable breast cancer (IBCSG Trial IX) [9]. This indicator showed a high discriminative capacity between patients on chemotherapy and those on tamoxifen within the first three months.

Using the same approach to QL assessment will allow us to make comparisons across IBCSG trials, using the extensive QL database, which will be available from other trials.

2. Objectives

QL will be described in regard to intermediate- and long-term sequelae of treatment and disease, and the treatments will be compared in regard to QL. Specifically, the hypotheses to be investigated are

2.1. Primary hypotheses

2.1.1 Patients receiving exemestane plus ovarian function suppression will report more menopausal symptoms than those with tamoxifen plus ovarian function suppression (see section 8.).

2.1.2 Patients receiving exemestane plus ovarian function suppression will report more sexual impairment than those with tamoxifen plus ovarian function suppression (see section 8.).

These hypotheses will be tested by comparing the treatment groups using serial measurements of QL indicators over time (see 5.1). The indicator for *hot flushes* included in the IBCSG QL Core Form and the indicator for *loss of sexual interest* included in the trial-specific QL module are the primary endpoints for sample size considerations.

2.2. Secondary hypotheses

2.2.1 The differences between treatments will persist over the whole treatment period (see 8.).

2.2.2 Those patients who report more severe menopausal symptoms during the first 6 months on endocrine therapy will also report delayed adaptation in other QL indicators both during and beyond that time (see 8.).

Physical well-being, mood and coping will be used to describe patients' adaptation over time [10]. The findings of this trial will be compared to that in other IBCSG adjuvant breast cancer trials.

Further exploratory analyses will address (i) the relationships among the QL measures (e.g., the impact of menopausal symptoms on global QL indicators, especially on overall treatment burden, physical well-being, coping and mood); (ii) bio-psychosocial interactions (e.g., the impact of initial prognostic factors on QL) [12].

3. Patient Selection

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 will be determined at the activation of the trial for each participating cooperative group.

Recruitment of 1872 patients will maximize the opportunity to detect clinically relevant treatment effects on QL.

4. Study Design

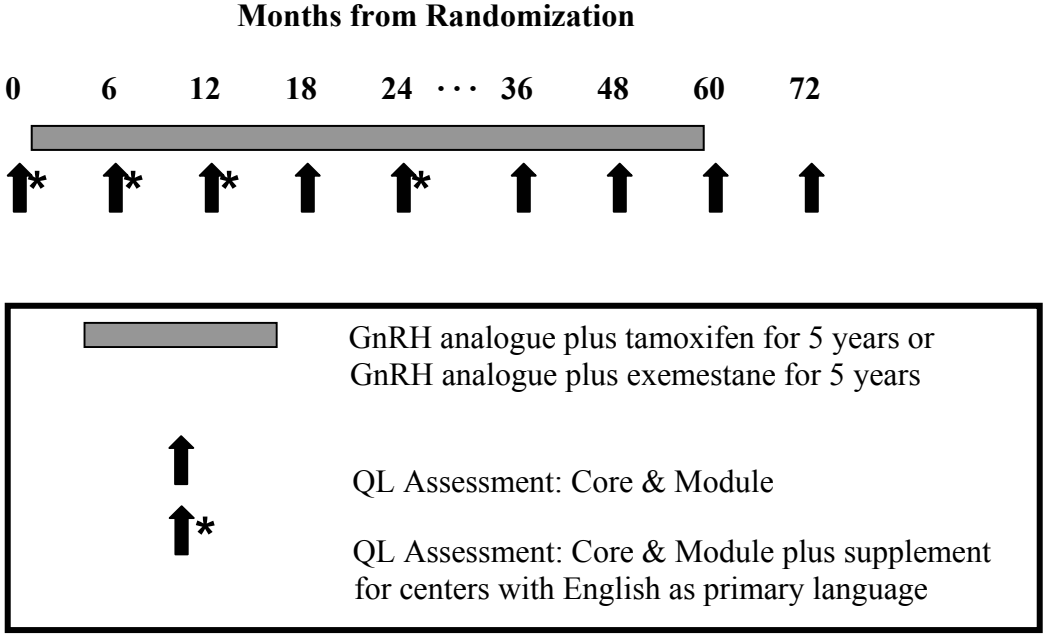
As in the other IBCSG trials with QL, a longitudinal design is used, including a baseline assessment, assessments to evaluate intermediate and long-term effects, and assessments following treatment failure to evaluate the impact of relapse. To the extent feasible, the assessment time schedule is compatible to that of the other trials to keep it as simple as possible and to allow comparisons across trials.

Patients are asked to complete a QL core form plus a trial-specific module

- at baseline, prior to randomization
- every 6 months during the first and second year,
- and annually in years 3 to 6.

All patients, regardless of disease status, are to be assessed on the same schedule. A detailed data collection schedule is displayed in *Figure 1*.

Figure 1: Quality of Life Assessment Time Points



To eliminate any differential anticipatory effects on baseline scores and to help insure compliance with the protocol requirements, a QL Core Form plus Module must be completed prior to randomization (i.e., it is an eligibility requirement for IBCSG participating centers).

5. Quality-of-Life Measures

5.1 Patient rated Quality of Life

The QL assessment consists of the *IBCSG QL Core Form* and a trial specific *module*.

The QL Core Form was developed in 1986 [8], and was subsequently revised for IBCSG Trials 10-93 through 14-93 [9], which started on May 1, 1993. The revised form is designed to address the endpoints in adjuvant trials more specifically while still keeping the questionnaire simple and short. It includes global linear analogue self-assessment (LASA) indicators for physical well-being, mood [13], coping (PACIS) [14], perceived social support and subjective health estimation (SHE) [15]. The indicators for physical well-being, mood and coping were confirmed to be responsive to cytotoxic side effects, mental distress and psychosocial dysfunction in patients with early breast cancer [16]. They are suitable to describe patients' adaptation over time. Validation studies are summarized elsewhere [9].

In addition, LASA indicators specific to symptoms of nausea and vomiting, tiredness, *hot flushes*, and restrictions in arm movement are included, covering possible QL effects of all of the treatment modalities involved in these trials (surgery, chemo-, endocrine and radiation therapy).

For the IBCSG Trial 25-02, a one-page module for endocrine symptoms will be used in addition to the QL Core form. Besides non-experimental studies, the selection of symptoms was based on two recent breast cancer prevention trials which compared the effects of tamoxifen with those of placebo [5, 6]. All symptoms are assessed in the LASA response format. In addition, one global indicator is included for overall treatment burden ("Overall, how much are you bothered by any treatment related difficulties?"). This indicator has been validated regarding side-effects of anti-emetic and cytotoxic therapies [17] and is expected to be similarly responsive to endocrine symptoms.

An expanded three-page IBCSG Trial 25-02 module will be used for participating centers having English as the primary language. The first page will be the same as the module completed at all participating centers in the study. The second and third page will contain additional questions from the Center for Epidemiologic Studies-Depression Scale (CES-D) [18] and the Medical Outcomes Study (MOS) sexual problems measures [19]. These questionnaires have been used frequently for US Intergroup studies. The CES-D and the MOS are included to provide cross-validation between responses to selected IBCSG core and module questions and these comprehensive measures. These questionnaires will also be used as common QL reference data for the IBCSG and CALGB trial. Their assessment is restricted to baseline, months 6, 12 and 24.

In clinical trials, the distinction between indicators of specific symptoms and global indicators sensitive to treatment as well as disease-related problems in the broadest sense is very useful. In the global indicators, the score reflects a patient's *subjective*, intuitive choice and weighting of different aspects, summarized in a single response. Specific disease and treatment-related indicators can be used to examine the changing impact of symptoms on overall measures over time and in different situations. This can be done within a treatment group (e.g., for patients receiving tamoxifen plus ovarian function suppression, how much of the variation in the coping measure can be explained by the major menopausal symptoms over the first year) or to explain differences in the global measures among treatment groups (e.g., does *hot flushes* explain differences in physical well-being among the randomized treatments at 12 months).

The conceptual basis of the IBCSG approach to QL assessment, along with a description of methodological issues, clinical findings and planned steps for further development, have been summarized elsewhere [9].

5.2 Sociodemographics and Co-morbidity

As in the other IBCSG QL trials, sociodemographic data and co-morbidity are part of the standard study documentation.

6. Timing Requirements, Data Collection and Local Data Management

6.1 Timing requirements

Assessment time points are determined by the interval from date of randomization, and coincide with the required clinical follow-up time points. The QL assessment time points are illustrated in Figure 1.

The schedule of QL assessment must be followed as closely as possible. The QL form has to be filled in always *prior to* diagnostic procedures. If exact timing is not possible, assessment should be done as close as possible to the required date.

For methodological reasons, the required schedule has to be followed exactly, with neither more nor fewer assessments. Shortly after randomization, the IBCSG operations office sends the local investigator a *schedule of the dates* of required QL assessments. This list should be put into each patient's chart to aid in the correct timing of the QL assessment.

6.2 Data Collection and Local Data Management

Within the first 6 years, every study patient is to fill in both the QL Core Form and the trial specific module at each scheduled assessment time point, as described in Figure 1; no form selection is acceptable.

If the patient does not complete the required QL Forms, then a Missing QL Assessment Form **must** be submitted for that assessment time point to provide the reason why the assessment was not completed.

The QL forms are to be filled in at the clinic. If the patient is being followed elsewhere, arrangements are to be made with the clinic or physician to have the patient fill in the forms as required. If, for administrative reasons, the form has not been presented to the patient, it may be filled in at home and mailed.

For the first assessment, the QL forms have to be explained to the patient, with particular emphasis on making sure the patient understands both LASA format (used in all questionnaires) and categorical response format (used only in supplemental questionnaires for centers with English as the primary language). For later assessments, the patient should be instructed to seek help only if she has problems in understanding any of the items in the form.

All questions on the QL Core Form and the QL Module should be answered. The forms should be checked after completion and, if necessary, the patients should be asked to fill in missing answers. Patients may wish to leave some questions unanswered if they make them feel very uncomfortable. They should be encouraged to answer all items, however, especially those concerning menopausal symptoms, as they represent a primary objective of the QL study

Detailed instructions for the QL assessment are given in the *IBCSG QL Manual*. Copies are available from the IBCSG Coordinating Center in Bern.

7. Central Data Management

Computerized data quality control measures will be used to monitor the submission rates of the QL forms and the timing of assessment as required by the study protocol. Institutions will receive feedback on their performance and specific problems on a regular basis.

8. Statistical Considerations

8.1 Sample Size Calculations

This phase III randomized clinical trial is designed to compare differences in QL between patients who receive GnRH analogue plus five years of tamoxifen and those who receive GnRH analogue plus five years of exemestane. According to investigator choice, patients can either receive no adjuvant chemotherapy or receive adjuvant chemotherapy to start at the same time as the GnRH analogue. The randomization is stratified according to chemotherapy use. QL will be described in regard to intermediate and long-term sequelae of treatment and disease. We will test the above hypotheses by comparing the treatment groups using serial measurements of QL indicators over time.

Many QL indicators are collected, but the indicators *hot flushes* and *loss of sexual interest* are selected to determine sample size. We will calculate the QL sample size to reflect both short and long term effects. First, to reflect the short-term effects we will base the QL sample size on the mean treatment difference of the change in *hot flush* scores from baseline to 6 months. Next, to reflect the long-term effects we will use the mean treatment difference of the change in *hot flush* scores from baseline to 24 months. Both sample size calculations were based on a two-sided 0.05 level test and respective standard deviations from IBCSG Trial IX were used to compute the 2 sample sizes.

To address the short-term effects, the common standard deviation, calculated from the pooled estimator of the variance of the change in *hot flush* scores from IBCSG Trial IX of Arm E (Tamoxifen) and Arm F (CMF -> Tamoxifen), was 35.1. 304 assessable patients per arm (608 total) are needed to achieve an 80% statistical power to detect a mean treatment difference in a change in *hot flush* score of 8 units on the original scale. In IBCSG Trial IX, 66% of the eligible patients filled out the indicator for *hot flushes* at baseline and 6 months post randomization. If we assume a similar compliance rate in Trial 25-02 we would need a total of 921 patients randomized to two-arms to detect an 8-unit difference in treatment means of the change in *hot flush* scores from baseline to 6 months with 80% power.

Table 1 illustrates the total number of patients **enrolled in two arms** needed to detect a range of given treatment differences of the change in *hot flush* scores from baseline to 6 months with 80% power

Table 1

Δ*	Total Assessed	Total Needed Assuming 66% Compliance
10	390	591
9	480	727
8	608	921
7	792	1200

*Mean treatment difference of the change in *hot flush* score from baseline to 6 month

To address the long-term effects, the pooled standard deviation from IBCSG Trial IX between the two treatment arms was 34.2. In order to detect an 8-unit mean treatment difference of the change in *hot flush* score from baseline to month 24 with 80% power we will need 288 assessable patients per treatment arm (576 total). Sixty percent of patients enrolled in IBCSG Trial IX responded to the *hot flush* indicator at baseline and at month 24. If we assume a 60% compliance rate in Trial 25-02, then we would need a total of 960 patients randomized to two-arms to detect an 8-unit mean treatment difference with 80% power.

Table 2 shows the total number of patients **enrolled in two arms** needed to detect a range of given treatment differences of the change in *hot flush* scores from baseline to month 24 with 80% power.

Table 2

Δ*	**Total Assessed**	**Total Needed Assuming 60% Compliance**
10	370	617
9	456	760
8	576	960
7	752	1253

*****Mean treatment difference of the change in *hot flush* score from baseline to 24 months

The indicator for *loss of sexual interest* included in the trial-specific QL Module is the primary endpoint for testing whether patients receiving exemestane plus ovarian function suppression will report more sexual impairment than those receiving tamoxifen plus ovarian function suppression. The use of the QL Module for IBCSG Trial 15-95 was the first time an indicator for the *loss of sexual interest* was collected in an IBCSG trial. Trial 15-95 had two treatment arms: Arm A (standard dose EC/AC x 4 -> CMFx3 -> Tamoxifen) and Arm B (high dose ECx3 -> Tamoxifen). With regard to addressing the short-term effects, these QL data have matured and a common standard deviation of 35.6 was observed from calculating the mean treatment difference of the change in *loss of sexual interest* from baseline to 6 months. To detect a mean treatment difference of 8 units on the original scale with 80% power, 312 assessable patients are required in each group (624 total).

In Trial 15-95, 50% of the patients answered the *loss of sexual interest* question at baseline and at month 6. Assuming a 50% compliance rate in Trial 25-02, we would need a total of 1248 patients randomized in two arms to detect a mean difference of 8 units with 80% power.

Table 3 shows the total number of patients **enrolled in two arms** needed to detect a given range of treatment differences with 80% power.

Table 3

Δ*	Total Assessed	Total Needed Assuming 50% Compliance
10	400	800
9	494	988
8	624	1248
7	814	1628

*****Mean treatment difference of the change in *loss of sexual interest* score from baseline to 6 months

Although IBCSG 24-02 and IBCSG 25-02 include slightly different patient populations and treatment programs, both studies include comparisons of ovarian function suppression plus tamoxifen versus ovarian function suppression plus exemestane. We, therefore, intend to perform an analysis of the primary hypotheses of this QL study combining the information from both trials. This will enhance the power to detect QL differences between the two treatment groups.

8.2 Statistical Analysis

The primary analyses will be based on treatment differences at each QL assessment time point. Wilcoxon Rank Sum tests will be used to test for statistical significance. In addition, longitudinal data analysis techniques will be used to examine QL change over time. The longitudinal model accommodates informative censoring (dropout due to events that also affect QL such as relapse or death) and adjusts for data missing at random [20-22]. We will be modeling jointly the QL measure and time-to-event, such as overall survival. The survival component of the model acts as a "missing data mechanism". Intermittent missingness (missing data that occurs before the patient's time-to-event) is considered ignorable in this model (missing at random).

We will be collecting information on reasons why the patient did not fill out the QL assessment form. This information will be used to impute QL scores for intermittent data not missing at random. A sensitivity analysis will be done in parallel with various imputation techniques to validate the effect that imputing values has on the parameter estimates. A SAS macro has been made available to estimate these longitudinal models of informatively censored data.

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IBCSG Trials IBCSG 24-02/ BIG 2-02, IBCSG25-02/BIG 3-02, IBCSG26-02/BIG 4-02
Appendix VI: Authorization Log

Principal Investigator: _____ Group Number: _____

Job Title: _____ Center No: _____

Study Personnel, whose specimen signatures and initials appear below, are authorized to perform the following study tasks indicated by codes "A" to "I", on my behalf within the dates indicated. I confirm that they are qualified and appropriately informed about the trial.

A* = finally determine eligibility	D = make CRF entries/corrections	G = _____
B* = obtain informed consent	E* = sign CRFs	H = _____
C = perform key trial measurements	F = dispense medication	I = _____

*** Functions marked with an asterisk are considered the sole responsibility of the Principal Investigator, but may be delegated to Co-investigators. Codes G, H, and I may be used to specify other tasks or any of the above functions in which study personnel assist the investigator.**

Principal Investigator

Printed Name	Signature	Initials	Date
_____	_____	_____	_____

Participating Center personnel (Please use BLOCK CAPITALS)	Authorization code(s) (see above)	Signature	Initials	Date Authorized From/To + Principal Inv.'s Initials
Name: _____ Job Title: _____ Function:				From: _____ To: _____ Init: _____
Name: _____ Job Title: _____ Function:				From: _____ To: _____ Init: _____
Name: _____ Job Title: _____ Function:				From: _____ To: _____ Init: _____
Name: _____ Job Title: _____ Function:				From: _____ To: _____ Init: _____
Name: _____ Job Title: _____ Function:				From: _____ To: _____ Init: _____
Name: _____ Job Title: _____ Function:				From: _____ To: _____ Init: _____

IBCSG Trials 24-02, 25-02, 26-02/BIG Trials 2-02, 3-02, 4-02 Appendix VII: Participating Group Specific Logistical Information for [*insert the name of the Group*]

Appendix VII contains 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. This Appendix was developed and is maintained by the [*insert the name of the coordinating center or the operations office of the Group*]. The following information can be found in this appendix.

1 Group specific contact information ……. VII-1

2 Randomization procedures …… VII-2

3 Drug supply information ……... VII-3

4 Serious adverse event reporting procedures ……..…….. VII-4

5 Data submission and query resolution procedures ……. VII-5

6 Participation in the quality-of-life (QL) study …… VII-6

7 Pathology specimen submission procedures …… VII-7

8 Country/Group specific regulations and procedures ……. VII-8

Each Group should complete the following sections to provide the logistical information that is required to conduct the trial for their Group members. [This is a template that can be modified to satisfy the needs of your Group if so desired.]

Email a copy of the original Appendix VII that is created for your Group as well as any subsequent revised Appendix VII to the IBCSG Coordinating Center at STP@ibcsg.org so that we can maintain accurate and current records.

1 Group specific contact information

[This section includes information on group specific contact information, study participants, etc.]

2 Randomization procedures

[This section includes instructions on how to enroll patients to the study.]

3 Data submission and query resolution procedures

[This section includes instructions on how to submit CRFs. Instructions concerning how to submit responses to queries are also given.]

4 Serious adverse event reporting procedures

[This section describes how to report serious adverse events.]

5 Drug supply information

[This section describes how to obtain study drug supplies that are provided free of charge by the protocol - specifically, exemestane and triptorelin.]

6 Pathology specimen submission procedure

[This section includes instructions on where and how to submit the protocol required pathology tissues and slides.]

7 Country/Group specific regulations and procedures

[This section includes any other country/group specific regulations or procedures that the Group Coordinating Center/Operations Office considers useful to communicate to facilitate local conduct of this global clinical trial.]

