INTERNATIONAL BREAST CANCER STUDY GROUP IBCSG 41-13

TREND

(TRial on the **E**ndocrine activity of **N**eoadjuvant **D**egarelix**)**

A randomized phase II trial evaluating the endocrine activity and efficacy of neoadjuvant degarelix versus triptorelin in premenopausal patients receiving letrozole for primary endocrine responsive breast cancer

EudraCT number:	**2012-005326-29**
NCT Number:	**NCT02005887**
Sponsor:	**International Breast Cancer Study Group (IBCSG)**

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Protocol Signature Page

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TREND

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Date

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Anita Hiltbrunner

_____ _____

Date

Principal Investigator Protocol Signature Page

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I have read the protocol and agree that it contains all necessary details for conducting this trial. I will conduct the trial 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 trial. I will discuss this material with them to assure that they are fully informed** regarding the drugs and the conduct of the trial. 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 trial for a minimum period of 15 years.

Name of Principal Investigator:_____

_____ _____

Signature Date

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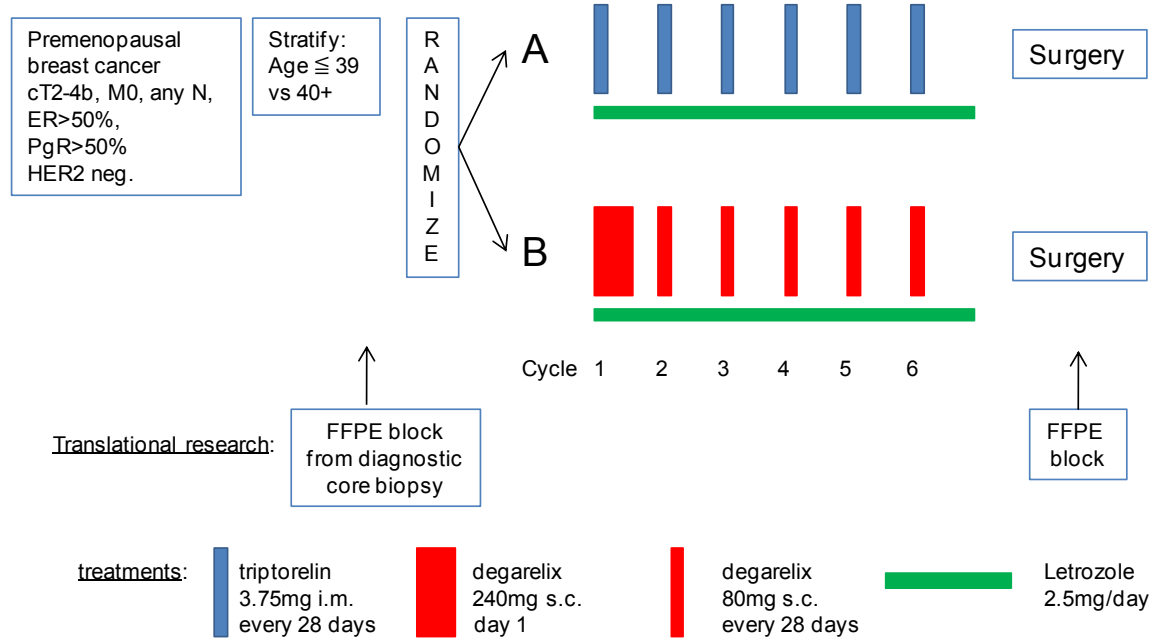
Appendices