INTERNATIONAL BREAST CANCER STUDY GROUP

IBCSG 25-02
BIG 3-02

Tamoxifen and Exemestane Trial (TEXT)

Amendment 3

A Phase III Trial Evaluating the Role of Exemestane Plus GnRH Analogue as Adjuvant Therapy for Premenopausal Women with Endocrine Responsive Breast Cancer

ovarian function suppression + tamoxifen versus
ovarian function suppression + exemestane

Coordinating Group: International Breast Cancer Study Group (IBCSG)

EudraCT Number: 2004-000168-28

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.

Protocol Amendment 3 Signature Page

IBCSG 25-02 / BIG 3-02

Tamoxifen and Exemestane Trial (TEXT)

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

Signature on file 14 Jul 11
Date

Protocol Amendment 2 Signature Page

IBCSG 25-02 / BIG 3-02

Tamoxifen and Exemestane Trial (TEXT)

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

(signature on file) *25Jul08*

Date

Protocol Amendment 1 Signature Page

IBCSG 25-02 / BIG 3-02

Tamoxifen and Exemestane Trial (TEXT)

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

IBCSG 25-02 / BIG 3-02

Tamoxifen and Exemestane Trial (**TEXT**).

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

(*Signature on File*) 17Apr03

Date

Principal Investigator Protocol Signature Page
Amendment 3

IBCSG 25-02/ BIG 3-02
Tamoxifen and Exemestane Trial (TEXT)

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

Tamoxifen and Exemestane Trial (TEXT)

A Phase III Trial Evaluating the Role of Exemestane Plus GnRH Analogue as Adjuvant Therapy for Premenopausal Women with Endocrine Responsive Breast Cancer

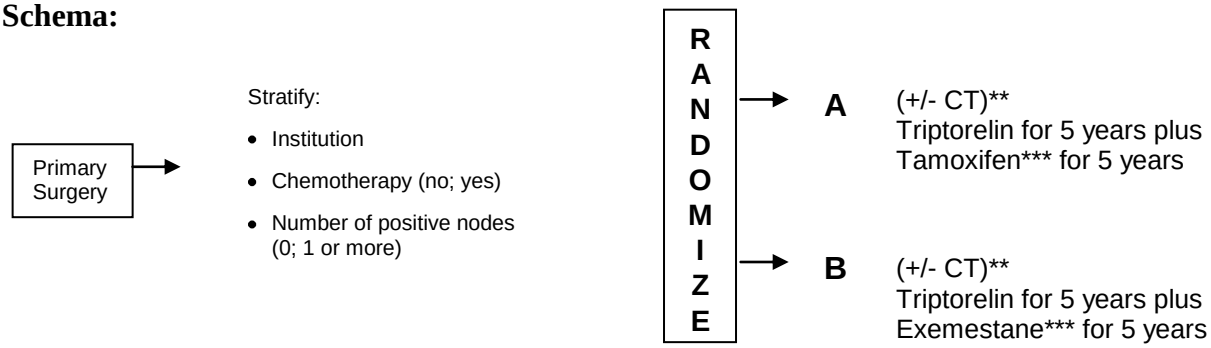
Patient Population: Premenopausal women with histologically proven, resected breast cancer with ER and/or PgR positive tumors.

Entry: Patients should be randomized within 12 weeks after surgery prior to commencing any adjuvant systemic therapy.

Stratification Factors:
- Institution
- Adjuvant 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)

Sample Size: ~~1845~~ 2639 patients

Schema:



* Randomization prior to receiving any adjuvant systemic therapy
**CT (chemotherapy), if used, should begin at the same time as triptorelin. Use of CT may be determined ~~by randomization in the PERCHE trial or~~ by investigator/patient choice.
***Tamoxifen or exemestane should start after adjuvant chemotherapy has been completed or approximately six to eight weeks after the initiation of triptorelin, whichever is later.

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 should commence chemotherapy after randomization at the same time as GnRH analogue. A planned duration of ≥ 2 months if an anthracycline is included (e.g. 4 cycles of EC or AC) or ≥ 4 months if no anthracycline is given (e.g. 6 cycles of CMF) is recommended. If an anthracycline is used, an epirubicin-containing regimen is recommended.

Adjuvant Endocrine Therapy:

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.

Tamoxifen: Tamoxifen 20 mg orally daily until 5 years from date of randomization, unless relapse or intolerance should occur earlier. Tamoxifen should start after adjuvant chemotherapy has been completed or approximately six weeks to eight weeks after the initiation of GnRH analogue, whichever is later.

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 start after adjuvant chemotherapy has been completed or approximately six to eight weeks after the initiation of GnRH analogue, whichever is later.

Translational Investigations:

TEXT-1 (patients randomized prior to 1 January 2008):

- Whole blood: A whole blood sample for DNA isolation according to the guidelines in the Manual for Blood Sample Logistics is required at the patient's next visit, after appropriate informed consent.

TEXT-2 (patients randomized after 1 January 2008):

- Whole blood: A whole blood sample for DNA isolation is required at baseline. It must be obtained prior to start of treatment but not more than 14 days prior to randomization, according to the guidelines in the Manual for Blood Sample Logistics.

Table of Contents

1 Introduction 13
1.1 Adjuvant therapy for premenopausal women with receptor positive breast cancer 13
1.2 The role of ovarian function suppression 14
1.3 Anti-aromatase agents 15
1.4 Bone mineral density 16
1.5 Translational research 17
2 Trial objectives 18
2.1 To compare GnRH analogue plus exemestane vs. GnRH analogue plus tamoxifen 18
2.2 Primary endpoint 18
2.3 Secondary endpoints 18
2.4 To investigate patient and tumor features that may contribute to inter-individual variability of responsiveness to GnRH analogue plus exemestane and GnRH analogue plus tamoxifen 19
3 Patient selection 19
3.1 Criteria for patient eligibility 19
3.2 Criteria for patient ineligibility 20
4 Randomization and stratification 21
4.1 Randomization timing 22
4.2 Registration procedures 22
4.3 Randomization help desk 22
4.4 Randomized groups 23
4.5 Stratification 23
5 Treatment details 23
5.1 Trial treatments 23
5.2 Side effects of study drugs 25
5.3 Concomitant treatments 26
5.4 Study drug supply 27
6 End points and definitions of treatment failure 28
6.1 Trial end points 28
6.2 Diagnosis of treatment failure 28
6.3 Translational endpoints 31
7 Study parameters 32
7.1 Table of study parameters 32
7.2 Adverse event reporting 36
7.3 Serious Adverse Event (SAE) reporting 36
7.4 Exposure in utero reporting 38
8 Data submission 38
8.1 Case report forms schedule—TEXT 39
8.2 Data management 41
8.3 Investigators' file 41
8.4 Authorization log 41
8.5 Patient identification log 42
8.6 Blood sample collection and submission 42
9 Statistical considerations 43
9.1 Study design, objectives, and stratification 43
9.2 Data analyses 43
9.3 Sample size considerations 43
9.4 Interim monitoring 45
9.5 Data and Safety Monitoring Committee (DSMC) 46
9.6 Sample size re-consideration 46
10 Quality of life 48
11 Additional protocol-specific parameters 48
11.1 Hormone receptors 48

11.2 Pathology and pathology material banking 49
11.3 Family history....50
11.4 Genetic markers of disease and drug metabolism and DNA banking 50
12 Regulatory approval procedures and patient informed consent 51
12.1 Ethics Review Board/Ethics Committee 51
12.2 Regulatory approval procedures....51
12.3 Requirements for Center Activation....51
12.4 Protection of human subjects 51
12.5 Informed consent procedures 52
12.6 Quality assurance....53
13 Administrative considerations 53
13.1 Insurance....53
14 References 53

Appendices

I. Requirements for Informed Consent
IA. Addendum to the Original Patient Information and Informed Consent
II. NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 available from the internet at: http://ctep.info.nih.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

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

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 the recent Early Breast Cancer Overview [56] the addition of LHRH agonists to tamoxifen, chemotherapy, or both reduced recurrence by 12.7% (p=0.02); and death after recurrence by 15.1% (p=0.03). LHRH agonists showed similar efficacy to chemotherapy. No trials had assessed an LHRH agonist versus chemotherapy with tamoxifen in both arms.

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. There is some evidence that GnRH analogues may have a direct beneficial effect on tumor cell death, for breast cancer and other cancers [22-25]. A trial conducted by the ECOG in postmenopausal patients (based on some anecdotal information [26]) confirmed some efficacy of GnRH analogue for the ER+ cohort, but no significant effect was observed for the ER- cohort [27]. Although it is clear that the effect of GnRH analogues, when given alone, is mainly through the indirect inhibition of endocrine ovarian function, antitumor efficacy via other mechanisms is not entirely elucidated. Furthermore, the combination of GnRH analogue and chemotherapy might also be useful to protect ovarian function from definitive cytotoxic-related damage. This might be advantageous especially for young women who choose to preserve fertility [28]. Therefore, use of GnRH analogue for five years is the method of choice to achieve ovarian function suppression in this clinical trial.

There are case studies of failure of ovarian function suppression under GnRH analogue [29]. 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 [30].

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 [31,32], 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) [33, 52]. 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) [53,54]. 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) [55].

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 [34]. 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 [35,36]. 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 [37].

Either the combination of a GnRH analogue with tamoxifen or the combination of a GnRH analogue with an aromatase inhibitor (exemestane) has the potential to improve survival in premenopausal women with endocrine responsive tumors over that seen with tamoxifen alone. This trial is designed to assess the role of GnRH analogue plus exemestane compared with GnRH analogue plus tamoxifen. 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 prevented loss of bone mineral density in postmenopausal women [38]. 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 [39]. ~~A pre-clinical trial by Goss et al. [40] 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.~~ A study conducted in healthy postmenopausal women by Goss et al. [40], to compare the effects of exemestane with the nonsteroidal aromatase inhibitors anastrozole and letrozole on serum and urine levels of bone turnover biomarkers, showed that exemestane increased serum levels of the bone formation marker PINP after 24 weeks, suggesting a specific bone-formation effect related to its androgenic structure.

1.5 Translational research

Optimizing the use of endocrine therapies by determining features of the disease or of the patients that suggest one or the other therapy is better for the individual woman is desirable so that treatments can be better tailored to the biological targets. Among the population of premenopausal women with hormone receptor-positive disease, TEXT offers a unique opportunity to investigate the roles of polymorphisms in patient- and disease-related genes and pathological tumor features as predictors of responsiveness to GnRH analogue plus tamoxifen or GnRH analogue plus the AI exemestane.

Estrogens mediate their action primarily via two nuclear estrogen receptors, ERα and ERβ. ERs are generally ligand activated transcription factors but several kinases in the growth factor signaling networks can also activate ER and its co-regulatory proteins, a process termed ligand-independent activation. Approximately 60% of all primary breast cancers are ERα positive, however, ERα is not a perfect biomarker for the prediction of endocrine responsiveness since some primary ERα positive tumors do not respond to tamoxifen (de novo resistance), and many that originally responded to tamoxifen eventually acquire drug resistance despite continued expression of ERα. Although much less is known about ERβ, it seems to have opposing activity on tumor growth as compared to ERα [57]. High levels of ERβ may help to inhibit tumor growth when the receptors are bound by tamoxifen [58], and low ERβ2 mRNA has been associated with worse outcomes in ERα positive tamoxifen-treated patients independently of other factors such as grade and nodal status [59]. Different ERα and ERβ polymorphisms have been recently described and associated with several possibly endocrine-mediated physiological mechanisms including bone remodeling [60-65]. Two common variants of ERα have been identified (Pvu II rs2234693 and Xbal rs9340799), which are 45 bp apart and located approximately 400 bp upstream of exon 2 of the ERα gene. In particular, Pvu II polymorphisms (variant P and p), located on intron 1, seem to be strong prognostic indicators of survival in postmenopausal women with ER-positive breast cancer. P-allele carriers have a significantly lower probability of death than non-carriers [66] and may also have higher transcription activity of ER, potentially achieving particular benefit from selective estrogen receptor modulators (SERMs) therapy [67]. Pvu II and Xbal are also associated with changes in bone remodeling markers; women with the Pvu II PP and Pp genotypes may have a greater risk of faster bone loss after menopause than those with the pp genotype [68].

The antiapoptotic protein Akt is a downstream target of EGFR signaling. Akt phosphorylation is associated with poor prognosis and resistance to endocrine therapy and chemotherapy. In patients with advanced phosphorylated-Akt (pAkt)-positive tumors, endocrine therapy (both SERMs and AIs) tends to be less effective than in pAkt-negative patients [69], suggesting that Akt activation induces endocrine resistance in metastatic breast cancer, irrespective of the endocrine agent being administered. Recently, two Akt1 polymorphisms (rs3730358 and rs2498799) have been described which may affect protein levels and cell resistance to apoptosis [70]. Both polymorphisms are quite common among Caucasians (minor allele frequency 30% and 11.8%). The major Akt haplotype is related to higher Akt levels and lower apoptotic response after γ-irradiation. It is conceivable that carriers of this haplotype are more likely to become resistant to endocrine therapy.

Much research has been recently conducted to elucidate the genetic determinants underlying inter-individual variability in drug pharmacokinetic parameters, safety and efficacy with the

ultimate goal of identifying subjects at risk for severe treatment toxicity or poor treatment response and the aim of personalized therapy selection. DNA variations in metabolism, transport and drug target genes have been shown to contribute to both efficacy and toxicities of adjuvant treatments of early breast cancer [71, 72]. Single nucleotide polymorphisms (SNPs) account for the majority of genetic variation in the human genome.

Tamoxifen undergoes extensive primary and secondary metabolism, and the concentrations of tamoxifen and its metabolites vary widely. 4-hydroxytamoxifen (4-OH TAM), despite representing less than 10% of tamoxifen metabolites, plays an important pharmacological role given its greater affinity for ER and its greater potency when compared with the parent drug. Another tamoxifen metabolite, 4-hydroxy-*N*-desmethyl TAM (endoxifen), has identical properties and potency compared with 4-OH TAM and 5- to 10-fold higher steady-state plasma concentrations [73]. The cytochrome P450 enzyme CYP2D6 is one of the key enzymes for the formation of 4-OH-TAM and endoxifen [74]. The frequency of non-functional CYP2D6 alleles varies widely by ethnicity: approximately 7% to 10% of white patients lack functional CYP2D6 [75]. Recent clinical studies have demonstrated that women receiving adjuvant tamoxifen who either carry genetic variants associated with low or absent CYP2D6 activity or who receive concomitant medications known to inhibit CYP2D6 activity have significantly lower levels of endoxifen and a worse disease outcome [76-79].

The CYP19A1 gene encodes the enzyme aromatase, which is responsible for the final step in the biosynthesis of estrogens. CYP19 is a complex gene with many polymorphic and splicing variants. Some polymorphisms have been related to abnormal activity of aromatase [80] and BMD [81-83]. The relationships between the ERs and both their ligand and the enzymes that synthesize it are not well understood; the interaction between polymorphisms of the aromatase gene and ERα have been reported to exert an important influence on BMD in postmenopausal women [84]. No pharmacogenetic studies have been published so far on the differential effectiveness or side effect profile of AIs.

2 Trial objectives

This trial will evaluate the worth of ovarian function suppression (achieved by long-term use of GnRH analogue) plus exemestane compared with GnRH analogue plus tamoxifen for premenopausal women with steroid hormone receptor positive early invasive breast cancer. Patients may either receive no chemotherapy or commence chemotherapy at the same time that GnRH analogue is initiated.

2.1 To compare GnRH analogue plus exemestane vs. GnRH analogue plus tamoxifen

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 recurrence-free 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

2.4 To investigate patient and tumor features that may contribute to inter-individual variability of responsiveness to GnRH analogue plus exemestane and GnRH analogue plus tamoxifen

2.4.1 To evaluate the prevalence of genetic variants of CYP2D6, CYP19A1, ERα, ERß, Akt1, and their prognostic impact on disease outcome (disease-free survival) and their predictive value for treatment responsiveness.

3 Patient selection

3.1 Criteria for patient eligibility

3.1.1 Premenopausal women [patients should have estradiol (E_2) in the premenopausal range (according to institution parameters) 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 should be randomized within 12 weeks after definitive surgery.

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.

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.

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.

3.1.11 Patients must be informed of and agree to the investigations required by the protocol for translational research.

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.

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.

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 any neoadjuvant or adjuvant endocrine therapy after their breast cancer diagnosis.

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 received any prior neoadjuvant or adjuvant chemotherapy. Neoadjuvant or adjuvant trastuzumab (Herceptin®) is allowable, as it is not considered to be chemotherapy for eligibility determination.

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 adjuvant systemic therapy, either GnRH analogue if no chemotherapy given or GnRH analogue plus chemotherapy if chemotherapy is given.

4.2 Registration procedures

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

4.2.1 Verify eligibility.

4.2.2 Obtain signed informed consent.

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, PMC Form 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). Do not mail Form A.

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) to 2 groups:

4.4.1 Triptorelin (GnRH analogue) for 5 years plus tamoxifen for 5 years.

4.4.2 Triptorelin (GnRH analogue) for 5 years plus exemestane for 5 years.

4.5 Stratification

4.5.1 Institution.

4.5.2 Adjuvant chemotherapy [the decision to use adjuvant chemotherapy may be made ~~by previous randomization in the PERCHE trial or~~ by investigator/patient choice]
- 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.

5 Treatment details

5.1 Trial treatments

5.1.1 Chemotherapy Patients in the chemotherapy stratum should commence chemotherapy after randomization at the same time as GnRH analogue (±1 week). A planned duration of ≥ 2 months if an anthracycline is included (e.g. 4 cycles of EC or AC) or ≥ 4 months if no

anthracycline is given (e.g. 6 cycles of CMF) is recommended. If an anthracycline is used, an epirubicin-containing regimen is recommended.

5.1.2 Triptorelin (GnRH analogue) 3.75 mg by intramuscular injection every 28 (±3) days until 5 years from 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. Bilateral surgical oophorectomy or bilateral ovarian irradiation (with biochemical confirmation of cessation of ovarian function after two months) is allowed after at least six months (or 6 injections) of triptorelin (GnRH analogue).

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 [29]. In such cases ovarian function suppression should be achieved by other means providing patient accepts an alternative method.

5.1.3 Tamoxifen 20 mg orally daily until 5 years from date of randomization, unless relapse or intolerance should occur prior to 5 years. Tamoxifen should start after adjuvant chemotherapy has been completed or approximately six to eight weeks (±2 weeks) after the initiation of GnRH analogue, whichever is later.

5.1.4 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. Exemestane should start after adjuvant chemotherapy has been completed or approximately six to eight weeks (±2 weeks) after the initiation of GnRH analogue, whichever is later. [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.] Exemestane will be provided free of charge.

5.1.5 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.

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 [41,42].

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 anthracycline-treated 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 [43]. 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 [44]. 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.

5.2 Side effects of study drugs

5.2.1 Chemotherapy: Side effects of chemotherapy will vary according to the regimen used.

5.2.2 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 during pregnancy and lactation. Cases of pregnancy have occurred in women receiving regular injections of GnRH analogue [29]. The role of non-hormonal 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.

5.2.3 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.

5.2.4 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. [53]. Updated results of this trial showed a non-significant excess of myocardial infarctions in those patients treated with exemestane compared with tamoxifen in this population (mean age 64 years) [54], a significant decrease in BMD compared to baseline, and a slight increase in bone fractures (OR=1.45, p=0.003) [85]. No patient with BMD in the normal range at trial entry developed osteoporosis. Bone resorption and formation markers also increased at all time points in women receiving exemestane ($p<0.001$).

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 [45]. 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) [46].

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 [29].

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. Six-month 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 events.

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 (non-breast) 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

6.3 Translational endpoints

6.3.1 Genetic variants of CYP2D6, CYP19A1, ERα, ERß, Akt1

DNA will be extracted in a central laboratory from a whole blood sample and single nucleotide polymorphisms (SNPs) will be assessed in: CYP2D6 {including CYP2D6*4, CYP2D6*3, CYP2D6*7, CYP2D6*2A}; CYP19A1 {including rs10046, rs700519}; ERα {including Pvu II (rs2234693), XbaI (rs9340799)}; ERβ {including 1082G/A, 1730G/A}; and Akt1 {including rs3730358, rs2498799}.

7 Study parameters

7.1 Table of study parameters

Visit	1[A]	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
Estradiol[B]	x															
Adverse Events (AE)[C]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Late AEs[D]																x
Laboratory tests																
Hematology[E]	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Blood chemistry[F]	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-ray[H] (PA and lateral views) or chest CT	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Bone scan[I]	y	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Abdominal US, CT or liver scan[J]	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Gynecological exam[K]	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Bone mineral densitometry[L]	y				y		y		y		y		y		y	
CRFs[M]																
Quality of Life[N]	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 CT, 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**

(Table 7.1 continued on next page.)

Table 7.1 (continued)

Translational investigations[O]																
Visit	1[A]	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	
TEXT-1:																
Whole blood	Required at next visit															
Form TR-1	Required at next visit															
TEXT-2:																
Whole blood	x															
Form TR-2	x															

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 (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 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. For patients receiving chemotherapy, hematology is also required on day 1 of each cycle.

F. Blood chemistry (includes liver function tests with alkaline phosphatase) must be done within 2 months prior to randomization and whenever medically indicated. For patients receiving chemotherapy, blood chemistry is also required on day 1 of each cycle.

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 25-02 Data Management Manual.

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

Patients on chemotherapy will be seen on day 1 of each cycle. A complete blood count should be performed at that time. 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.

Translational investigations

O. The requirements for translational investigations depend on a patient's trial enrollment date.
TEXT-1 (patients randomized prior to 1 January 2008):

- Whole blood: A whole blood sample for DNA isolation is required at the patient's next visit along with appropriate informed consent, according to the guidelines in the Manual for Blood Sample Logistics.
- Form 25-TR-1: Form 25-TR-1 is required at the patient's next visit to document that the sample was obtained, or the reason why it cannot be obtained.

TEXT-2 (patients randomized after 1 January 2008):

- Whole blood: A whole blood sample for DNA isolation is required at baseline. It must be obtained prior to start of treatment but not more than 14 days prior to randomization, according to the guidelines in the Manual for Blood Sample Logistics.
- Form 25-TR-2: Form 25-TR-2 is required at baseline.

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 25/26-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 25-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—TEXT

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

RANDOMIZATION FORMS		
IC Form	Informed Consent Form	Obtain before randomization and keep with patient records.
Forms 25/26-QLC, 25/26-QLM, 25/26-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 25-A	Confirmation of TEXT-2 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.
Form 25/26-PMC	Pathology Material Consent Form	DataFax after randomization with Form 25-A
BASELINE FORMS		
Form 25/26-B	Clinical Form	DataFax within 1 month of randomization.
Form 25/26-C*	Surgery Form	DataFax within 1 month of randomization.
Form 25/26-H	Prior Treatment History Form	DataFax within 1 month of randomization.
Form 25/26-F*	Hormone Receptor Form	DataFax within 1 month of randomization with hormone receptor report.
Form 25/26-P*	Pathology Form	DataFax within 1 month of randomization with a copy of the original pathology report.
Form 25/26-AE	Adverse Event Form	Complete prior to starting protocol treatment (tamoxifen, exemestane, triptorelin) and DataFax within 1 month of randomization. This form is also required at follow-up (see instructions below.)
Form 25/26-CCM	Concomitant Medications Form	Complete prior to starting protocol treatment (tamoxifen, exemestane, triptorelin) and DataFax within 1 month of randomization. This form is also required at follow-up (see instructions below.)
Form 25-TR-2	TEXT-2 Translational Research Form (only for patients randomized **after** 1 January 2008)	DataFax within 1 month of randomization.
FOLLOW-UP FORMS		
Form 25/26-E	Follow-Up Form	DataFax every 3 months in Year 1, every 6 months during Years 2-6, and yearly thereafter.
Form 25/26-OFS	Ovarian Function Suppression Form	DataFax at each follow-up period until completion of OFS.
Form 25/26-TE	Tamoxifen/Exemestane Form	DataFax at each follow-up period until the completion of tamoxifen and/or exemestane.
Form 25/26-AE	Adverse Event Form	DataFax at each follow-up period during protocol therapy (tamoxifen, exemestane, triptorelin), and with Form 25/26-E at 6 and 12 months after the last dose of protocol therapy. This form is also required at baseline.
Form 25/26-CCM	Concomitant Medications Form	DataFax at each follow-up period during protocol therapy (tamoxifen, exemestane, triptorelin), and with Form 25/26-E at 6 and 12 months after the last dose of protocol therapy. This form is also required at baseline.
Form 25-TR-1	TEXT-1 Translational Research Form (only for patients randomized **prior to** 1 January 2008)	DataFax at visit when blood sample is taken; keep IC for the blood sample with patient records.
Forms 25/26-QLC, 25/26-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 25/26-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 25/26-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--TEXT (continued on next page)

8.1 Case report forms schedule--TEXT (continued from previous page)

EVENT-DRIVEN FORMS		
Form 25/26-R*	Radiotherapy Form	DataFax after completion of radiotherapy, or if radiotherapy was planned but not given.
Form 25/26-CT	Chemotherapy Form	Data Fax after completion of chemotherapy, or if chemotherapy was planned but not given.
Form 25/26-SAE-A	Serious Adverse Event Form (Section A)	DataFax within 24 hours when SAE occurs, see Section 7.3.
Form 25/26-SAE-B	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 25/26-EIU	Exposure in Utero Form	DataFax if patient becomes pregnant during protocol therapy (tamoxifen, exemestane, triptorelin), and when pregnancy outcome is known.
Form 25/26-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 25/26-E.
Form 25/26 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. 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 TEXT 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:

- 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
- Manual for Blood Sample Logistics

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.

8.6 Blood sample collection and submission

8.6.1. Timing of blood sample

The requirements for translational investigations depend on the patient's trial enrollment date.

TEXT-1 (patients randomized prior to 1 January 2008):
A 10 ml whole blood sample for DNA isolation is required at the patient's next visit along with appropriate informed consent.

An Addendum to the original patient information and informed consent form covering this translational research has been prepared (Appendix IA). Patient's consent needs to be reported on Form 25-TR-1. Blood collection and shipment and patient's consent to translational research will be reimbursed by IBCSG.

TEXT-2 (patients randomized after 1 January 2008):
A 10 ml whole blood sample for DNA isolation is required at baseline. It must be obtained prior to start of treatment but not more than 14 days prior to randomization.

Blood collection and shipment will be reimbursed by IBCSG.

8.6.2. Blood sample storage and collection

Blood collection kits will be sent to the participating institutions and must be used for collection, storage and shipment. Whole blood samples will be processed and stored locally at -80° until shipment on dry ice to a national central facility designated in the Manual for Blood Sample Logistics. In order to keep shipping costs at an affordable level, participating centers are requested to store blood samples at -80°C until shipment in batches. Shipment costs will be covered by IBCSG. The national central facility will ship all samples to the Central Biomarker Laboratory at the European Institute of Oncology in Milan, Italy, where samples will be assayed as detailed in section 6.3.

All details are described in the Manual for Blood Sample Logistics.

8.6.3. Sample identification

All samples must be labelled with pre-printed, self-adhesive bar code labels contained in the blood collection kits. All assay results will be identified with the bar code numbers and submitted to IBCSG.

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 GnRH analogue plus tamoxifen versus five years of GnRH analogue plus exemestane. The trial is designed to answer the following question for premenopausal patients with hormone-receptor positive breast cancer:
Do results differ between GnRH analogue plus tamoxifen for five years and GnRH analogue plus exemestane for five years?

The randomization will be stratified according to participating institution, use of adjuvant chemotherapy (no; yes), and number of positive axillary and/or internal mammary lymph nodes (0 – including pN0(sn), pN0(i+)(sn) and pNx; 1 or more – including pN1mi). In addition to the overall study population, treatment comparisons will be performed separately according to chemotherapy and nodal status strata.

9.2 Data analyses

Primary treatment comparisons 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 alpha level of 0.05. Kaplan-Meier estimates of the DFS distributions will be calculated for each of the two arms. Cox proportional hazards regression models will be used to investigate whether the treatment comparison is modified by adjustments for various covariates.

Other factors will be used to characterize the patients enrolled in the study and to provide descriptive statistics of outcomes according to subgroups of the population. These factors include age at randomization, type and schedule of 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

~~Because all women will receive GnRH analogue, the patients enrolled in this protocol are likely to be younger premenopausal women. We will assume that most of the women enrolled in the~~

~~trial will receive chemotherapy together with GnRH analogue. 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].~~

~~Premenopausal women with ER-positive, 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). If we assume that a little over 60% of the cases enrolled in this trial will be node-positive, the 5-year DFS with chemotherapy alone is estimated at 51%. A 40% reduction in risk of relapse by adding tamoxifen [3] and a hypothesized 25% additional risk reduction associated with GnRH analogue puts the estimated baseline risk for the GnRH analogue plus tamoxifen control group at 74.1%.~~

~~The treatment comparison will be based on a logrank test with an overall two-sided level of 0.05. Table 9.1 shows the operating characteristics of three alternative designs that would allow the detection of 20%, 25%, and 30% reduction in hazard by using exemestane instead of tamoxifen.~~

~~Table 9.1. Operating characteristics for the GnRH analogue plus exemestane versus GnRH analogue plus tamoxifen comparison.~~

~~Reduction in hazard~~	~~20%~~	~~**25%**~~	~~30%~~
~~GnRH analogue + tamoxifen 5-yr DFS~~	~~74.1%~~	~~**74.1%**~~	~~74.1%~~
~~GnRH analogue + exemestane 5-yr DFS~~	~~78.6%~~	~~**79.8%**~~	~~81.0%~~
~~Two-sided alpha level~~	~~.05~~	~~**.05**~~	~~.05~~
~~Required number of events*~~	~~653~~	~~**396**~~	~~260~~
~~Power~~	~~.80~~	~~**.80**~~	~~.80~~
~~Accrual rate (pts/year)~~	~~410~~	~~**410**~~	~~410~~
~~Total accrual time (yrs)~~	~~4.5~~	~~**4.5**~~	~~4.5~~
~~Sample size~~	~~1845~~	~~**1845**~~	~~1845~~
~~Total Study duration with 4 interim + 1 final analyses (yrs)*~~	~~10.4~~	~~**6.9**~~	~~5.3~~

~~* Under the alternative hypothesis with 4 interim analyses and 1 final analysis [47].~~

~~For planning purposes, we will target a 25% reduction in hazard. This will require recruitment of **1845 patients** (410 patients per year for 4.5 years with 2.4 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. Approximately 9% were less than 35 years of age and about 25% were less than 40. Thus, we anticipate approximately 40 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 originally planned sample size was 1845. It was projected that 4.5 years of accrual, plus 2.4 years of additional follow up would be sufficient to observe the 396 target number of DFS events. This number of events would provide 80% power to detect a hazard ratio of 0.75 for GnRH + exemestane versus GnRH + tamoxifen (79.8% versus 74.1% 5-yr DFS, respectively) using a 2-sided, 0.05 level test. The study opened to enrollment in August 2003. The initial accrual goal was achieved ahead of schedule and 2039 patients had enrolled by November 2007, when recruitment was suspended. The patient population had characteristics more favorable than originally anticipated, and Amendment 2 (25Jul08) increased the target sample size to 2639. In March 2011, enrollment was closed with 2672 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 1.7% per year compared with the protocol-specified 6% per year. Consequently, at the October 2010 estimated event rate, an additional seven (7) years of follow up (end of 2017) would be required to observe the protocol-specified 396 target number of the DFS events (at which time the median follow up would be 10.5 years). The Steering Committee considered this delay in the reporting of the trial results (14 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 6 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 (396 DFS events in TEXT) to a 'time-driven' plan (with a data cut-off defined for the fall of 2013), the Steering Committee recognizes that the statistical power for the original primary comparison (OFS + exemestane versus OFS + tamoxifen within TEXT) will be reduced. We estimate the power of this comparison to detect a 0.75 hazard ratio will be approximately 60% in the fall of 2013. Therefore, the primary analysis for comparing OFS + exemestane versus OFS + tamoxifen will be the originally planned combined analysis of TEXT and the Suppression of Ovarian Function Trial (SOFT) described below.

We prospectively plan to combine the data available for the TEXT study with the arms comparing exemestane plus ovarian function suppression (OFS) versus tamoxifen plus OFS in the complementary Suppression of Ovarian Function Trial (SOFT: IBCSG 24-02). We note that TEXT and SOFT differ with respect to patient selection and treatment for women who receive chemotherapy; TEXT enrolls patients following surgery and uses concurrent GnRH analogue and chemotherapy, while SOFT enrolls patients who remain premenopausal following chemotherapy and initiates OFS (GnRH analogue, surgical oophorectomy or ovarian irradiation) following the completion of 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 comparison (at the 0.05 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 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 [47]. The target number of events for the final analysis is 396, and interim analyses will be planned after 99 (25%), 158 (40%), 237 (60%), and 317 (80%) events have been observed. We anticipate~~

~~that this monitoring scheme will provide annual formal analyses from the time that 99 events have been observed. At each interim analysis and at the final analysis, testing will be performed using the O'Brien-Fleming boundaries (3.969, 3.297, 2.659, 2.284, 2.036) [48].~~

Originally the protocol included a group sequential design with four interim and one final 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 99th 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.

9.6 Sample size re-consideration

~~As described above, at trial initiation the specified sample size was 1845 patients (Section 9.3) with the final analysis to be performed when 396 events are observed (Section 9.4). Enrollment opened in August 2003 and was suspended on 30 November 2007, having reached the planned enrollment. A date to suspend enrollment was specified which would allow patients who had already discussed the trial to have adequate time to decide whether to enroll, and as of this date 2039 patients were enrolled.~~

~~As described below, two features of enrollment to date will necessitate an increase in the additional follow-up time to reach 396 events for the final analysis. The trial enrollment will be increased by 600 patients to ensure that the primary trial question is reported with adequate power in a timely manner and to provide adequate power for the translational objectives.~~

~~9.6.1 Primary trial objective~~

~~With the original assumptions, the protocol trial design required 396 events at the final analysis to provide 80% power and could be achieved with the enrollment of 1845 patients over 4.5 years (410/year) and 2.4 years of additional follow-up (6.9 years total duration).~~

- ~~The protocol assumed uniform accrual, but the accrual rate increased over time, averaging 24.6 patients per month (295/year) over the first two years, 51/month over the third year (612/year), and 65/month (780/year) over the last year.~~
- ~~The characteristics of enrolled patients are lower risk than assumed for the estimation of the baseline risk for the GnRH analogue plus tamoxifen control group (74.1% 5-year DFS). The estimation assumed a predominance of younger women, most receiving chemotherapy and 60% of whom would have node-positive disease; the actual median age is 43 years, 62% are receiving chemotherapy and 48% have node-positive disease. Thus, the estimate of 74.1% 5-year DFS may be too low. In a recent overview analysis of GnRH analogues as adjuvant~~

~~therapy [56], patients treated with GnRH analogue plus tamoxifen had an estimated 5-year breast cancer recurrence probability of about 18%. Thus we estimate that an 80% 5-year DFS for patients randomized to GnRH plus tamoxifen might be expected in TEXT patients, with a corresponding improvement to 84.6% 5-year DFS for patients randomized to GnRH plus exemestane (maintaining the assumed 25% reduction in hazard).~~

~~With the observed accrual and revised control 5-year DFS estimate, with 1845 patients we anticipate an increase of 1.7 years of additional follow-up needed to reach 396 events (8.6 years total duration). A total of 2039 patients had enrolled when recruitment was suspended on 30 November 2007. We estimate that increasing the sample size by an additional 600 patients (to 2639 patients total) will enable 396 events to be reached within 0.5 years of that anticipated in the original protocol (7.4 years total duration).~~

~~Given that prior to this protocol modification the median follow-up of the 2039 enrolled patients was less than one year, no information about the observed recurrence rate was used to modify the protocol.~~

9.6.2 Translational objectives

9.6.2.1. Evaluate the prevalence of genetic variants of CYP2D6, CYP19A1, ERα, ERß and Akt1, and their prognostic impact on disease outcome (DFS) and their predictive value for treatment responsiveness.

We assume 2000 (75%) patients will be assessable (1000/arm), including all 600 TEXT-2 patients and about 70% of TEXT-1 patients. Further we assume that the genetic variants are dichotomized as “adverse” and “non-adverse” and consider prevalence varying from rare (5% prevalence) to very common (50%), as prevalence of the different variants/genotypes ranges widely.

Prevalence of each variant will be summarized as genotype frequencies with 95% CI; the half-widths of 95% CIs are summarized in Table 9.2.

The primary objective is to evaluate the prognostic and predictive value, in terms of DFS, of different genetic variants. The analysis will use multivariable Cox modeling. Sample size calculations assume 2000 patients (324 events), 82.3% 5-year DFS (80% GnRH+T vs. 84.6% GnRH+E 5-year DFS), 2-sided α=0.05, 80% power (Table 9.2 [86]). Given the lower DFS event rate estimated in October 2010, analyses for the translational research objectives described below are anticipated to be available at the time of the first 2 year efficacy update.

- Predictive value of CYP2D6, CYP19A1: within a specific treatment arm (n=1000), DFS will be compared between groups defined by genetic variants.
- Prognostic and predictive value of ERα, ERβ or Akt1: DFS will be compared between groups defined by a genetic variant, regardless of treatment (n=2000).
- The treatment-by-variant interaction on DFS will be tested, investigating heterogeneity in the relative treatment effect between groups defined by a genetic variant. Power is limited for prevalence below 30%, but there is good power (around 80%) to detect an interaction scenario of a strong treatment effect (GnRH+E vs. GnRH+T) in one group (HR≈0.50) vs. a small treatment effect in the other group (HR≈1.0).

Table 9.2. Detectable effect sizes for "adverse" variant prevalence ranging 5-50% (80% power).

Prevalence of adverse variant	5%	10%	20%	30%	40%	50%
Half-width of 95% CI (n=1000, one arm)	± 1.3	± 1.9	± 2.5	± 2.8	± 3.0	± 3.1
Half-width of 95% CI (n=2000, all patients)	± 1.0	± 1.3	± 1.8	± 2.0	± 2.2	± 2.2
Detectable hazard ratio (n=1000, one arm)	2.8	2.1	1.7	1.6	1.5	1.5
Detectable hazard ratio (n=2000, all patients)	2.1	1.7	1.5	1.4	1.3	1.3

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 ER-positive 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 [49] and second primaries [50]. In addition, research is ongoing to determine whether genetically-associated breast cancer responds differently to treatment [51].

11.4 Genetic markers of disease and drug metabolism and DNA banking

Optimizing the use of endocrine adjuvant therapies by determining features of the disease or of the patients that suggest one or the other therapy is better for the individual woman is desirable so that treatments can be better tailored to the biological targets. Among the population of premenopausal women with hormone receptor-positive disease, TEXT offers a unique opportunity to investigate the roles of polymorphisms in patient- and disease-related genes, of pathological tumor features as predictors of responsiveness to GnRH analogue plus tamoxifen or GnRH analogue plus the AI exemestane.

11.4.1 Planned studies

TEXT-2 patients (randomized after 1 January 2008) will provide a blood sample at baseline, after appropriate informed consent, from which DNA will be extracted in a central laboratory and genetic variants of CYP2D6, CYP19A1, ERα, ERß and Akt1 will be determined.

TEXT-1 patients (randomized prior to 1 January 2008) will be asked to provide a blood sample for DNA extraction at the next study visit, after appropriate informed consent. Because these translational objectives were not specified when the TEXT-1 patients enrolled, the patients may decline to provide the blood sample; the form 25-TR-1 is required for all patients randomized prior to 1 January 2008 to document whether or not the sample was obtained and patient consent.

Guidelines for blood sampling and handling are provided in the Manual for Blood Sample Logistics.