1. Protocol Summary and Schema

TITLE	A randomized phase II trial evaluating the endocrine activity and efficacy of neoadjuvant degarelix versus triptorelin in premenopausal patients receiving letrozole for primary endocrine responsive breast cancer (**TREND**)
SPONSOR	International Breast Cancer Study Group (IBCSG)
PHARMA PARTNER	Ferring
INDICATION	Primary breast cancer
CLINICAL PHASE	Phase II
POPULATION	Premenopausal patients with histologically confirmed primary breast cancer and with primary tumor which is ER+ and PgR+ (>50%) and HER2-negative or not amplified
TREATMENT	Patients will be randomized to one of two treatment arms. Cycles last 28 days: **Arm A:** Triptorelin 3.75 mg i.m. on day 1 of every cycle + letrozole 2.5 mg/day orally for 6 cycles **Arm B:** Degarelix 240 mg s.c. given as two subcutaneous injections of 120 mg on day 1 of cycle 1, followed by 80 mg s.c. on day 1 of cycles 2 to 6 + letrozole 2.5 mg/day orally for 6 cycles Arms A and B: Letrozole 2.5 mg/day orally should be started on day 1, concurrently with triptorelin or degarelix.

STUDY SCHEMA



RATIONALE

Preoperative chemotherapy enables breast-conserving surgery for some patients with breast cancer, and it might be advantageous in several other ways. For example, the response to primary treatment may be used as a prognostic marker, since it has been demonstrated to be associated with a longer disease-free survival (DFS) compared with no response. In particular the degree of response (pathological complete remission (pCR)) predicts overall outcome in terms of DFS.

However, pCR can be achieved only in a minority of patients with estrogen receptor (ER)-positive disease. Studies in the medical literature indicate that pCR rates range from 2% to 10% in those patients whose tumors express ER suggesting that objective response and decrease of Ki67 must be considered within this subset of tumors.

The results of phase II studies and randomized phase III trials have clearly shown that preoperative endocrine therapy is a feasible and safe option among patients with hormone-receptor positive tumors. Letrozole has been shown to induce greater rates of clinical responses and of breast-conserving surgery in postmenopausal women as compared with tamoxifen.

In premenopausal women with ER and PgR positive breast cancer, the preoperative endocrine therapy includes a combination of a gonadotropin-releasing hormone analogue (GnRH) plus tamoxifen. Recent studies suggest that neoadjuvant endocrine therapy with a combination of GnRH analogue and aromatase inhibitors (AIs: letrozole or anastrozole) is effective in selected premenopausal patients. The GnRH analogue, also known as a luteinizing hormone-releasing hormone agonist (LHRH agonist) or LHRH analogue, is a synthetic peptide drug modeled after the human hypothalamic gonadotropin-releasing hormone (GnRH). A GnRH analogue is designed to interact

	with the GnRH receptor and modify the release of pituitary gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) for therapeutic purposes. Upon administration of a GnRH analogue, an initial stimulating action of the hypophysis occurs – termed a "flare" effect – which eventually causes a paradoxical and sustained drop in gonadotropin secretion. This second effect has been termed "downregulation" and can be observed after about 10 days. While this phase is reversible following cessation of medication, it can be maintained when GnRH agonists' use is continued for a long time. For a select group of patients, there is a delay of approximately 2-4 months before downregulation of the gonadotropins is observed. Degarelix (INN) or degarelix acetate (USAN) (tradename: Firmagon) is a hormonal therapy approved for the treatment of prostate cancer. Since testosterone, a male hormone, promotes the growth of many prostate tumors, reduction of circulating testosterone to very low (castration) levels is often the treatment goal in the management of advanced prostate cancer. Degarelix, an antagonist of GnRH, has immediate onset of action through binding to GnRH receptors in the pituitary gland and blocking their interaction with GnRH. The result is a fast and profound reduction in LH, FSH and in turn, testosterone suppression. Its activity in suppressing the ovaries of premenopausal women might therefore be faster than other GnRH analogues, possibly by several weeks. The probable difference in onset of action could have significant clinical value for patients who are candidates for short-term neoadjuvant endocrine treatment.
ELIGIBILITY	**<u>Inclusion criteria:</u>** • Female gender • Premenopausal status determined locally: Estradiol (E2) must be above 54 pg/mL (or above 198 pmol/L), measured within 14 days prior to randomization. • Age ≥ 18 years • Performance Status – Eastern Cooperative Oncology Group (ECOG) 0-1 • Histologically confirmed invasive breast cancer: - Primary tumor greater than 2 cm diameter, measured by clinical examination and mammography or echography (cT2-4b) - Any nodal stage - No evidence of metastasis (M0) • Primary tumor must have ER and PgR >50% of the cells • Primary tumor must be HER2-negative (by IHC and/or ISH) • Hematopoietic status: - Absolute neutrophil count ≥ 1.5×10^9/L - Platelet count ≥ 100×10^9/L - Hemoglobin ≥ 9 g/dL • Hepatic status: - Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN). In the case of known Gilbert's syndrome, a higher serum total