11.4.2 DNA Banking

Surplus DNA will be stored by the IBCSG for use in unspecified future research. All biological materials will be stored by the IBCSG Central Pathology Office. As part of the informed consent process, patients are asked to indicate whether they agree to donate their sample for such

research. The patient's decision is recorded on the Form 25/26 IBCSG PMC (TEXT-2 patients randomized after 1 January 2008) or Form 25-TR-1 (TEXT-1 patients randomized prior to 1 January 2008). If she agrees, her DNA will be stored. If she refuses, any surplus DNA will be destroyed. If she specifies that she wants to be asked to consent to any such future study, then the material will be kept and the patient will be approached for such a specific consent when a new project has been approved.

The use of the DNA for unspecified future research will be under the auspices of the IBCSG Biological Protocols Working Group and any project has to be approved by the IBCSG Ethical Committee.

Testing for genes that are associated with inherited risk of breast cancer in the family is not a part of this study.

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.

TEXT-1 patients (randomized prior to 1 January 2008) will receive an Addendum to the patient information sheet and informed consent to be signed before the blood sample for translational investigations is taken. Because these translational objectives were not specified when the TEXT-1 patients entered the study, the patient may decline to provide the blood sample.

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
IA. Addendum to the Original Patient Information and 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

INTERNATIONAL BREAST CANCER STUDY GROUP

IBCSG 25-02
BIG 3-02

Tamoxifen and Exemestane Trial (TEXT)

Amendment 1

A Phase III Trial Evaluating the Role of Exemestane Plus GnRH Analogue as Adjuvant Therapy for Premenopausal Women with Endocrine Responsive Breast Cancer

ovarian function suppression + tamoxifen versus
ovarian function suppression + exemestane

Coordinating Group: International Breast Cancer Study Group (IBCSG)

EudraCT Number: 2004-000168-28

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.

Protocol Amendment 1 Signature Page

IBCSG 25-02 / BIG 3-02

Tamoxifen and Exemestane Trial (TEXT)

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

IBCSG 25-02 / BIG 3-02

Tamoxifen and Exemestane Trial (**TEXT**).

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

(*Signature on File*)

_____ _____

Date

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

(*Signature on File*)

_____ _____

Date

Principal Investigator and Co-investigator Protocol Signature Page

IBCSG 25-02 / BIG 3-02

Tamoxifen and Exemestane Trial (TEXT).

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Name of Principal Investigator:_____

Signature:

_____ _____

Date

Name of Co-investigator:_____

Signature:

_____ _____

Date

Name of Co-investigator:_____

Signature:

_____ _____

Date

Name of Co-investigator:_____

Signature:

_____ _____

Date

Name of Co-investigator:_____

Signature:

_____ _____

Date

Protocol Summary and Schema

Tamoxifen and Exemestane Trial (TEXT)

A Phase III Trial Evaluating the Role of Exemestane Plus GnRH Analogue as Adjuvant Therapy for Premenopausal Women with Endocrine Responsive Breast Cancer

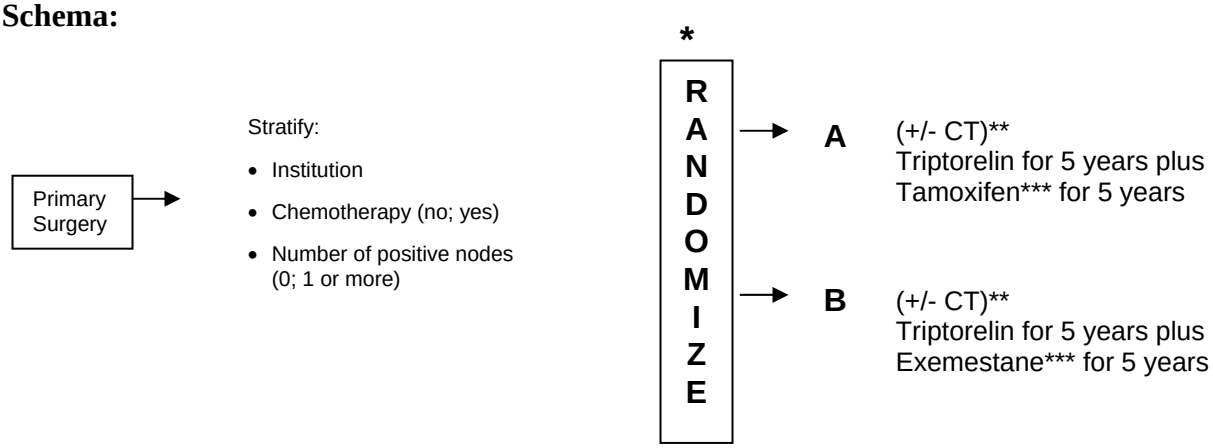
Patient Population: Premenopausal women with histologically proven, resected breast cancer with ER and/or PgR positive tumors.

Entry: Patients should be randomized within 12 weeks after surgery prior to commencing any adjuvant systemic therapy.

Stratification Factors:
- Institution
- Adjuvant 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)

Sample Size: 1845 patients (410 per year for 4.5 years with 2.4 years of additional follow-up)

Schema:



* Randomization prior to receiving any adjuvant systemic therapy

**CT (chemotherapy), if used, should begin at the same time as triptorelin. Use of CT may be determined by randomization in the PERCHE trial or by investigator/patient choice.

***Tamoxifen or exemestane should start after adjuvant chemotherapy has been completed or approximately six to eight weeks after the initiation of triptorelin, whichever is later.

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 should commence chemotherapy after randomization at the same time as GnRH analogue. A planned duration of ≥ 2 months if an anthracycline is included (e.g. 4 cycles of EC or AC) or ≥ 4 months if no anthracycline is given (e.g. 6 cycles of CMF) is recommended. If an anthracycline is used, an epirubicin-containing regimen is recommended.

Adjuvant Endocrine Therapy:

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.

Tamoxifen: Tamoxifen 20 mg orally daily until 5 years from date of randomization, unless relapse or intolerance should occur earlier. Tamoxifen should start after adjuvant chemotherapy has been completed or approximately six weeks to eight weeks after the initiation of GnRH analogue, whichever is later.

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 start after adjuvant chemotherapy has been completed or approximately six to eight weeks after the initiation of GnRH analogue, whichever is later.

TABLE OF CONTENTS

Section			Page
1	**Introduction**		11
2	**Trial objectives**		14
3	**Patient selection**		15
	3.1	Criteria for patient eligibility	15
	3.2	Criteria for patient ineligibility	16
4	**Randomization and stratification**		18
	4.1	Randomization timing	18
	4.2	Registration procedures	18
	4.3	Randomization help desk	19
	4.4	Randomized groups	19
	4.5	Stratification	19
5	**Treatment details**		20
	5.1	Trial treatments	20
	5.2	Side effects of study drugs	21
	5.3	Concomitant treatments	22
	5.4	Study drug supply	23
6	**End points and definitions of treatment failure**		24
	6.1	Trial end points	24
	6.2	Diagnosis of treatment failure	25
7	**Study parameters**		28
	7.1	Table of study parameters	28
	7.2	Adverse event reporting	30
	7.3	Serious Adverse Event (SAE) reporting	31
	7.4	Exposure in utero reporting	33
8	**Data submission**		33
	8.1	Case report forms schedule	34
	8.2	Data management	36
	8.3	Investigators' file	36
	8.4	Authorization log	36
	8.5	Patient identification log	37

9 Statistical considerations 37
9.1 Study design, objectives, and stratification 37
9.2 Data analyses 37
9.3 Sample size considerations 38
9.4 Interim monitoring 39
9.5 Data and safety monitoring committee 39

10 Quality of life (see Appendix V) 40

11 Additional protocol-specific parameters 40
11.1 Hormone receptors 40
11.2 Pathology and pathology material banking 41
11.3 Family history 42

12 Regulatory approval procedures and patient informed consent 42
12.1 Ethical Review Board/Ethics Committee 42
12.2 Regulatory approval procedures 42
12.3 Requirements for Center Activation 42
12.4 Protection of human subjects 43
12.5 Informed consent procedures 43
12.6 Quality assurance 44

13 Administrative considerations 44
13.1 Insurance 44

14 References 45

Appendices

I. Requirements for Informed Consent
II. NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 3 [available from the internet at: http://ctep.info.nih.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

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

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. There is some evidence that GnRH analogues may have a direct beneficial effect on tumor cell death, for breast cancer and other cancers [22-25]. A trial conducted by the ECOG in postmenopausal patients (based on some anecdotal information [26]) confirmed some efficacy of GnRH analogue for the ER+ cohort, but no significant effect was observed for the ER- cohort [27]. Although it is clear that the effect of GnRH analogues, when given alone, is mainly through the indirect inhibition of endocrine ovarian function, antitumor efficacy via other mechanisms is not entirely elucidated. Furthermore, the combination of GnRH analogue and chemotherapy might also be useful to protect ovarian function from definitive cytotoxic-related damage. This might be advantageous especially for young women who choose to preserve fertility [28]. Therefore, use of GnRH analogue for five years is the method of choice to achieve ovarian function suppression in this clinical trial.

There are case studies of failure of ovarian function suppression under GnRH analogue [29]. 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 [30].

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 [31,32], 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) [33, 52]. 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) [53,54]. 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) [55].

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 [34]. 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 [35,36]. 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 [37].

Either the combination of a GnRH analogue with tamoxifen or the combination of a GnRH analogue with an aromatase inhibitor (exemestane) has the potential to improve survival in premenopausal women with endocrine responsive tumors over that seen with tamoxifen alone. This trial is designed to assess the role of GnRH analogue plus exemestane compared with GnRH analogue plus tamoxifen. 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 [38]. 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 [39]. A pre-clinical trial by Goss et al. [40] 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 long-term use of GnRH analogue) plus exemestane compared with GnRH analogue plus tamoxifen for premenopausal women with steroid hormone receptor positive early invasive breast cancer. Patients may either receive no chemotherapy or commence chemotherapy at the same time that GnRH analogue is initiated.

2.1 To compare GnRH analogue plus exemestane vs. GnRH analogue plus tamoxifen

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
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 [patients should have estradiol (E_2) in the premenopausal range (according to institution parameters) 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 should be randomized within 12 weeks after definitive surgery.

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.

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.

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.

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.

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 any neoadjuvant or adjuvant endocrine therapy after their breast cancer diagnosis.

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 received any prior neoadjuvant or adjuvant chemotherapy. Neoadjuvant or adjuvant trastuzumab (Herceptin®) is allowable, as it is not considered to be chemotherapy for eligibility determination.

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 adjuvant systemic therapy, either GnRH analogue if no chemotherapy given or GnRH analogue plus chemotherapy if chemotherapy is given.

4.2 Registration procedures

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

4.2.1 Verify eligibility.

4.2.2 Obtain signed informed consent.

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). Do not mail Form A.

4.3 Randomization help desk

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

Business Hours: 7:30-18:00 US Eastern Time
FSTRF Randomization Help Desk
Frontier Science & Technology Research Foundation (FSTRF)
4033 Maple RD, Amherst, NY 14226 USA
Phone: +1 716 898 7301
Fax: +1 716 898 7082
Email: bc.helpdesk@fstrf.org

4.4 Randomized groups

Randomization (1:1) to 2 groups:

4.4.1 Triptorelin (GnRH analogue) for 5 years plus tamoxifen for 5 years.

4.4.2 Triptorelin (GnRH analogue) for 5 years plus exemestane for 5 years.

4.5 Stratification

4.5.1 Institution.

4.5.2 Adjuvant chemotherapy [the decision to use adjuvant chemotherapy may be made by previous randomization in the PERCHE trial or by investigator/patient choice]
- 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.

5 Treatment details

5.1 Trial treatments

5.1.1 Chemotherapy Patients in the chemotherapy stratum should commence chemotherapy after randomization at the same time as GnRH analogue (±1 week). A planned duration of ≥ 2 months if an anthracycline is included (e.g. 4 cycles of EC or AC) or ≥ 4 months if no anthracycline is given (e.g. 6 cycles of CMF) is recommended. If an anthracycline is used, an epirubicin-containing regimen is recommended.

5.1.2 Triptorelin (GnRH analogue) 3.75 mg by intramuscular injection every 28 (±3) days until 5 years from 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. Bilateral surgical oophorectomy or bilateral ovarian irradiation (with biochemical confirmation of cessation of ovarian function after two months) is allowed after at least six months (or 6 injections) of triptorelin (GnRH analogue).

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 [29]. In such cases ovarian function suppression should be achieved by other means providing patient accepts an alternative method.

5.1.3 Tamoxifen 20 mg orally daily until 5 years from date of randomization, unless relapse or intolerance should occur prior to 5 years. Tamoxifen should start after adjuvant chemotherapy has been completed or approximately six to eight weeks (±2 weeks) after the initiation of GnRH analogue, whichever is later.

5.1.4 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. Exemestane should start after adjuvant chemotherapy has been completed or approximately six to eight weeks (±2 weeks) after the initiation of GnRH analogue, whichever is later. [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.] Exemestane will be provided free of charge.

5.1.5 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.

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 [41,42].

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 anthracycline-treated 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 [43]. 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 [44]. 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.

5.2 Side effects of study drugs

5.2.1 Chemotherapy: Side effects of chemotherapy will vary according to the regimen used.

5.2.2 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 during pregnancy and lactation. Cases of pregnancy have occurred in women receiving regular injections of GnRH analogue [29]. The role of non-hormonal contraception should therefore be discussed.

5.2.3 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.

5.2.4 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. [53]. In a subsequent updated oral presentation of this trial [54], a non-significant excess of myocardial infarctions was noted in those treated with exemestane compared with tamoxifen in this 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 [45]. 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) [46].

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 [29].

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. Six-month 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.

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 events.

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 (non-breast) 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	1[A]	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
Estradiol[B]	x															
Adverse Events (AE)[C]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Late AEs[D]																x
Laboratory tests																
Hematology[E]	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Blood chemistry[F]	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-ray[H] (PA and lateral views) or chest CT	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Bone scan[I]	y	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Abdominal US, CT or liver scan[J]	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Gynecological exam[K]	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	
Bone mineral densitometry[L]	y				y		y		y		y		y		y	
CRFs[M]																
Quality of Life[N]	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 CT, 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 (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 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
- 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. For patients receiving chemotherapy, hematology is also required on day 1 of each cycle.

F. Blood chemistry (includes liver function tests with alkaline phosphatase) must be done within 2 months prior to randomization and whenever medically indicated. For patients receiving chemotherapy, blood chemistry is also required on day 1 of each cycle.

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 25-02 Data Management Manual.

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

Patients on chemotherapy will be seen on day 1 of each cycle. A complete blood count should be performed at that time. 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 25/26-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 25-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—TEXT

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

RANDOMIZATION FORMS		
IC Form	Informed Consent Form	Obtain before randomization and keep with patient records.
Forms 25/26-QLC, 25/26-QLM, 25/26-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 25-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 25/26-B	Clinical Form	DataFax within 1 month of randomization.
Form 25/26-C*	Surgery Form	DataFax within 1 month of randomization.
Form 25/26-H	Prior Treatment History Form	DataFax within 1 month of randomization.
Form 25/26-F*	Hormone Receptor Form	DataFax within 1 month of randomization with the hormone receptor report.
Form 25/26-P*	Pathology Form	DataFax within 1 month of randomization with a copy of the original pathology report.
Form 25/26-AE	Adverse Event Form	Complete prior to starting protocol treatment (tamoxifen, exemestane, triptorelin) and DataFax within 1 month of randomization. This form is also required at follow-up (see instructions below.)
Form 25/26-CCM	Concomitant Medications Form	Complete prior to starting protocol treatment (tamoxifen, exemestane, triptorelin) and DataFax within 1 month of randomization. This form is also required at follow-up (see instructions below.)
FOLLOW-UP FORMS		
Form 25/26-E	Follow-Up Form	DataFax every 3 months in Year 1, every 6 months during Years 2-6, and yearly thereafter.
Form 25/26-OFS	Ovarian Function Suppression Form	DataFax at each follow-up period until completion of OFS.
Form 25/26-TE	Tamoxifen/Exemestane Form	DataFax at each follow-up period until the completion of tamoxifen and/or exemestane.
Form 25/26-AE	Adverse Event Form	DataFax at each follow-up period during protocol therapy (tamoxifen, exemestane, triptorelin), and with Form 25/26-E at 6 and 12 months after the last dose of protocol therapy. This form is also required at baseline.
Form 25/26-CCM	Concomitant Medications Form	DataFax at each follow-up period during protocol therapy (tamoxifen, exemestane, triptorelin), and with Form 25/26-E at 6 and 12 months after the last dose of protocol therapy. This form is also required at baseline.
Forms 25/26-QLC, 25/26-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 25/26-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 25/26-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--TEXT (continued on next page)

8.1 Case report forms schedule--TEXT (continued from previous page)

EVENT-DRIVEN FORMS		
Form 25/26-R*	Radiotherapy Form	DataFax after completion of radiotherapy, or if radiotherapy was planned but not given.
Form 25/26-CT	Chemotherapy Form	Data Fax after completion of chemotherapy, or if chemotherapy was planned but not given.
Form 25/26-SAE-A	Serious Adverse Event Form (Section A)	DataFax within 24 hours when SAE occurs, see Section 7.3.
Form 25/26-SAE-B	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 25/26-EIU	Exposure in Utero Form	DataFax if patient becomes pregnant during protocol therapy (tamoxifen, exemestane, triptorelin), and when pregnancy outcome is known.
Form 25/26-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 25/26-E.
Form 25/26 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. 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 TEXT 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:

- 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
- 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 GnRH analogue plus tamoxifen versus five years of GnRH analogue plus exemestane. The trial is designed to answer the following question for premenopausal patients with hormone-receptor positive breast cancer:
\Do results differ between GnRH analogue plus tamoxifen for five years and GnRH analogue plus exemestane for five years?

The randomization will be stratified according to participating institution, use of adjuvant chemotherapy (no; yes), and number of positive axillary and/or internal mammary lymph nodes (0 – including pN0(sn), pN0(i+)(sn) and pNx; 1 or more – including pN1mi). In addition to the overall study population, treatment comparisons will be performed separately according to chemotherapy and nodal status strata.

9.2 Data analyses

Primary treatment comparisons 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 alpha level of 0.05. Kaplan-Meier estimates of the DFS distributions will be calculated for each of the two arms. Cox proportional hazards regression models will be used to investigate whether the treatment comparison is modified by adjustments for various covariates.

Other factors will be used to characterize the patients enrolled in the study and to provide descriptive statistics of outcomes according to subgroups of the population. These factors include age at randomization, type and schedule of 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, systemic disease-free survival, 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

Because all women will receive GnRH analogue, the patients enrolled in this protocol are likely to be younger premenopausal women. We will assume that most of the women enrolled in the trial will receive chemotherapy together with GnRH analogue. 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].

Premenopausal women with ER-positive, 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). If we assume that a little over 60% of the cases enrolled in this trial will be node-positive, the 5-year DFS with chemotherapy alone is estimated at 51%. A 40% reduction in risk of relapse by adding tamoxifen [3] and a hypothesized 25% additional risk reduction associated with GnRH analogue puts the estimated baseline risk for the GnRH analogue plus tamoxifen control group at 74.1%.

The treatment comparison will be based on a logrank test with an overall two-sided level of 0.05. Table 9.1 shows the operating characteristics of three alternative designs that would allow the detection of 20%, 25%, and 30% reduction in hazard by using exemestane instead of tamoxifen.

Table 9.1. Operating characteristics for the GnRH analogue plus exemestane versus GnRH analogue plus tamoxifen comparison.