bilirubin (< 2 × ULN) is allowed.
  - AST and ALT ≤ 2.5 × ULN
  - Alkaline phosphatase ≤ 2.5 × ULN
- Renal status: Creatinine ≤ 1.5 ×ULN
- Negative serum pregnancy test, within 2 weeks (preferably 7 days) prior to randomization. Pregnancy test has to be repeated before treatment start if treatment does not start within 15 days of the previous test.
- The patient must be willing to use effective non-hormonal contraception (barrier method – condoms, diaphragm – also in conjunction with spermicidal jelly, or total abstinence) after the pregnancy test and up to surgery. Oral, injectable, or implant hormonal contraceptives or medicated IUD are not allowed within 2 months prior to randomization and during the trial.
- Prior fertility treatment is allowed but must have been stopped at least 12 months before randomization.
- The patient has completed the baseline patient-reported symptoms questionnaire.
- Written Informed Consent (IC) must be signed and dated by the patient and the Investigator prior to randomization.
- The patient has been informed of and agrees to data transfer and handling, in accordance with national data protection guidelines.
- The patient accepts blood samples to be taken according to the schedule in section 17.4 for the determination of the primary endpoint.
- The patient agrees to make tumor (diagnostic core biopsy and surgical specimen) available for submission for central pathology review and to conduct translational studies as part of this protocol.

  NOTE: Central Pathology Review on the primary tumor is mandatory for this trial, but patients will evaluated for eligibility according to tumor characteristics as determined by the local Pathologist. Both the diagnostic breast core biopsy specimen and the final breast surgical specimen must be submitted for Central Pathology Review.

Exclusion criteria:

- Postmenopausal
- Any hormonal treatment (e.g., oral, injectable, implant, or medicated IUD) in the previous 2 months
- Presence of HER2 overexpression or amplification
- Received any prior treatment for primary invasive breast cancer
- Received any GnRH analog or SERM or AI within 12 months prior to randomization
- A history of malignant neoplasms within the past 10 years, except for curatively treated
  - Basal and squamous cell carcinoma of the skin
  - Carcinoma in situ of the cervix
  - Carcinoma in situ of the bladder

	• Previous ipsilateral breast cancer (invasive or in situ) at any time • Inflammatory breast cancer • Bilateral invasive breast cancer • Known history of uncontrolled or symptomatic angina, clinically significant arrhythmias, congestive heart failure, transmural myocardial infarction, uncontrolled hypertension (≥ 180/110), unstable diabetes mellitus, dyspnea at rest, or chronic therapy with oxygen • Concurrent disease or condition that would make the subject inappropriate for study participation or any serious medical disorder that would interfere with the subject's safety • Unresolved or unstable, serious adverse events from prior administration of another investigational drug • Active or uncontrolled infection CTCAE v.4 grade 2 or higher • Dementia, altered mental status, or any psychiatric condition that would prevent the understanding or rendering of Informed Consent • Treatment with an investigational agent must have stopped at least 30 days before randomization. • Pregnant or lactating women; lactation has to stop before randomization.
STUDY OBJECTIVES AND ENDPOINTS	**<u>Primary objective</u>** The primary objective is to compare the endocrine activity of neoadjuvant degarelix and triptorelin in premenopausal patients receiving letrozole for primary endocrine responsive breast cancer. The endocrine activity is measured by time to optimal ovarian function suppression. **Primary endpoint:** Time to optimal ovarian function suppression: time from the first injection of degarelix or triptorelin to the first assessment of centrally assessed 17-β-estradiol (E2) level in the range of optimal ovarian function suppression (≤2.72 pg/mL or ≤10 pmol/L) during the 6 cycles of neoadjuvant treatments. Time for patients who do not reach the targeted E2 level will be censored at the last E2 assessment date. **Secondary endpoints:** • Tolerability: adverse events according to CTCAE version 4 • Ki67 proliferation marker changes • The Preoperative Endocrine Prognostic Index (PEPI) score determined after completion of neoadjuvant therapy or at the time of surgery • Best overall (disease) response: defined as best response recorded from the start of treatment across all time points until disease progression. Confirmation of partial or complete response by an additional scan is not required in this trial. Best overall response will be determined by a team consisting of the study chair, co-chair and IBCSG Head of Medical Affairs.