Reduction in hazard	20%	**25%**	30%
GnRH analogue + tamoxifen 5-yr DFS	74.1%	**74.1%**	74.1%
GnRH analogue + exemestane 5-yr DFS	78.6%	**79.8%**	81.0%
Two-sided alpha level	.05	**.05**	.05
Required number of events*	653	**396**	260
Power	.80	**.80**	.80
Accrual rate (pts/year)	410	**410**	410
Total accrual time (yrs)	4.5	**4.5**	4.5
Sample size	1845	**1845**	1845
Total Study duration with 4 interim + 1 final analyses (yrs)*	10.4	**6.9**	5.3

* Under the alternative hypothesis with 4 interim analyses and 1 final analysis [47].

For planning purposes, we will target a 25% reduction in hazard. This will require recruitment of **1845 patients** (410 patients per year for 4.5 years with 2.4 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. Approximately 9% were less than 35 years of age and about 25% were less

than 40. Thus, we anticipate approximately 40 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.

We prospectively plan to combine the data available for the TEXT study with the arms comparing exemestane plus ovarian function suppression (OFS) versus tamoxifen plus OFS in the complementary Suppression of Ovarian Function Trial (SOFT: IBCSG 24-02). We note that TEXT and SOFT differ with respect to patient selection and treatment for women who receive chemotherapy; TEXT enrolls patients following surgery and uses concurrent GnRH analogue and chemotherapy, while SOFT enrolls patients who remain premenopausal following chemotherapy and initiates OFS (GnRH analogue, surgical oophorectomy or ovarian irradiation) following the completion of 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 comparison (at the 0.05 level) to detect a 20%, 25%, or 30% reduction in hazard with OFS + exemestane versus OFS + tamoxifen would be at least 88%, 98%, and 99%, respectively, assuming that both SOFT and TEXT recruit as planned and the combined analysis is performed 6.9 years from the opening of the two studies.

9.4 Interim monitoring

A group sequential design with four interim analyses and one final analysis will be used [47]. The target number of events for the final analysis is 396, and interim analyses will be planned after 99 (25%), 158 (40%), 237 (60%), and 317 (80%) events have been observed. We anticipate that this monitoring scheme will provide annual formal analyses from the time that 99 events have been observed. At each interim analysis and at the final analysis, testing will be performed using the O'Brien-Fleming boundaries (3.969, 3.297, 2.659, 2.284, 2.036) [48].

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 99th 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 ER-positive 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 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 Coordinating Center Office in Bern (**IBCSG Coordinating Center, Effingerstrasse 40, CH-3008 Bern**). The Australia-New

Zealand Group will maintain a tumor bank within Australia. The H&E section is sent for central pathology review, and 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 expression 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 [49] and second primaries [50]. In addition, research is ongoing to determine whether genetically-associated breast cancer responds differently to treatment [51].

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

INTERNATIONAL BREAST CANCER STUDY GROUP

IBCSG Trial 25-02
BIG Trial 3-02

Tamoxifen and Exemestane Trial (TEXT)

Amendment 2

Rationale for Amendment

1. To restart enrollment to a target accrual of 2639 patients

The TEXT protocol will re-start accrual with this Amendment. At the time of its suspension on 30 November 2007, TEXT had accrued 2039 patients. The protocol has been revised to increase the accrual by 600 patients, to the target accrual of 2639. The trial enrollment will be increased to ensure that the primary trial question is reported with adequate power in a timely manner, as two features of enrollment to date would otherwise necessitate an increase in the additional follow-up time to reach 396 events for the final analysis:

- The protocol assumed uniform accrual, but the accrual rate increased over time, averaging 24.6 patients per month (295/year) over the first two years, 51/month over the third year (612/year), and 65/month (780/year) over the last year.
- The characteristics of enrolled patients are lower-risk (based on nodal status, age, and prior chemotherapy) than assumed for the estimation of the baseline risk for the GnRH analogue plus tamoxifen control group.

2. To include translational investigations

This amendment includes a single whole blood sample for DNA isolation to be used for specified patient-related pharmacogenetics and disease-related gene polymorphisms and unspecified future studies. For these investigations, the protocol distinguishes between patients already randomized before this amendment (i.e. prior to 1 January 2008), called TEXT-1, and those entered after this amendment (i.e. after 1 January 2008), called TEXT-2. New requirements are:

- TEXT-1: A whole blood sample at the patient's next visit
- TEXT-2: A whole blood sample for DNA isolation at baseline. It must be obtained prior to start of treatment but not more than 14 days prior to randomization

Specific Reasons for the Amendment

The specific changes mostly relate to the two areas explained above

1. To increase the sample size to 2639 patients
2. To provide background information on the translational studies
3. To add a translational trial objective
4. To add an eligibility criteria stating that TEXT-2 patients must be informed of and agree to the investigations required by the protocol for translational research
5. To describe the translational trial endpoints

6. To provide statistical considerations on the revised sample size and translational studies
7. To outline requirements for collection of whole blood. Details will be in a separate Manual for Blood Sample Logistics
8. To describe the planned translational investigations and DNA banking
9. To remove the possibility to determine prior chemotherapy by randomization to PERCHE (due to the closure of PERCHE)
10. To modify the Patient Information Sheet/Informed Consent Appendix I for TEXT-2 patients to include the translational studies
11. To create a supplemental Patient Information Sheet/Informed Consent Appendix IA for TEXT-1 patients.
12. To add revised and additional CRFs
    a. Form A (revised)
    b. Form PMC (revised)
    c. Form TR-1 (new)
    d. Form TR-2 (new)

Revised documents include:

1. A working protocol incorporating the changes from Amendment 2 (highlighting all changes in red)
2. Revised Appendix I
3. New Appendix IA
4. Revised and new CRFs

This document contains changes to the IBCSG Trial 25-02/BIG Trial 3-02 protocol made in Amendment 2, dated 25 July 2008. Specific text additions are highlighted and in **bold.**

AMENDMENT 2 CHANGES:

Section	Prior version	New Version
Contact Information		Updated all contact information
Protocol Signature Page	Two signatures collected	One signature collected
Principal Investigator Protocol Signature Page		The Principal Investigator/Co-Investigator Protocol Signature Page has been replaced by the Principal Investigator page which requires only one signature from the Principal Investigator.
Protocol Summary and Schema	**Sample Size:** 1845 patients	**Sample Size: 2639** patients
Protocol Summary and Schema	Use of CT may be determined by randomization in the PERCHE trial or by investigator/patient choice.	Use of CT may be determined by investigator/patient choice.
Treatment Schedules	N/A	**Translational Investigations:** **TEXT-1 (patients randomized prior to 1 January 2008):** • **Whole blood: A whole blood sample for DNA isolation according to the guidelines in the Manual for Blood Sample Logistics is required at the patient's next visit, after appropriate informed consent.** **TEXT-2 (patients randomized after 1 January 2008):** • **Whole blood: A whole blood sample for DNA isolation is required at baseline. It must be obtained prior to start of treatment but not more than 14 days prior to randomization, according to the guidelines in the Manual for Blood Sample Logistics.**
1.2	N/A	**In the recent Early Breast Cancer Overview [56] the addition of LHRH agonists to tamoxifen, chemotherapy, or both reduced recurrence by 12.7% (p=0.02); and death after recurrence by 15.1% (p=0.03). LHRH agonists showed similar efficacy to chemotherapy. No trials had assessed an LHRH agonist versus chemotherapy with tamoxifen in both arms.**
1.4	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	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 prevent**ed** loss of bone mineral density in postmenopausal women [38]. In an adjuvant

Section	Prior version	New Version
	postmenopausal women [38]. 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 [39]. A pre-clinical trial by Goss et al. [40] 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.	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 [39]. **A study conducted in healthy postmenopausal women by Goss et al. [40], to compare the effects of exemestane with the nonsteroidal aromatase inhibitors anastrozole and letrozole on serum and urine levels of bone turnover biomarkers, showed that exemestane increased serum levels of the bone formation marker PINP after 24 weeks, suggesting a specific bone-formation effect related to its androgenic structure.**
1.5	N/A	New section
2.4	N/A	New section
3.1.11	N/A	**Patients must be informed of and agree to the investigations required by the protocol for translational research.**
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.	When randomization is complete, fill in Confirmation of Registration Form (A) and fax Form A, **PMC Form** 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.
4.5.2	Adjuvant chemotherapy [the decision to use adjuvant chemotherapy may be made by previous randomization in the PERCHE trial or-by investigator/patient choice]	Adjuvant chemotherapy [the decision to use adjuvant chemotherapy may be made by investigator/patient choice]
5.2.4	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,	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

Section	Prior version	New Version
	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**.** [53]**.** In a subsequent updated oral presentation of this trial, a non-significant excess of myocardial infarctions was noted in those treated with exemestane compared with tamoxifen in this population (mean age 64 years).	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**.** [53]**. Updated results of this trial showed** a non-significant excess of myocardial infarctions in those **patients** treated with exemestane compared with tamoxifen in this population (mean age 64 years) [54], **a significant decrease in BMD compared to baseline, and a slight increase in bone fractures (OR=1.45, p=0.003) [85]. No patient with BMD in the normal range at trial entry developed osteoporosis. Bone resorption and formation markers also increased at all time points in women receiving exemestane (p<0.001).**
6.3	N/A	New section
Table 7.1	N/A	Modified to include Translational Investigations.
Legend to Table 7.1	N/A	Modified to include Translational Investigations.
8.1	N/A	The following forms have been added to the Case Report Forms Schedule: Form 25/26 PMC, Form 25-TR-2, and Form 25-TR-1.
8.3	N/A	The Manual for Blood Sample Logistics has been added to the list.
8.6	N/A	New section
9.6	N/A	New section
11.2.2	The IBCSG has established a central repository for tissue blocks and slides from every patient enrolled in IBCSG clinical trials. The required pathological material (described in the previous section) is submitted to, catalogued, and maintained in the IBCSG Coordinating Center Office in Bern (**IBCSG Coordinating Center, Effingerstrasse 40, CH-3008 Bern**). The Australia-New Zealand Group will maintain a tumor bank within Australia. The H&E section is sent for central pathology review, and 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 expression and the proliferative fractions (Ki-	The IBCSG has established a central repository for tissue blocks and slides from every patient enrolled in IBCSG clinical trials. The required pathological material (described in the previous section) is submitted to, catalogued, and maintained in the IBCSG Coordinating Center Office in Bern (**IBCSG Coordinating Center, Effingerstrasse 40, CH-3008 Bern**). The Australia-New Zealand Group will maintain a tumor bank within Australia. The H&E section is sent for central pathology review, and 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 expression and the proliferative fractions (Ki-67 immunostaining). **Testing for genes that are associated with inherited risk of breast**

Section	Prior version	New Version
	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.	**cancer in the family 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.
11.4	N/A	New section
12.3	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.	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.
12.5	N/A	New paragraph added at end of section: **TEXT-1 patients (randomized prior to 1 January 2008) will receive an Addendum to the patient information sheet and informed consent to be signed before the blood sample for translational investigations is taken. Because these translational objectives were not specified when the TEXT-1 patients entered the study, the patient may decline to provide the blood sample.**
14	N/A	References updated to reflect protocol changes.
NOTE: The changes below refer only to the IBCSG Patient Information and Informed Consent Appendix. Changes to the North American Patient Information and Informed Consent are in the Changes document dated 03Sept08.		
IBCSG Appendix 1 Purpose of the Study	You have been diagnosed with a type of breast cancer that is known to respond to hormonal treatment in the majority of patients, because it expresses hormone receptors. The disease has been confined to the breast, possibly to lymph nodes under the axilla, but there is no evidence of spread elsewhere in your body. Standard local therapy consists of surgery with or without radiation therapy. In addition, standard therapy involves hormonal therapy which is known, in patients with breast cancer similar to yours, to decrease the chance of the cancer reappearing in your body at a later date. Standard hormonal treatment includes an estrogen modulator called tamoxifen. More recently, another family of hormonal drugs called aromatase inhibitors, to which the drug exemestane (Aromasin®) belongs, has shown initial promising results in post-menopausal women. It is still unclear whether tamoxifen or an aromatase inhibitor is the best preventive treatment for post-menopausal breast cancer patients.	You have been diagnosed with a type of breast cancer that is known to respond to hormonal treatment in the majority of patients, because it expresses hormone receptors. The disease has been confined to the breast, possibly to lymph nodes under the axilla, but there is no evidence of spread elsewhere in your body. Standard local therapy consists of surgery with or without radiation therapy. In addition, standard therapy involves hormonal therapy which is known, in patients with breast cancer similar to yours, to decrease the **risk** of the cancer reappearing in your body at a later date. Standard hormonal treatment includes an estrogen modulator called tamoxifen. More recently, another family of hormonal drugs called aromatase inhibitors, to which the drug exemestane (Aromasin®) belongs, has shown initial promising results in post-menopausal women. It is still unclear whether tamoxifen or an aromatase inhibitor is the best preventive treatment for post-menopausal breast cancer patients. Aromatase inhibitors are not efficient on their own in premenopausal women as high levels of estrogens are present. In

Section	Prior version	New Version
	Aromatase inhibitors are not efficient on their own in premenopausal women as high levels of estrogens are present. In addition, premenopausal patients also benefit from suppression of the ovaries to simulate menopause. This ovarian function suppression can be achieved by either radiation therapy, surgical resection of the ovaries or by a class of drugs, known as the GnRH analogues, given as monthly injections for five years. The addition of aromatase inhibitors will further decrease the level of circulating estrogen. Chemotherapy has also been shown to lower the risk of recurrence in premenopausal patients with breast cancer, independent of whether the cancer is sensitive to hormone therapy or not, and could be added to your treatment plan. This study will compare the effectiveness of exemestane with tamoxifen, both given orally for 5 years. All patients will also receive monthly GnRH analogue (triptorelin) injections to suppress ovarian function for 5 years. The hormonal treatment could be stopped earlier in case of evidence of disease recurrence. Chemotherapy, if needed, will be given at the beginning, concomitantly to the start of the monthly injections.	addition, premenopausal patients also benefit from suppression of the ovaries to simulate menopause. This ovarian function suppression can be achieved by either radiation therapy, surgical resection of the ovaries or by a class of drugs, known as the GnRH analogues, given as monthly injections for five years. The addition of aromatase inhibitors will further decrease the level of circulating estrogen. Chemotherapy has also been shown to lower the risk of recurrence in premenopausal patients with breast cancer, independent of whether the cancer is sensitive to hormone therapy or not, and could be added to your treatment plan. This study will compare the effectiveness of exemestane with tamoxifen, both given orally for 5 years. All patients will also receive monthly GnRH analogue (triptorelin) injections to suppress ovarian function for 5 years. **Laboratory investigations are conducted to increase the knowledge about the prognosis and outcome of breast cancer, and the benefit and tolerability of the therapy.** The hormonal treatment could be stopped earlier in case of evidence of disease recurrence. Chemotherapy, if needed, will be given at the beginning, concomitantly to the start of the monthly injections of **Triptorelin**.
IBCSG Appendix 1 Description of the Clinical Research Study	Patients will be assigned randomly (similar to the toss of a coin) to receive the current standard therapy with tamoxifen and the monthly injection of triptorelin or the combination of exemestane and the same monthly injection. Your doctor will choose the type of chemotherapy, if deemed necessary. This study will permit the estimation of the effects of the treatment on the patients' likelihood of recurrence and death from breast cancer and on their quality of life. A total of 1845 patients are expected to be enrolled in this study over a period of four years at many centers around the world.	Patients will be assigned randomly (similar to the toss of a coin) to receive **either** tamoxifen **or exemestane in combination with monthly injections of Triptorelin**. Your doctor will choose the type of chemotherapy, if deemed necessary. This study will permit the estimation of the effects of the treatment on the patients' likelihood of recurrence and death from breast cancer and on their quality of life. A total of **2639** patients are expected to be enrolled in this study over a period of **six** years at many centers around the world.
IBCSG Appendix 1 Treatment	The drug given as a monthly injection to suppress the ovaries on this study is triptorelin and its use in early stage breast cancer is experimental. The injections will be given intramuscularly. With triptorelin, the ovaries may start working again when injections are stopped. In rare circumstances your physician may suggest a different drug for injection (goserelin), but it will not be provided by the study.	**In this study Triptorelin is given as a monthly injection to suppress the ovaries. Its use in early stage breast cancer is experimental.** The injections will be given intramuscularly. With triptorelin, the ovaries may start working again when injections are stopped. In rare circumstances your physician may suggest a different drug for injection (goserelin), but it will not be provided by the study. .

Section	Prior version	New Version
IBCSG Appendix 1 Treatment	Paragraph removed: As described in detail below, hormone treatments produce some side effects. It is important that you tell your physician about additional medication that you take during or after treatment. Your physician will recommend medications to help with these side effects. For women with vaginal dryness and/or dyspareunia (pain with intercourse) vaginal moisturizers and lubricants may be used. If these do not help the symptoms, local vaginal estrogens may be considered. If you have troublesome hot flushes your doctor might recommend a serotonin reuptake inhibitor medication. Because any of the treatments in this study may increase the risk of osteoporosis, adequate calcium intake or supplements and weight bearing exercise may be recommended. Women who have evidence of bone density loss (osteoporosis) may be recommended to have specific treatments for osteoporosis, such as alendronate (Fosamax®).	**Individual features such as genetic characteristics of estrogen receptors and drug metabolizing enzymes (genes or other parts of the blood that process breast cancer treatments) are becoming important indicators not only for the prognosis and outcome of breast cancer but also for the responsiveness and tolerability of the treatments. A blood sample of 10 ml will be collected from you before start of treatment. The blood sample will be sent to a central laboratory and used for extraction of DNA (genetic material) and subsequent determination of estrogen receptor subtypes and genetic variants of drug metabolizing enzymes. We will not examine if cancer is hereditary in your family.** **Because any of the treatments in this study may increase the risk of osteoporosis, adequate calcium intake or supplements and weight bearing exercise may be recommended. Bone densitometry is recommended yearly during 6 years. Women who have evidence of bone density loss (osteoporosis) may be recommended to have specific treatments for osteoporosis.**
IBCSG Appendix 1 – New Section		**Blood draw** **The needle used to take blood might be uncomfortable. You might get a bruise, or rarely, an inflammation or infection at the site of the needle puncture.**
IBCSG Appendix 1 Expenses	You will receive no payment for taking part in this study. Exemestane and triptorelin will be supplied to you on this study free of charge if you are randomized to a treatment using one of those drugs. All other expenses, including the cost of tamoxifen, chemotherapy, surgery or radiation and routine standard examinations will be handled similarly as if you were receiving standard treatment and not participating in a clinical trial.	You will receive no payment for taking part in this study. **Triptorelin will be supplied to you on this study free of charge. If you are randomized to Exemestane, this drug will be supplied free of charge as well. DNA isolation and examination will be free of charge.** All other expenses, including the cost of tamoxifen, chemotherapy, surgery or radiation and routine standard examinations will be handled similarly as if you were receiving standard treatment and not participating in a clinical trial.
IBCSG Appendix 1 Collection of Biological Material	If you participate in this study, it is planned that a sample of tissue obtained at the time of your surgery for breast cancer will be sent to a central laboratory or institute for pathology review, and at a later stage for use in research projects to investigate biologic properties of breast cancer. Samples may be collected and stored at the IBCSG Coordinating Center. The use of the material for research will be	If you participate in this study, it is planned that a sample of tissue obtained at the time of your surgery for breast cancer will be sent to a central laboratory or institute for pathology review, and at a later stage for use in research projects to investigate biologic properties of breast cancer. Samples may be collected and stored at the IBCSG Coordinating Center**. Blood samples for DNA-isolation will be stored and analyzed at a**

Section	Prior version	New Version
	under the supervision of the Scientific Committee of the IBCSG and will be submitted to the appropriate Ethical Committees. The pathology review at a central laboratory or institute is a requirement for this study. You may decide to grant advance authorization for possible future new studies on your stored tissue specimens, with the understanding that their confidential nature will be fully protected and that a prior approval of an appropriate ethics committee will be obtained. Alternatively, you will be asked to consent to any such future study. On the other hand, you have the right to refuse consent to storage and further research on your tissue specimens except for the needs of the present study.	**central laboratory.** The use of the material for research will be under the supervision of the Scientific Committee of the IBCSG and will be submitted to the appropriate Ethic**s** Committees. The pathology review at a central laboratory or institute is a requirement for this study. You may decide to grant advance authorization for possible future new studies on your stored tissue **and blood** specimens, with the understanding that their confidential nature will be fully protected and that a prior approval of an appropriate ethics committee will be obtained. Alternatively, you will be asked to consent to any such future study. On the other hand, you have the right to refuse consent to storage and further research on your tissue specimens except for the needs of the present study.
Patient Informed Consent	N/A	**Collection of blood sample: The blood sample will be sent to a central laboratory for the investigations explained in the patient information sheet. At a later stage, the isolated DNA may be used in research projects to investigate biologic properties of breast cancer. Please indicate if your blood sample can also be used for further medical research:** ☐ **yes** ☐ **no**

INTERNATIONAL BREAST CANCER STUDY GROUP

IBCSG Trial 25-02
BIG Trial 3-02

Tamoxifen and Exemestane Trial
(TEXT)

Amendment 3

Reasons for Amendment:
The protocol has been revised for the following reasons:

1. To modify the statistical analysis plan. Accrual has been completed with 2672 patients enrolled. It is not possible to increase the sample size. Patients are doing much better than originally anticipated. The estimated event rate is 1.7% per year as opposed to 6% per year in the original protocol. Consequently, the original event-driven analysis plan would require an additional 7 years of follow up (end of 2017) before providing the first report of results. The Steering Committee, with the endorsement from the Data Safety Monitoring Committee, therefore decided to implement a time-driven analysis plan with a cut-off defined for the fall of 2013 at a median follow up of approximately 6 years.
2. To include breast cancer-free interval (BCFI) and distant recurrence-free interval (DRFI) as secondary endpoints replacing systemic disease free survival. The BCFI and DRFI endpoints are consistent with the Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials proposed by Hudis et al. J Clin Oncol 25:2127-2131, 2007.
3. To collect additional targeted adverse event information on glucose intolerance (diabetes) and anti-diabetic concomitant medications. Increased risk of diabetes has been suggested by epidemiologic studies in men being treated with GnRH agonists for prostate cancer. Diabetes has been added to the case report forms as a targeted adverse event.