	Tumor assessment will use WHO response criteria. • Node-negative disease at surgery • Breast-conserving surgery (BCS) rate • Patient-reported symptoms (PRS) outcomes
TRANSLA-TIONAL RESEARCH	A tumor block from the diagnostic core biopsy and one from final surgery will be collected and banked for central review and future translational research at the IBCSG Tissue Bank hosted by the European Institute of Oncology in Milan, Italy (Prof. G. Viale).
PATIENT-REPORTED SYMPTOMS	The patient-reported symptoms (PRS) will be assessed using the Functional Assessment of Cancer Therapy Endocrine Subscale (FACT-ES) comprising 18 items (each has score range from 0 to 4) with a possible maximum total score of 72. Functional Assessment of Chronic Illness Therapy (FACIT) guidelines will be used for scoring and interpretation of the FACT-ES total score. Patients will be asked to complete a PRS Form at *baseline* (prior to randomization), at *day 1 of cycle 2*, at *day 1 of cycle 4*, and *prior to surgery*. The objectives are: • To assess the differences in PRS score over time between the two treatment arms • To correlate the estradiol (E2) levels and total PRS score measured on day 1 of cycle 2 and day 1 of cycle 4 of triptorelin or degarelix administration • To summarize each of the 18 individual (endocrine symptom) items of the FACT-ES descriptively over time as the proportion of patients with "clinically significant" symptoms (those scoring 3 or 4)
STRATIFI-CATION	Stratification will be performed according to: • Age (in years): less than or equal to 39 versus 40 or more
STATISTICAL CONSIDE-RATIONS	To achieve the primary objective, E2 levels will be determined centrally from samples taken at day 1 of the first treatment cycle before the administration of the first dose of degarelix or triptorelin (baseline), and thereafter at 24 and 72 hours, 7 days and 14 days after the first injection, and on day 1 of cycles 2 to 6 before the administration of degarelix or triptorelin. For sample size calculation, we assume that the cumulative percentages of patients in the triptorelin arm achieving optimal ovarian function suppression (defined as E2 ≤2.72 pg/mL or ≤10 pmol/L) will be 30% within 2 weeks, 60% within 4 weeks and 75% within 8 weeks, and that degarelix will provide more rapid suppression (i.e., 60% within 2 weeks, 95% within 4 weeks and 100% within 8 weeks). Enrollment of 25 patients in each treatment arm will provide at least 90% power to detect a difference in time to optimal ovarian function suppression between the two groups, using a two sample log-rank test with a two-sided significance level of 0.05.

	Randomized patients who receive at least one injection of triptorelin or degarelix will be included in the primary analysis. The primary endpoint will be compared between the two treatment arms using a stratified two-sample log-rank test, with age as stratification factor. The distribution of the primary endpoint will be summarized using the method of Kaplan-Meier and the two-sided 95% confidence interval (CI) for the difference in proportion of patients who achieve optimal ovarian function suppression between the two treatment arms at the end of the 1st, 2nd and 4th cycle will also be provided. The toxicity, changes in Ki67 expression levels, the Preoperative Endocrine Prognostic Index (PEPI) score at the time of surgery, disease response, node-negative disease status at surgery and breast-conserving surgery (BCS) rate will also be summarized and differences assessed between treatment arms with confidence intervals. The primary endpoint for patient-reported symptoms (PRS) analysis is the total PRS score measured at baseline, day 1 of cycle 2 and day 1 of cycle 4 of triptorelin or degarelix administration, and prior to surgery. The differences in PRS measurements between the two treatment arms over time will be explored using the repeated measures analysis based on generalized estimating equation (GEE) model.
NUMBER OF PATIENTS	50 patients will be enrolled: (Arm A: 25; Arm B: 25)
DURATION OF TRIAL	Recruitment will last approximately 24 months with an additional 7 months follow up after the last patient is enrolled. The end of the trial will be approximately 31 months after randomization of the first patient.

2. Trial schedule

	≤14 days prior to rando	Day 1 of every 28 days cycle						Prior to surgery	30 days after surgery
Cycle		**1**	**2**	**3**	**4**	**5**	**6**		
Informed consent	x								
History	x								
Physical examination, ECOG PS	x	x	x	x	x	x	x	x	
Serum pregnancy test[1]	x								
Baseline symptoms	x								
Adverse events		x	x	x	x	x	x	x	x
Concomitant medications	……continuously……								
Tumor evaluation (clinical)	x	x	x	x	x	x	x	x	
PRS	x		x		x			x	
Neoadjuvant Treatment									
GnRH agonist[2] (arm A) or GnRH antagonist[3] (arm B)		x	x	x	x	x	x		
Letrozole[4]		....…….continuously……..							
Laboratory tests									
Hematology[5]	x				x			x	
Blood chemistry[6]	x				x			x	
CEA and Ca 15.3[7]	x				x			x	
Estradiol[8]	x	x	x	x	x	x	x	x	
Tumor Evaluation									
Mammography[9]	x				x			x	
Breast Ultrasound[9]	x				x			x	
Chest x-ray[10]	x								
Abdominal US or CT[11]	√								
Bone scan[12]	√								
Other tests									
ECG	√								
Echocardiography	√								
Pathology eval (local)	x								x
Biological samples									
FFPE sample[13]	x								x
Serum sample[14]	x	x[14]	x	x	x	x	x		

x = mandatory √ = if medically indicated

Legend for trial schedule:

1. Pregnancy test has to be repeated before treatment start, if treatment does not start within 15 days of the previous test.

Neoadjuvant treatment: 6 cycles of 28 days each

2. Triptorelin 3.75 mg i.m. on day 1 of every cycle
3. Degarelix, Firmagon®
   - Day 1 of cycle 1: 240 mg s.c. given as two subcutaneous injections of 120 mg
   - Day 1 of cycles 2-6: 80 mg s.c.
4. Letrozole 2.5 mg/day orally, continuously for 6 cycles

Laboratory tests

5. Hematology (Hemoglobin, platelet count, white blood cell count including differential (absolute neutrophil count)) must be done within 14 days prior to randomization, before the start of cycle 4 treatment and at the visit prior to surgery.
6. Blood chemistry (blood urea nitrogen, creatinine, alkaline phosphatase, AST and ALT, total bilirubin, calcium, urea, total cholesterol, LDL and HDL cholesterol, tryglycerides) must be done within 14 days prior to randomization, before the start of cycle 4 treatment and at the visit prior to surgery.
7. CEA and CA 15.3 must be done within 14 days prior to randomization, beginning of cycle 4 and at the visit prior to surgery.
8. 17-β-estradiol (E2) must be done within 14 days prior to rando, at baseline (day 1 of cycle 1, before treatment start), and then at the start of cycles 2 to 6, prior to injection of GnRH agonist or GnRH antagonist, and before surgery. Menopausal status will be assessed by the Investigator according to local laboratory estradiol level for menopausal status. Refer to section 9.2 for criteria for stopping neoadjuvant treatment in case of insufficient ovarian function suppression.

   NOTE: For the trial primary endpoint, estradiol levels will be assessed centrally, see note 14 below.