Revised documents include:
1. A working protocol incorporating the changes from Amendment 3 (highlighting all changes in green)
2. Appendix IV (Pathology)
3. Revised Adverse Event (25/26-AE) Form

This document contains changes to the IBCSG Trial 25-02/BIG Trial 3-02 protocol and appendices made in Amendment 3. Specific text additions are highlighted and in **bold.**

Section	Prior version	New Version
Contact Information		Updated contact information
2.3.2	Systemic disease-free survival	**Replaced with:** **Breast cancer-free interval and distant recurrence-free interval**
4.3 Randomization help desk		Updated contact information
5.2.2 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 during pregnancy and lactation. Cases of pregnancy have occurred in women receiving regular injections of GnRH analogue [29]. The role of non-hormonal contraception should therefore be discussed.	**First two paragraphs remain unchanged. The following paragraph is added at the end:** **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.**
6.1.2	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	**Replaced the first two paragraphs with the following:** **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.**

Section	Prior version	New Version
	systemic relapse, appearance of second (non-breast) primary tumor, or death, whichever occurs first. See Section 6.2.7 for exceptions.	**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.**
Legend to 7.1	N/A	**Inserted in section C** • **Glucose Intolerance (Diabetes) and/or anti-diabetes treatment** • **Hyperglycemia**
8.3 Investigator's file	N/A	**Inserted in list of documentation**: • **Health Authority Approval** • **Correspondence with Health Authority**
9.3 Sample size considerations	Because all women will receive GnRH analogue, the patients enrolled in this protocol are likely to be younger premenopausal women. We will assume that most of the women enrolled in the trial will receive chemotherapy together with GnRH analogue. 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]. Premenopausal women with ER-positive, 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). If we assume that a little over 60% of the cases enrolled in this trial will be node-positive, the 5-year DFS with chemotherapy alone is estimated at 51%. A 40% reduction in risk of relapse by adding tamoxifen [3] and a hypothesized 25% additional risk reduction associated with GnRH analogue puts the estimated baseline risk for the GnRH analogue plus tamoxifen control group at 74.1%. The treatment comparison will be based on a logrank test with an overall two-sided level of 0.05. Table 9.1 shows the operating characteristics of three alternative designs	**Replaced the first four paragraphs of Section 9.3 and Table 9.1 with the highlighted text below:** **The originally planned sample size was 1845. It was projected that 4.5 years of accrual, plus 2.4 years of additional follow up would be sufficient to observe the 396 target number of DFS events. This number of events would provide 80% power to detect a hazard ratio of 0.75 for GnRH + exemestane versus GnRH + tamoxifen (79.8% versus 74.1% 5-yr DFS, respectively) using a 2-sided, 0.05 level test. The study opened to enrollment in August 2003. The initial accrual goal was achieved ahead of schedule and 2039 patients had enrolled by November 2007, when recruitment was suspended. The patient population had characteristics more favorable than originally anticipated, and Amendment 2 (25Jul08) increased the target sample size to 2639. In March 2011, enrollment was closed with 2672 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 1.7% per year compared with the protocol-specified 6% per year. Consequently, at the October 2010 estimated event rate, an additional seven (7)**

Section	Prior version	New Version
	that would allow the detection of 20%, 25%, and 30% reduction in hazard by using exemestane instead of tamoxifen. Table 9.1. Operating characteristics for the GnRH analogue plus exemestane versus GnRH analogue plus tamoxifen comparison – *inserted here*. For planning purposes, we will target a 25% reduction in hazard. This will require recruitment of **1845 patients** (410 patients per year for 4.5 years with 2.4 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. Approximately 9% were less than 35 years of age and about 25% were less than 40. Thus, we anticipate approximately 40 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. We prospectively plan to combine the data available for the TEXT study with the arms comparing exemestane plus ovarian function suppression (OFS) versus tamoxifen plus OFS in the complementary Suppression of Ovarian Function Trial (SOFT: IBCSG 24-02). We note that TEXT and SOFT differ with respect to patient selection and treatment for women who receive chemotherapy; TEXT enrolls patients following surgery and uses concurrent GnRH analogue and chemotherapy, while SOFT enrolls patients who remain premenopausal following chemotherapy and initiates OFS (GnRH analogue, surgical oophorectomy or ovarian irradiation) following the completion of 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 comparison (at the 0.05 level) to detect a 20%, 25%, or 30% reduction in hazard with OFS + exemestane versus OFS + tamoxifen would be at least 88%, 98%, and 99%, respectively, assuming	**years of follow up (end of 2017) would be required to observe the protocol-specified 396 target number of the DFS events (at which time the median follow up would be 10.5 years). The Steering Committee considered this delay in the reporting of the trial results (14 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 6 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 (396 DFS events in TEXT) to a 'time-driven' plan (with a data cut-off defined for the fall of 2013), the Steering Committee recognizes that the statistical power for the original primary comparison (OFS + exemestane versus OFS + tamoxifen within TEXT) will be reduced. We estimate the power of this comparison to detect a 0.75 hazard ratio will be approximately 60% in the fall of 2013. Therefore, the primary analysis for comparing OFS + exemestane versus OFS + tamoxifen will be the originally planned combined analysis of TEXT and the Suppression of Ovarian Function Trial (SOFT) described below.** **Revised the last paragraph in Section 9.3 and added a sentence as shown below:** We prospectively plan to combine the data available for the TEXT study with the arms comparing exemestane plus ovarian function suppression (OFS) versus tamoxifen plus OFS in the complementary Suppression of Ovarian Function Trial (SOFT: IBCSG 24-02). We note that TEXT and SOFT differ with respect to patient selection and treatment for women who receive chemotherapy; TEXT enrolls patients following surgery and uses concurrent GnRH analogue and chemotherapy, while SOFT enrolls patients who remain premenopausal following

Section	Prior version	New Version
	that both SOFT and TEXT recruit as planned and the combined analysis is performed 6.9 years from the opening of the two studies.	chemotherapy and initiates OFS (GnRH analogue, surgical oophorectomy or ovarian irradiation) following the completion of 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 comparison (at the 0.05 level) to detect a 20%, 25%, or 30% reduction in hazard with OFS + exemestane versus OFS + tamoxifen would be at least **63%, 84%, and 95%**, respectively, assuming that both SOFT and TEXT **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 [47]. The target number of events for the final analysis is 396, and interim analyses will be planned after 99 (25%), 158 (40%), 237 (60%), and 317 (80%) events have been observed. We anticipate that this monitoring scheme will provide annual formal analyses from the time that 99 events have been observed. At each interim analysis and at the final analysis, testing will be performed using the O'Brien-Fleming boundaries (3.969, 3.297, 2.659, 2.284, 2.036) [48].	**Replaced with:** **Originally the protocol included a group sequential design with four interim and one final 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 99th 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.	**Deleted third sentence, new version reads:** 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. 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.
9.6	As described above, at trial initiation the	**Deleted first two paragraphs**

Section	Prior version	New Version
Sample size re-consideration	specified sample size was 1845 patients (Section 9.3) with the final analysis to be performed when 396 events are observed (Section 9.4). Enrollment opened in August 2003 and was suspended on 30 November 2007, having reached the planned enrollment. A date to suspend enrollment was specified which would allow patients who had already discussed the trial to have adequate time to decide whether to enroll, and as of this date 2039 patients were enrolled. As described below, two features of enrollment to date will necessitate an increase in the additional follow-up time to reach 396 events for the final analysis. The trial enrollment will be increased by 600 patients to ensure that the primary trial question is reported with adequate power in a timely manner and to provide adequate power for the translational objectives.	
9.6.1 Primary trial objective	With the original assumptions, the protocol trial design required 396 events at the final analysis to provide 80% power and could be achieved with the enrollment of 1845 patients over 4.5 years (410/year) and 2.4 years of additional follow-up (6.9 years total duration). • The protocol assumed uniform accrual, but the accrual rate increased over time, averaging 24.6 patients per month (295/year) over the first two years, 51/month over the third year (612/year), and 65/month (780/year) over the last year. • The characteristics of enrolled patients are lower-risk than assumed for the estimation of the baseline risk for the GnRH analogue plus tamoxifen control group (74.1% 5-year DFS). The estimation assumed a predominance of younger women, most receiving chemotherapy and 60% of whom would have node-positive disease; the actual median age is 43 years, 62% are receiving chemotherapy and 48% have node-positive disease. Thus, the estimate of 74.1% 5-year DFS may be too low. In a recent overview analysis of GnRH analogues as adjuvant therapy [56], patients treated with GnRH analogue plus tamoxifen had an estimated 5-year breast cancer recurrence probability of about 18%. Thus we estimate that an 80% 5-year	**Deleted section**

Section	Prior version	New Version
	DFS for patients randomized to GnRH plus tamoxifen might be expected in TEXT patients, with a corresponding improvement to 84.6% 5-year DFS for patients randomized to GnRH plus exemestane (maintaining the assumed 25% reduction in hazard). With the observed accrual and revised control 5-year DFS estimate, with 1845 patients we anticipate an increase of 1.7 years of additional follow-up needed to reach 396 events (8.6 years total duration). A total of 2039 patients had enrolled when recruitment was suspended on 30 November 2007. We estimate that increasing the sample size by an additional 600 patients (to 2639 patients total) will enable 396 events to be reached within 0.5 years of that anticipated in the original protocol (7.4 years total duration). Given that prior to this protocol modification the median follow-up of the 2039 enrolled patients was less than one year, no information about the observed recurrence rate was used to modify the protocol.	
9.6.2.1 Translational objectives	**Third paragraph:** The primary objective is to evaluate the prognostic and predictive value, in terms of DFS, of different genetic variants. The analysis will use multivariable Cox modeling. Sample size calculations assume 2000 patients (324 events), 82.3% 5-year DFS (80% GnRH+T vs. 84.6% GnRH+E 5-year DFS), 2-sided α=0.05, 80% power (Table 9.2 [86]).	**Revised third paragraph as shown below:** The primary objective is to evaluate the prognostic and predictive value, in terms of DFS, of different genetic variants. The analysis will use multivariable Cox modeling. Sample size calculations assume 2000 patients (324 events), 82.3% 5-year DFS (80% GnRH+T vs. 84.6% GnRH+E 5-year DFS), 2-sided α=0.05, 80% power (Table 9.2 [86]). **Given the lower DFS event rate estimated in October 2010, analyses for the translational research objectives described below are anticipated to be available at the time of the first 2 year efficacy update.**
11.2.1 Pathology requirements	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	**Revised last two paragraphs:** The tissue blocks, particularly in case of small tumors, may be returned to the participating center upon request. All reports, slides, and blocks must be marked with the randomization number The **IBCSG** 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.

Section	Prior version	New Version
	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 Coordinating Center Office in Bern (**IBCSG Coordinating Center, Effingerstrasse 40, CH-3008 Bern**). The Australia-New Zealand Group will maintain a tumor bank within Australia. The H&E section is sent for central pathology review,. 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 expression 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.	**Revised the following:** 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** (**IBCSG Central Pathology Office, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy**. The Australia-New Zealand Group will maintain a tumor bank within Australia. **Immunohistochemistry characterization is done as part of** central pathology review**, and the respective sections are stored in the central repository thereafter.** 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.
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	**Removed "Coordinating Center" from 2nd last sentence.** 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

Section	Prior version	New Version
	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.	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 prior to enrollment of the first patient. The IBCSG Ethics Committee also approves the protocol and reviews it annually.
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.	**Removed "Coordinating Center" from last sentence.** 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. Logistics for transmitting regulatory documents and ethics and health authority approvals for participating groups are described in Appendix VII.
References	47. EaSt 2000 (Early Stopping) statistical software package. Cytel Corporation, Cambridge, MA, USA, 2000. 48. O'Brien PC, Fleming TR: A multiple testing procedure for clinical trials. Biometrics 35:549-556, 1979.	**Deleted**
Appendix IV Pathology	N/A	General updates

International Breast Cancer Study Group Statistical Center

TEXT (Trial 25-02/BIG 3-02) and SOFT (Trial 24-02/BIG 2-02)

Statistical Analysis Plan

AI Question and OFS Question

Meredith Regan, ScD

Anita Giobbie-Hurder, MS

1. Introduction

1.1 Background

In 2003 IBCSG initiated a suite of three complementary tailored treatment investigations, the SOFT, TEXT and PERCHE trials, designed to answer questions concerning adjuvant treatment for premenopausal women with endocrine-responsive early breast cancer: 1) What is the role of ovarian function suppression (OFS) for women who remain premenopausal and are treated with tamoxifen? 2) What is the role of aromatase inhibitors for women treated with OFS? 3) What is the role of chemotherapy for women treated with OFS plus oral endocrine therapy?

The conduct of these randomized phase III trials required world-wide participation through collaboration of the Breast International Group (BIG) network and the North American Breast Cancer Groups. Pfizer is the primary pharmaceutical industry partner and Ipsen provides triptorelin outside of North America.

Over a 7.5-year period from 2003 to 2011, 5742 premenopausal women were enrolled at over 500 centers in 27 countries on 6 continents in:

TEXT (Tamoxifen and Exemestane Trial): designed to determine the role of AIs for women who receive OFS from the start of adjuvant therapy;

SOFT (Suppression of Ovarian Function Trial): designed to determine the role of OFS and the role of AIs for women who remain premenopausal after completion of (neo)adjuvant chemotherapy, or who are premenopausal following surgery and tamoxifen alone is a reasonable treatment option;

PERCHE (Premenopausal Endocrine-Responsive Chemotherapy): designed to determine the value of adding chemotherapy to combined endocrine therapy with OFS plus oral endocrine therapy.

TEXT and SOFT successfully enrolled the targeted number of patients. PERCHE closed prematurely in 2006 with only 29 patients enrolled (25 of 29 were co-enrolled in TEXT; (Regan et al., Ann Onc 2008).

Completion of TEXT and SOFT enrollment was anticipated within 5 years and first reporting about 7 years after the trials' initiation. However the characteristics of the enrolled patients differ from those anticipated in the protocols, and patients' outcomes are better than expected, necessitating an adaptation of the trials' analysis plans, in protocol amendments released in 2011. The original designs of TEXT and SOFT and the adaptations to overcome these challenges and ensure timely answers to questions concerning adjuvant treatment for premenopausal women with endocrine-responsive early breast cancer were described recently (Regan et al., Breast 2013).

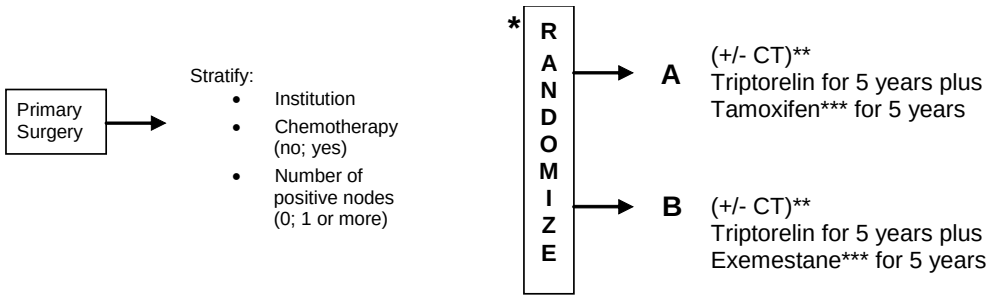
1.2 Trial Designs

The designs of TEXT and SOFT are summarized below.

TEXT (IBCSG 25-02 / BIG 3-02)

Title:	**Tamoxifen and Exemestane Trial (TEXT):** A phase III trial evaluating the role of exemestane plus GnRH analogue as adjuvant therapy for premenopausal women with endocrine responsive breast cancer.
Patient Population:	Premenopausal women (estradiol (E2) levels in the premenopausal range) with histologically proven, resected breast cancer with ER and/or PgR positive tumors (ER and/or PgR ≥ 10%).
Entry:	Patients should be randomized within 12 weeks after surgery prior to commencing any adjuvant systemic therapy.
Activation Date:	04Aug03 (First patient randomized 7Nov03)
Target Accrual:	2639 patients
Closure Date:	11Mar11 (Last patient randomized 7Apr13)
Final Accrual:	2672 patients

TEXT Schema:



* Randomization prior to receiving any adjuvant systemic therapy

**CT (chemotherapy) is determined by investigator/patient choice and if used, should begin at the same time as triptorelin.

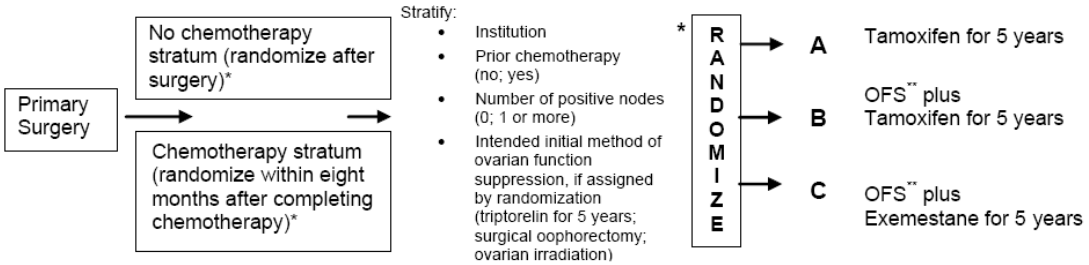
***Tamoxifen or exemestane should start after adjuvant chemotherapy has been completed or approximately six to eight weeks after the initiation of triptorelin, whichever is later.

IBCSG 25-02 (TEXT) is an international, non-blinded, randomized phase III trial designed to investigate the efficacy the aromatase inhibitor (AI) exemestane with OFS, achieved by long-term use of GnRH analogue, compared with tamoxifen+OFS. TEXT focuses the AI question on premenopausal patients whom the physician feels OFS is most appropriate from the start of adjuvant therapy. Eligibility required enrollment within 12 weeks of definitive surgery and excluded patients who had already received any (neo)adjuvant chemotherapy or endocrine therapy. Randomization used 1:1 allocation and stratified by whether adjuvant chemotherapy was planned (no; yes), and number of positive nodes (0; 1 or more). Patients would either receive no chemotherapy or commence chemotherapy at the same time as GnRH analogue is initiated. Patients had to use GnRH analogue for at least 6 months and then could change to permanent OFS with surgery or radiation at any time thereafter.

SOFT (IBCSG 24-02 / BIG 2-02)

Title:	**Suppression of Ovarian Function Trial (SOFT):** A phase III trial evaluating the role of OFS and the role of exemestane as adjuvant therapies for premenopausal women with endocrine-responsive breast cancer.
Patient Population:	Premenopausal women (estradiol (E2) levels in the premenopausal range†) with histologically proven, resected breast cancer with ER and/or PgR positive tumors (ER and/or PgR ≥ 10%) 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 E2 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 E2 levels in the premenopausal range between 2 weeks and 8 months after the final dose of chemotherapy.
Activation Date:	04Aug03 (First patient randomized 17Dec03)
Target Accrual:	3000 patients
Closure Date:	31Jan11 (Last patient randomized 27Jan11)
Final Accrual:	3066 patients

SOFT Schema:



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

IBCSG 24-02 (SOFT) is an international, three-arm, non-blinded, randomized phase III trial designed to investigate the role of OFS and the role of the AI exemestane, originally planned with three primary comparisons: tamoxifen+OFS versus tamoxifen alone; exemestane+OFS versus tamoxifen alone; and exemestane+OFS versus tamoxifen+OFS. SOFT focuses the OFS question on those who biologically would be most likely to benefit, i.e., women with endocrine-responsive breast cancer with premenopausal status either after completion of (neo)adjuvant chemotherapy or following surgery alone.

Eligibility required enrollment either: (a) within 8 months of the final dose of chemotherapy once premenopausal status was confirmed by estradiol levels (e.g., patients with temporary chemotherapy-induced amenorrhea who regained premenopausal status within 8 months were eligible); or (b) within 12 weeks of definitive surgery if no adjuvant chemotherapy was to be given. Patients could have received adjuvant oral endocrine therapy (but not GnRH analogues) for up to 8 months prior to randomization. The 8-month criterion was an early protocol amendment (from 6 months) to overcome logistical challenges of enrolling a patient who presented after regaining premenopausal status at a 6-months post-chemotherapy standard-of-care visit.

Randomization used 1:1:1 allocation, and was stratified according to prior (neo)adjuvant chemotherapy (yes;no), lymph node status (0; 1+) and intended method of OFS (GnRH analogue, oophortectomy; ovarian irradiation). For patients randomized to receive OFS, the use of GnRH analogue, bilateral oophorectomy or bilateral ovarian irradiation was by patient preference and patients who began with GnRH analogue could opt to undergo surgery or irradiation at any time.

1.2.1 Design Commonalities

As a planned suite of trials, a majority of trial design features were common to both trials. Briefly, the trials enrolled premenopausal women with histologically-proven, resected, hormone receptor-positive (defined as ER≥10% and/or PgR≥10%) early invasive breast cancer. P remenopausal status was defined by estradiol levels in the premenopausal range according to institutional parameters. The tumor was to be confined to the breast and axillary lymph nodes without detected metastases elsewhere. Patients must have had proper local-regional treatment for primary breast cancer with no known residual loco-regional disease. Study visits were every 3 months during year one, every 6 months during the next 5 years, and yearly follow-up thereafter.

The oral endocrine therapy was either tamoxifen or the steroidal AI exemestane. OFS was by GnRH analogue triptorelin administered 4-weekly for 5 years, bilateral surgical oophorectomy, or bilateral ovarian irradiation (with biochemical confirmation of cessation of ovarian function after 2 months).

1.2.2 Original statistical design assumptions and sample size considerations

TEXT planned enrollment was 1845 patients. The design projected that 4.5 years of uniform accrual, plus 2.4 years of additional follow-up, would be sufficient to observe the target of 396 DFS events, which would provide 80% power to detect 25% reduction in hazard with exemestane+OFS versus tamoxifen+OFS (HR=0.75; 79.8% versus 74.1% 5-year DFS, respectively) using a 2-sided 0.05 α-level logrank test and assuming exponential distribution of DFS. Four interim analyses prior to the final analysis were planned. By November 2007, 2039 of the planned 1845 patients had enrolled, and enrollment was suspended. Because of the faster-than-expected enrollment rate and lower-risk characteristics of enrolled patients than anticipated, Amendment 2 (Jul08) re-opened enrollment with an increased target sample size of 2639 patients. A revised estimate of 80% 5-year DFS in the tamoxifen+OFS control group (with corresponding 25% reduction in hazard to 84.6% 5-year DFS for exemestane+OFS) was hypothesized based on the 2007 overview analysis of GnRH analogues in which the 5-year breast cancer recurrence was around 18% among patients treated with GnRH analogue plus tamoxifen. With the observed enrollment pattern and revised hazard rates, the increased sample size was projected to reach the target of 396 DFS events within 0.5 years of the original design, or 7.4 years since first enrollment.

SOFT planned enrollment was 3000 patients for the 3 arms. The design projected that 5 years of uniform accrual, plus 1.9 years of additional follow-up would be sufficient to observe the target of 783 DFS events (522 per pairwise comparison) to have 80% power to detect a 25% reduction in hazard relative to control 5-year DFS of 67% (HR=0.75; 74.1% versus 67.0% 5-year DFS; 2-sided α=0.0167). If tamoxifen+OFS would result in a 25% reduction in hazard to 74.1% 5-year DFS, then power was 68% to detect a further 25% reduction with exemestane+OFS to 79.8% 5-year DFS. Four interim analyses prior to the final analysis were planned.

From the outset, the protocols planned to combine the data of TEXT with the two arms of SOFT comparing exemestane+OFS versus tamoxifen+OFS. Differences in the two trials with respect to selection and treatment for women who received chemotherapy (i.e., TEXT enrolled patients following surgery and used concurrent GnRH analogue and chemotherapy, while SOFT enrolled patients who remained premenopausal following chemotherapy and initiated OFS after completion of chemotherapy) were taken into account in the combined analysis plan. The statistical power of such a combined comparison (at the two-sided α=0.05 level) would be at least 88%, 98% and 99% to detect a 20%, 25%, and 30% reduction in hazard, respectively, with exemestane+OFS versus tamoxifen+OFS under the protocol assumptions about accrual duration and additional follow-up.

1.2.3 Adaptations in the statistical design and analysis plans

As of October 2010, the overall DFS event rates—blinded to treatment assignment—were substantially lower than originally anticipated: approximately 1.7% and 2% per year versus the protocol-specified 6% and 8% per year in TEXT and SOFT, respectively. IBCSG projected an additional 7 and 13 years of follow-up to observe the targeted 396 and 783 DFS events in TEXT and SOFT, respectively (at median follow-up of 10.5 and 15 years). Increasing the sample size could hasten reaching the required events, but finances constrained this possibility.

The Steering Committee considered this delay to be unacceptably long (reporting 14 and 20 years after first enrollment versus 6.9 years originally-anticipated). The Committee decided to change the timing of analysis from “event-driven” to “time-driven” with a planned data cut-off during the third quarter of 2013, when the median follow-up should be at least 6 and 5 years in TEXT and SOFT, respectively. It was recognized that an analysis with fewer events than targeted would substantially reduce statistical power for the original protocol-planned primary objectives (approximately 60% in TEXT and 35% in SOFT to detect 25% reductions in hazards, assuming the October 2010 event rates continued). Therefore amendments of the TEXT and SOFT protocols (July 2011) revised the analysis plans for the first reporting of the trial objectives:

1. **AI Question**: the primary analysis comparing exemestane+OFS versus tamoxifen+OFS would implement the originally-planned combined analysis of TEXT and SOFT. The power of such a combined comparison (two-sided α=0.05 level) would be at least 95%, 84% and 63% to detect a 30%, 25% and 20% reduction in hazard, respectively, with exemestane+OFS.
2. **OFS Question**: the primary analysis from SOFT would focus on the unique comparison of tamoxifen+OFS versus tamoxifen alone, tested at the two-sided α=0.05 level. IBCSG estimated power to be at least 80%, 69%, 52% and 34% to detect 33.5%, 30%, 25% and 20% reductions in hazard, respectively, with tamoxifen+OFS.

These power calculations assumed a data cut-off in the third quarter of 2013 and persistence of the October 2010 DFS event rates, which project 250 DFS events in TEXT and 280 DFS events in SOFT (about 93 per group under the null hypothesis) at the time of data cut-off. The revised analysis plans removed planned interim efficacy analyses. The revised analysis plans removed planned interim efficacy analyses.

The Steering Committee's decision was endorsed by the IBCSG DSMC. These committees did not receive, nor did the IBCSG Statistical Center have knowledge of, outcome data according to treatment group prior to this decision. The first report of the combined analysis of the **AI Question** is anticipated in mid-2014. The report of the **OFS Question** from SOFT is anticipated in late 2014 after about 6 additional months of follow-up and a median follow-up of at least 5 years is reached.

Patient follow-up will continue and updates of efficacy results are planned approximately every two years after the first reports.

2. Efficacy Analysis Plans

2.1 Objectives

Based on revised statistical analysis plans in the 2011 amendments (i.e., SOFT Amendment 2 (24Aug11); and TEXT Amendment 3 (24Aug11)):

2.1.1 Primary Objective

AI Question: To evaluate the efficacy of exemestane+OFS compared with tamoxifen+OFS, across both trials combined, as adjuvant endocrine therapy for premenopausal women with endocrine-responsive early invasive breast cancer.

OFS Question: To evaluate the role of OFS+tamoxifen compared with tamoxifen alone, as adjuvant endocrine therapy for premenopausal women with endocrine-responsive early invasive breast cancer.

2.1.2 Secondary Objectives

- Assess overall survival, breast cancer-free interval, and distant recurrence-free interval
- Assess quality of life (see separate analysis plan)
- Investigate sites of first treatment failure
- Assess late side effects of early menopause
- Assess the incidence of second (non-breast) malignancies and causes of death without cancer event
- TEXT: Investigate patient and tumor features that may contribute to inter-individual variability of responsiveness to GnRH analogue plus exemestane and GnRH analogue plus tamoxifen (see separate analysis plan)

2.2 Analysis Populations

The primary analysis will use an intention-to-treat (ITT) approach. The ITT population will include all randomized patients, regardless of eligibility status; the possible exceptions are patients who immediately withdrew consent prior to treatment initiation and declined all participation, patients

determined (e.g., via audit) to be without documented informed consent, and/or patients at a participating center determined not to be compliant with protocol procedures. Any exclusions from the ITT population will be determined prior to the analysis and will be summarized in listing and CONSORT in the trial report.

AI Question: The AI Question ITT population will include

- All patients randomized in TEXT (exemestane+OFS and tamoxifen+OFS);
- SOFT patients randomized to the two OFS-containing arms (exemestane+OFS and tamoxifen+OFS).

OFS Question: The OFS Question ITT population will include

- SOFT patients randomized to the two tamoxifen-containing arms (tamoxifen+OFS and tamoxifen alone).

2.3 Endpoint Definitions

2.3.1 Primary endpoint

- Disease-free survival (DFS) is defined as the duration of time from randomization to the first indication of the following events: invasive recurrence at local (including recurrence restricted to the breast after breast conserving treatment), regional or distant sites; a new invasive cancer in the contralateral breast; any secondary (non-breast) malignancy; or a death without prior cancer event. Appearance of DCIS or LCIS either in the ipsilateral or in the contralateral breast will not be considered as an event for DFS. In the absence of an event, DFS is censored at the date of last follow-up.

2.3.2 Secondary endpoints

- Breast cancer-free interval (BCFI) is defined as the duration of time from randomization to the first indication of the following events: invasive breast recurrence at local, regional or distant sites; a new invasive cancer in the contralateral breast. In the absence of an event, BCFI is censored at the date of last follow-up or date of death without prior breast cancer event. (Second non-breast malignancies are ignored)
- Distant recurrence-free interval (DRFI) is defined as the duration of time from randomization to the first indication of invasive breast recurrence at a distant site. In the absence of an event, DRFI is censored at the date of last follow-up or date of death without distant recurrence.
- Overall survival (OS) is defined as the duration of time from randomization to death from any cause, or is censored at the date last known alive. (Note, for patients who withdrew consent or were lost to follow-up but follow-up for survival was possible through hospital or registry records, OS is censored at the date last known alive rather than date of last follow-up/withdrawn consent).
- Site of First Failure*:* Hierarchy of failures from least to worst, following standard IBCSG definition:
  - Local
  - Contralateral Breast
  - Regional ± above

- Soft Tissues/Distant Nodes ± above
- Bone ± above
- Viscera (including 'other') ± above

As well as 2nd (non-breast) malignancy; and death without prior cancer event.

For "site of first failure," if there are 2 or more failure sites within 2 months of each other, then the "worst" site is considered as the site of first failure. For example if there is a regional recurrence and a bone recurrence within 2 months of each other, then the bone would be considered the "worst" site of failure and considered as "site of first failure." If second malignancy is coincident with breast cancer recurrence then site of first failure is considered as the breast cancer recurrence.

Also per IBCSG standard, the date of DFS event is the date a proven recurrence was first suspected. In rare cases the date suspected is prior to randomization and then date of randomization is considered as date of event.

2.4 Follow-up

Median follow-up will be calculated separately for the AI Question and OFS Question analyses to guide the timing for the database locks. The 2011 amendments anticipated both analyses having concurrent data cut-offs in fall 2013 (Q3 2013). However because of the differential accrual patter and median follow-up in the two trials, as of Q4 2012 we anticipate that the respective data cut-offs and database locks will be separate for the two analyses (hence 2 database locks for SOFT and 1 database lock for TEXT) about 6 months apart.

- AI Question: The data (follow-up) cut-off for the AI Question analysis is planned for prior to 1 September 2013 (Q3 2013) when we have at least 5 years median follow-up for that analysis (estimated ~6yr for TEXT and <5yr for SOFT), with database lock in Q1 2014.
- OFS Question: The data (follow-up) cut-off for the OFS Question analysis is anticipated as prior to 1 April 2014, with database lock in Q3 2014 to have 5 years median follow-up.

Median follow-up is calculated from the Kaplan-Meier estimate of overall survival, with the event/censoring indicator inverted (i.e. alive as event and dead as censored).

Updated results will be presented every two years thereafter until the last patient enrolled has been followed for at least 10 years.

2.5 Tests and Estimates

The primary objectives will be investigated by comparing DFS between two treatment groups using two-sided stratified logrank test (H0: DFS1=DFS2; Ha: DFS1≠DFS2), with an overall experiment-wise α=0.05 (i.e., α=0.05 for AI Question analysis; and α=0.05 for OFS Question analysis). The test statistic and p-value will be taken from the stratified Cox PH model score test. Hazard ratios (AI Question: E+OFS / T+OFS; OFS Question: OFS+T / T) will be estimated from a stratified Cox PH model, with 95% CIs. Kaplan-Meier estimates of the DFS distributions will be calculated for each of the treatment arms, with reporting of the 5yr DFS.

We will check the proportional hazards assumption by visually assessing the plot of log(-log(survival)) versus log of survival time for parallelism. This will be done overall, and according to strata.

2.5.1 Stratification variables for logrank tests and HRs

AI Question analysis:

- Trial (TEXT; SOFT);
- Prior/Intended chemotherapy (no; yes);
- Number of positive nodes (0; 1+).

OFS Question analysis:

- Prior chemotherapy (no;yes);
- Number of positive nodes (0; 1+), and
- Intended initial method of OFS if assigned by randomization (triptorelin; oophorectomy or ovarian irradiation [may need to combine ovarian irradiation with oophorectomy because few patients indicated this option]).

Note about values of strata as provided at randomization vs. actual values: The randomization (RA) form collects the values entered into the IBCSG randomization system and used for stratification of the randomization assignment. If these values are incorrect then they are amended on the Registration form (A-form). The intention is to use the actual values entered in the A form; we will cross-tabulate the stratification variables between RA and A forms to compare the information obtained at randomization versus that on the A forms.

Note also, there may be rare cases when a patient in SOFT without prior chemotherapy later does receive chemotherapy after randomization, or in TEXT where the intended chemotherapy use differs from what occurs after randomization (e.g., chemotherapy intended and then patient refuses; or chemotherapy not intended and then based on second opinion the treatment plan is changed); in these cases the variable remains as prior/intended chemotherapy at randomization.

2.5.2 Cohorts

The TEXT and SOFT trial populations include four cohorts of patients:

- Patients in TEXT who were randomized within 12 weeks of surgery and for whom chemotherapy was not planned;
- Patients in SOFT who did not receive chemotherapy and were randomized within 12 weeks of surgery;
- Patients in TEXT who were randomized within 12 weeks of surgery and for whom chemotherapy was planned to begin after randomization, concurrently with GnRH analogue;
- Patients in SOFT who are premenopausal after prior (neo)adjuvant chemotherapy and are randomized within 8 months of completion chemotherapy.

Therefore in addition to having trial and chemotherapy as stratification factors, it is of interest to estimate the treatment effect within cohorts of the trials' patient populations. Note, the two cohorts of TEXT and SOFT who will not receive chemotherapy may differ, considering that in TEXT all patients would receive OFS whereas in SOFT the patients may have been randomized not to receive OFS.

(n.b., We will use the chemotherapy stratification factor, which in TEXT is intended chemotherapy and therefore may be different from actual chemotherapy receipt, in a few patients).

AI Question: In addition to the overall treatment comparison, the HRs (95% CI) will be estimated within each of the 4 trial-by-chemotherapy cohorts separately. To obtain these estimates, we will refit the primary Cox model, stratified only by nodal status, to also estimate an HR without stratification for trial and chemo strata; and then the 4 cohort HR estimates will be obtained from adding the trial-by-chemotherapy-by-treatment interaction and using contrasts to estimate HRs and CIs within each of the 4 cohorts.

OFS Question: In addition to the overall treatment comparison, the HRs (95% CI) will be estimated within each of the chemotherapy cohorts separately (SOFT prior chemo; SOFT no prior chemo) as described above.

2.6 Analysis Components

2.6.1 Patient enrollment, eligibility and follow-up compliance

This section summarizes TEXT and SOFT accrual, eligibility, exclusions from ITT population, institutional CRF and follow-up compliance. Some information will be reported for the entire SOFT trial population, and sometimes just for the relevant analysis population.

2.6.1.1 All randomized patients, by trial

Tables:

- Enrollment by group/country (rows), according to year and to strata (columns); by trial and overall
- Patient randomization treatment assignment and strata; by trial and overall
- Institutional follow-up compliance group/country (rows); by trial and overall
- Case report form submission status (baseline forms)

Figures:

- Enrollment over time; x-axis time in 6-montly intervals; y-axis number enrolled

2.6.1.2 CONSORT

In the manner of the CONSORT diagram, the following will be summarized.

Tables:

- CONSORT diagram content numbers by treatment assignment
    - Number of patients randomized
    - Number of patients included vs excluded from analysis population, with reasons
        - Listing of patients excluded from analysis population (patid, randomizing institution, randomization date, reason excluded, treatment assignment)
    - Number in analysis population who never started protocol treatment
    - Number in analysis population who WC/LFU
    - Number of patients analyzed in analysis population [same/as number included]

2.6.1.3 Analysis population

Tables:

- Enrollment by group/country (rows), by cohort and overall
- Patient randomization assignment and strata
- Eligibility status and reasons ineligible, overall and by treatment assignment
- Listing of ineligible patients (patid, randomizing institution, randomization date, reason ineligible, treatment assignment)
- Withdrawn consent and lost to follow-up status

2.6.2 Patient characteristics

Characteristics of the analysis population will be summarized overall and by treatment group. Notes about variable definitions are provided in the Appendix. Continuous variables are summarized as mean, SD, min/max, and quartiles. Categorical variables are summarized as N(%); for variables with unavailable (missing, unknown, not done) values, the default approach is to include an unknown category that is included in the denominator for percentages (rather than just listing the number of unknowns as a category).

For patients with bilateral invasive cancer, to define disease characteristics, the laterality with the highest-stage disease (defined based on number of positive nodes, tumor size and grade, primary histology; selection was reviewed by medical reviewer) was identified (by statistician and head of medical affairs) and all characteristics of that side were retained (with the exception that a patient's disease is defined as HER2-positive disease if either tumor is HER2+).

Tables (overall and by treatment group (AI Question also for 4 cohorts), unless otherwise specified):

- Patient:
    - Age at randomization (continuous; categorized in 5-year intervals)
    - Race/ethnicity
    - Performance status at randomization
    - BMI at randomization
    - Menstrual/endocrine history (age menarche, menstruation status at randomization, history hysterectomy, pregnancy history, pregnant at diagnosis, history of diabetes); family history of breast/ovarian cancer
    - Symptoms (from baseline AE form)
- Treatment (see also section 2.5.6):
    - Local therapy (combining surgery [Mx/BCS] and radiotherapy [yes/no] as would be reported in manuscript)
    - Surgery details (C-form as collected including use of ALND and SNB);
    - Radiotherapy details (R-form as collected)
    - Chemotherapy (whether used; timing relative to randomization, regimen [anthracycline-based; taxane-based; both; other], duration [dichotomized at 12 wks]);
    - HER2-directed therapy use [prior or concomitant]
    - Prior endocrine therapy (chemoprevention prior to diagnosis; ET after diagnosis prior to randomization in SOFT)
- Disease:
    - ER/PgR status and details

- HER2 status
- Nodal involvement (number axillary nodes positive and examined; number IM nodes positive and examined)
- Tumor size and grade, presence of peritumoral-vascular invasion (PVI), primary histology (and other details from P-form)
- Disease laterality and location (B-form)

2.6.3 Primary efficacy analysis

The primary efficacy analysis will proceed as summarized in Section 2.4 above. The data cut-off and database lock dates used for the analyses and the median follow-up duration will be reported.

2.6.3.1 Subgroup Analyses and Covariate-adjusted HR Estimates

The protocols pre-specified factors that 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 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 status. These analyses will be considered as secondary and descriptive.

The plans for these variables are summarized below (see notes in Appendix):

- Age (5-year age groups (<35,35-39,40-44,45-49,≥50))
- Chemotherapy (anthracycline-based, taxane-based, both, other, none)
- Surgery/RT (Mx+RT; Mx alone; BCS+RT; BCS alone; unknown)
- Tumor size (≤2 vs >2 cm; unknown)
- Tumor Grade (1,2,3,unknown)
- ~~ER, PgR level: because of heterogeneity of reporting of ER,PgR, a variable to provide more of a continuum of ER and PgR levels is to be derived~~ <wait until central values available>
- ER/PgR subgroup (+/+; +/-; -/+; other):
- HER2 status (positive, negative, unknown) and HER2-directed therapy use (yes,no)
- No. of metastatic lymph nodes (0, 1-3, 4+)

Stratified Cox PH regression models will be used to: estimate HRs (95% CI) for treatment effect, adjusted for these covariates; and estimate HRs (95% CI) for treatment effect within subgroups by including treatment-by-covariate interaction in the model (but not other covariates) and using contrasts.

In order for the entire analysis population to be used for each model, categorical variables will include a level for missing/unknown values. (Post-hoc note: these missing/unknown, unknown/not done, and small other groups will NOT be part of the reported test for covariate-by-treatment because they're not a meaningful part of the hypothesis test; the exception would be if there was a clinically-meaningful unknown/not done or "other" group that is of adequate size with at least 10 events per treatment group (10 arbitrarily used as rule-of-thumb), then such a group would be included.

Post-hoc note about treatment variables: subgroup analyses for treatment characteristics (local therapy—RT in particular, chemotherapy type and HER2-therapy) are also being performed separately according to cohort, because the timing of these treatments relative to randomization differs by cohort (i.e SOFT chemo cohort the chemo is prior to rando and HER2-therapy usually started prior to rando

and RT was at least initiated prior to rando; SOFT no chemo cohort often already started and possibly finished RT prior to rando; TEXT all RT,chemo,HER2-directed rx was after rando) therefore looking at heterogeneity separately by cohort may be more informative and methodologically appropriate; these were not planned analyses.

2.6.3.2 Tables and Figures

Tables:

- Primary treatment comparison: N events and patients, HR, 95% CI, log-rank test statistic and p-value, 5yr DFS, SE and 95% CI
- Cohort treatment comparisons (4): N events and patients, HR, SE, 95% CI,5yr DFS, SE and 95% CI
- Treatment effects within subgroups: N events and patients within each subgroup, treatment HR, 95% CI, p-value for test of treatment-by-variable interaction

Figures:

- KM plot of DFS, by treatment group, for entire analysis population *(y-axis: Percent Alive and Disease-Free; x-axis: Time since Randomization (12-month intervals); x-axis limited to 6 years (median survival plus 1 year) and numbers at risk at each 12-monthly interval)*
- KM plots of DFS, by treatment group, for 4 cohorts *(axes as above)*
- Forest plot of DFS, overall and for cohorts
- Forest plot of DFS, overall and for subgroups

2.6.4 Secondary efficacy analyses

Breast cancer-free interval, distant recurrence-free interval and overall survival will be summarized as described for DFS. Post-hoc note: of clarification, because of expected lower number of events, no subgroup analyses for distant recurrence-free interval or overall survival (other than according to cohort).

Sites of first treatment failure will be summarized overall and by treatment group as N (%).

Second (non-breast) malignancies as site of first failure, and deaths without prior cancer event will be summarized overall and by treatment group.

Tables:

- Primary treatment comparison for each of the 3 endpoints: N events and patients, HR, 95% CI, log-rank test statistic and p-value, 5yr DFS, SE and 95% CI
- Cohort treatment comparisons (4) for each of the 3 endpoints: N events and patients, HR, SE, 95% CI,5yr DFS, SE and 95% CI
- Sites of first failure, overall and by treatment group
- Types of second non-breast malignancies, as site of first failure, overall and by treatment group.

Figures:

- KM plots of BCFI, by treatment group, for entire analysis population and for each of the 4 cohorts *(y-axis: Percent Free from Breast Cancer; x-axis: Time since Randomization (12-month intervals); x-axis limited to 6 years (median survival plus 1 year) and numbers at risk at each 12-monthly interval)*

- KM plots of DRFI, by treatment group, for entire analysis population and for each of the 4 cohorts *(y-axis: Percent Free from Distant Recurrence; x-axis: Time since Randomization (12-month intervals); x-axis limited to 6 years (median survival plus 1 year) and numbers at risk at each 12-monthly interval)*
- KM plot of OS, by treatment group, for entire analysis population and for each of the 4 cohorts *(y-axis: Percent Alive; x-axis: Time since Randomization (12-month intervals); x-axis limited to 6 years (median survival plus 1 year) and numbers at risk at each 12-monthly interval)*

2.6.5 Toxicity / Safety

2.6.5.1 Toxicity population

The toxicity population is the subset of patients in the ITT analysis population who started protocol treatment. Any patients without at least 1 post-baseline AE form submitted will not be able to contribute; note any such patients in trial report.

2.6.5.2 Toxicity analysis

Targeted AEs, and other grade 3-5 AEs, are collected on CRFs. The grade and causality attribution are recorded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. In TEXT, chemotherapy-related AEs are collected separately.

The targeted AEs will be summarized by AE type and maximum grade over time, regardless of causality attribution. The maximum grade consolidates the reports of a given type of AE for a patient over time since randomization (i.e., baseline reports are excluded) by taking the maximum across time (i.e., a patient appears only once for a given type of AE). Patients with reports of multiple AEs of different types are reported multiple times under the relevant AE categories. Maximum grade 0 indicates that the AE type has not been reported.

Note, during a period of trial conduct, the IBCSG audit team was asking sites to record grade 3+ weight gain and obesity as other AEs; discussed among StatC/DMC/CC that CRFs record weight serially on E-form and any analysis of weight changes and/or obesity [in these or other IBCSG adjuvant trials] would use the actual weight, not the AE; as a result the audit team changed their practice. Therefore the weight change and obesity “other grade 3+” AEs will be deleted from dataset before summarizing other grade 3+ AEs because the incidence will not be interpretable.

Tables:

- Targeted AEs reported according to treatment group
- Targeted AEs reported according to cohort [focused on chemotherapy use (none, prior to randomization, after randomization)] and treatment assignment
- Tables above repeated for the subset of events deemed possibly, probably or definitely related to study treatment(s)

Other grade 3 or higher AEs are also requested on CRFs, by write-in text. All will be tabulated, similarly according to max grade, but the intention is to focus on those deemed possibly, probably or definitely related to study treatment(s), which will also be tabulated.

95% exact CIs will be calculated for each, according to treatment group.

2.6.6 Treatment

2.6.6.1 Protocol treatment

Data are from the internal Treatment Summary form; see SDMC Treatment Summary Form Guidelines for details of how data are recorded.

Protocol treatment status as of the clinical data cut-off will be summarized. In this report, status will be summarized overall and by treatment assignment, and also by trial and/or cohort. To describe adherence with protocol-assigned treatment, the variables to be calculated are:

- Duration of protocol-assigned T/E treatment from randomization to end (as treatment duration is defined as 5y from randomization)
    - Time to protocol-assigned T/E cessation, defined from randomization to cessation of assigned T/E, or censored at last follow-up on T/E;
    - Duration of time from from randomization to protocol-assigned T/E start;
    - Duration of protocol-assigned T/E treatment, from T/E start to T/E end (if ended).
- Duration of OFS
    - Time under medical or surgical/radiation-induced OFS, defined from starting point of randomization, and an event is cessation of GnRH analogue without additional surgical/radiation OFS; for patients who continue on GnRH analogue the time is censored at last follow-up; for patients who have surgical/radiation OFS the time is censored at last follow-up (i.e., because they remain under surgical/radiation-induced OFS).
    - Duration of time from randomization to start of OFS [in TEXT, this is start of GnRH analogue, whereas in SOFT it may be any method];
    - Duration of GnRH analogue, from start to stop (if stopped).

For adherence, time until cessation of protocol treatment(s) will be summarized by the cumulative incidence of cessation, with competing risk of a DFS event leading to cessation [unless treatment stopped earlier].

To summarize exposure to protocol-assigned treatment(s), time until cessation of protocol treatment(s) will be summarized as 1-KM estimate of cessation, where cessation regardless of reason, is a cessation event.

- Status of (protocol-assigned) T/E and OFS (See also SDMC TS Form completion Guidelines)

Protocol-assigned T/E	Notes
Never started	Never started protocol-assigned T/E; includes pt who has recurrence before opportunity to start T/E
Stopped early	Started, but stopped early within ~54m since rando [excludes those who stopped b/o DFS event)
Completed when DFS event occurred	Started and continued per protocol until death or at least suspicion of proven DFS event within 60m of rando (if event is > ~60m from rando then it counts as completed at 5y). Many pts continued until DFS event proven, and so cessation date usually coincides with date proven.

Completed 5y (T/E for ~5y from rando)	Took T/E until at least 54m since rando; but if CRF indicates RC or AE as reason then it remains as stopped early(above). If pt continues on to complete 5y total or to extended adjuvant, that is also completed.
Continuing	Not otherwise in categories above

OFS (if assigned)	Notes
Never started	SOFT: never received any OFS TEXT: never received any OFS*
Stopped GnRH early	Started, but stopped early within 54m of rando [excl. pts with stopped within 60m for death/RC] without further ooph/boi; see (?) below
Stop b/o DFS event	Started and continued GnRH per protocol until death or suspicion of proven DFS event; In case of local recur and some 2p, GnRH could continue beyond the DFS event, and those are *not* counted in this category
Completed (GnRH for ~5y from rando; or ooph/boi)	Took GnRH until at least 54m since rando; but if stopped within 60m and CRF indicates RC or AE as reason then it remains as stopped early(above). Had ooph/boi; but there are a few exceptions(?)
Continuing	Not otherwise in categories above

Notes re OFS:

*In TEXT, even though 6m of GnRH was required before opting for oopn/boi; in rare cases that pt does not have GnRH then #injections and duration of GnRH is 0, and pt is *not* considered as never started

*if pts got ooph/boi >3m after GnRH stop early, then this is considered as stopped early

*if pts got ooph/boi after RC proven then this is ignored (because we don't receive post-RC treatment information consistently) & reason will be stop GnRH b/o DFS event

A special case is local recurrence and some second malignancies (eg thyroid) where protocol treatment could continue; if protocol treatment continued beyond the DFS event then treatment is judged based on whether or not it continued until 5y from rando.

2.6.6.2 Non-protocol treatment

In future analyses when all patients are at least 5y from randomization, we will plan to describe:

- ET to complete 5 years (if protocol-assigned T/E is stopped early);
- [OFS question] Use of OFS among patients assigned tamoxifen-alone
- Concomitant bisphosphonates use
- Extended adjuvant ET use

2.6.6.3 Tables and Figures

Tables:

- Treatment status, overall and by treatment group and trial

Figures:

- Cumulative incidence of early treatment discontinuation, by treatment group; and secondarily by cohort and treatment group; with competing risk of DFS event that leads to treatment cessation.

Appendix

Table. Variables for the analysis *(working version, notes about variable definitions)*; there are other variables also to be kept in *patients* dataset that aren't listed here

Variable	CRF	Field	Formulas for derived variables
Trial	--	trial trial_lab	24; 25 1=TEXT; 2=SOFT
ITT population	--	--	
AI Question population	RA	--	TEXT both arms; SOFT arms B & C
OFS Question population	RA	--	SOFT arms A & B
Chemo strata	A(RA)		yes vs no Use A form value; otherwise RA value
Nodal status strata	A(RA)		0 vs 1+ Use A form value; otherwise RA value e.g, max(nposn,lymr24,lyml24) which accounts for different versions of form
Intended OFS strata	A(RA)	methoxp, rmox	SOFT: use A form value; otherwise RA
Age	RA	agegf	Agerand, calculated as integer; Grouped (<35,35-39,40-44,45-49,≥50)
Race	B	Race, Narace	derived as 'newrace' combining different questions from NA vs ROW
BMI	B	wt, ht	BMI=kg/m2; categorized: <25, 25-29.9,≥30
Age at menarche	B	agem	as recorded
Menstruation	B	menstr	as recorded
Hysterectomy	B	hyst	as recorded
History of Diabetes	B	diabe	as recorded
Previous Pregnancies (Ever, No. of preg)	B	epreg nopregp pregdx	as recorded
Performance status	B	perfr	as recorded
Family relative with Breast or ovarian ca	B	frel, male	as recorded
Actual Chemotherapy Received	SOFT H; TEXT CT	Ctp; cypl, cym, cnns, cnse	SOFT: derived variable from ctp (Q2) on H form; if no CRF, use A then RA TEXT: derived variable from CT form, variables 'cypl', 'cym', 'cnns', 'cnse'; if no CRF, use A then RA
Time from diagnosis to randomization	C; MP	pdxd, mprnd	(mprnd-pdxd) / 30.4375 (pdxd as adapted for bilateral pts)
Time from surgery to randomization	A; MP		(mprnd-surgdate) / 30.4375 surgdate as reported on A (or RA if missing) e.g., max(exsurgd,exr24d,exl24d)
Time from last dose of chemo	A(RA); MP	ctldp, mprnd	(mprnd-ctldp) / 30.4375 as reported on A (or RA if missing)
Local Treatment: Surg	C,A(RA)	type1-5, typeos	mx vs bcs; use C; otherwise A or RA
Local Treatment: RT actual	R,A(RA)	exrty, riort, mara, rtpoc	yes vs no vs unk note if not ongoing/planned (A) then no R-form required and these are no
Local Treatment			cross-group of surg and RT actual

Variable	CRF	Field	Formulas for derived variables
Local Treatment: LN	C	sndone axdxp	SNB y/n; AXLD y/n as recorded on C
No. metastatic axillary LN	P	axmt	Grouped (0,1-3,4+); also continuous
No. metastatic axillary and/or IM LNs	P	axmt,nimm	sum
No. axLN examined	P		as recorded
No. ax+IM LN examined	P		sum
Tumor size	P	diinv	continuous as recorded; grouped (cut at 1,2,5)
Tumor grade	P		Derived hierarchically (1,2,3): use BRE sum(tub,nuc,mitb); otherwise differentiation (well, mod, poor)
Tumor Laterality	B	prsidp	from B; otherwise A(or RA)
Tumor Location	B	primr, priml	from B
Histologic type	P	Hityd2	Primary histology, grouped as ductal, lobular, DCIS/LCIS, other
Local ER /PgR status	F	hprer, hprgr pce, pceo; ppcp, ppcpo	combine ER&PgR status vars; also tbd more continuous variable—local path reports too heterogeneous in reporting, wait for CPR before reporting continuous values
HER2 status	P	Her2f2, her2o2, her22 Her2t2	her2status derived, (pos, neg, unk); pos= amplified by FISH, or pos by ISH, or 3+ by IHC; if bilateral, then HER2+ if either side is HER2+
HER2-directed therapy (Trastuzumab) taken?	24-H TEXT:25-CT,CCM		trastuzumab (or lapatinib—very occasional) SOFT: H, Q5, rx after diagnosis; TEXT: CT Q4xyz other regimens, CCM
History chemoprevention	H	Q1 cptam--cpno	yes vs no; agent
Chemo history (SOFT)	24-H	Q4	Agent types: anthracyline y/n, taxane y/n, other Duration, 1e dichotomized at 12wks, also contin.
Prior ET history (SOFT)	24-H	Q5	prior tam/serm yes/no & duration prior AI yes/no & duration
Chemo concurr. (TEXT)	25-CT	Q4	s/a SOFT chemo history
Concur. bisphosphonate	CCM		ever use; duration (may be ongoing)
Protocol rx	TS; T/E,OFS		T/E: use/status, duration, reason stop OFS: use/status, duration GnRH; reason stop
Non-prototocol rx	TS; T/E,OFS, CCM, GYN		SERM/AI: use, duration OFS: use, duration
Baseline AEs	AE	–	To use baseline AE (fmno=1) keep grades + trt(y/n) variables; from others: hx of gr3 headache/migraine, carpal tunnel
Post-baseline AEs	AE		Targeted AEs; max grade over time
Site of first failure		fst_fail	IBCSG standard definition
Censoring date for time-to-event (other than OS)		censordate	last follow-up which is surv status date on MP (see SOP, E-form date except occasionally DOD from DM review); if WC/LFU then censor at WC/LFU date
Notes re TTE endpoints			All are in days; months = days / 30.4375 years = days / 365.25

Variable	CRF	Field	Formulas for derived variables
DFS		dfs_mos; dfs_ind	(DFS event date – rando date [mprnd]+1) Event date: date first suspected from RC form; death date for DWR;
BCFI		bcfi_mos; bcfi_ind	(event date - rando date + 1), where event date is date a proven local, regional, distant BC recurrence or contra BC is first suspected
DRFI		drfi_mos; drfi_ind	(event date – rando date + 1), where event is date a proven distant recurrence first suspected
OS		os_mos; os_ind	(Date death – rando date + 1) Censoring date: date last known alive [surv status date on MP]; for some WC/LFU the censoring date is WC/LFU date but others have continued survival updates
Safety population			All patients who started any protocol treatment.
Consent CPR		PMC	
Consent future research		PMC	
Co-SOFT population			yes/no (n=86)
SOFT-EST substudy			yes/no (n=123)
QL population		<Weixiu>	yes/no
TEXT TR population (consent for TEXT-TR)		TR-1,TR-2	yes/no
TEXT TR consent for future research		TR-1,TR-2	yes/no