Tumor evaluation

9. A bilateral mammography, breast ultrasound and caliper measurement must be done prior to randomization, after 3 cycles of treatment (denoted as day 1 of cycle 4 in the schedule) and prior to surgery.

Other procedures

10. A chest X-ray is not required in patients who have undergone a PET scan.
11. Abdominal ultrasound or CT scan is required if alkaline phosphatase or AST is >2.5×ULN; not required in patients who have undergone a PET scan.
12. Bone scan is required if alkaline phosphatase is >2.5×ULN or if the patient has unexplained bone pain; not required in patients who have undergone a PET scan.

Biological studies

13. Two formalin-fixed, paraffin-embedded (FFPE) tumor blocks, one from the diagnostic core biopsy and one from the surgical specimen must be submitted for central pathology review and stored in the IBCSG Tissue Bank for future translational research studies.
14. For determination of FSH, LH, E2 by a central laboratory, serum samples must be taken and stored at -80°C at day 1 of treatment **before the administration of the first dose**, thereafter at 24 and 72 hours, 7 days and 14 days after first injection, and on day 1 of cycles 2 to 6 **before the administration of the next dose of the GnRH agonist or antagonist.**

3. Introduction

3.1. The role of primary systemic therapy in breast cancer

Primary systemic therapy (PST) for operable breast cancer has been evaluated in a number of trials (1,2). So far the only demonstrated benefit related to treatment effect is sufficient tumor shrinkage to enable breast-conserving surgery, although the theoretical likelihood of decreasing the spreading of micrometastasis after surgical resection and minimizing the potential drug resistance have been hypothesized. The response to the primary treatment may be used as a prognostic marker, since it was demonstrated to be associated with a longer DFS compared with no response (3,4). The effect of treatment on the clinical and biological characteristics of the tumor may represent an objective assessment of its responsiveness, thus allowing any further treatment to be tailored according to the results observed. Moreover, the achievement of pathological complete remission (pCR) can predict overall outcome in terms of disease free survival (DFS) and overall survival (OS) (4).

3.2. Primary endocrine therapy in postmenopausal breast cancer patients

Preoperative treatment of endocrine responsive tumors represents a challenge for medical oncologists. Although chemotherapy is able to induce a high number of objective responses, the chance of obtaining a pCR is from 2 to 7-fold lower than in hormone receptor negative tumors and usually ranges from 6% to 14% (5,6,7). It is reasonable to speculate that these tumors might benefit from an endocrine treatment.

Endocrine therapy has been historically limited to patients who were not suitable for chemotherapy and surgery. Earlier phase II studies with tamoxifen focused primarily on elderly and/or frail patients, often unselected for hormone receptor status of the tumor and showed a response rate ranging from 49% to 68% (8). The proven superiority of third-generation aromatase inhibitors in the advanced disease stimulated the investigation of these agents in the preoperative (neoadjuvant) setting among post-menopausal women with hormone receptor positive tumors (9). Initially, phase II studies showed a response rate up to 80% for letrozole and prompted comparison studies of aromatase inhibitors with tamoxifen (8).

In a phase III study including 330 postmenopausal women, letrozole was shown to increase the response rate (55% vs 36% p<.001) and the breast-conserving surgery rate (45% vs 35%, p=.022) as compared with tamoxifen (10). Interestingly, subgroup analyses showed that patients with HER1 and/or HER2 overexpressing tumors benefited from letrozole (RR= 88% vs 21%), while in tumors not overexpressing HER1 and/or HER2, response rate was similar between the two treatments (54% vs 42%) (11).

The second randomized trial, the IMPACT trial, comparing anastrozole vs tamoxifen vs the combination of the two agents, failed to show any difference regarding response rate among treatments (37% vs 36% vs 39%), although patients receiving anastrozole were significantly more likely to undergo breast-conserving surgery (46% vs 22% vs 26% with anastrozole, tamoxifen, and combination therapy, respectively). In this study, again, patients with HER2 overexpressing tumors presented a higher response rate with the aromatase inhibitor when compared with tamoxifen although the difference was not statistically significant (58% vs 22% vs 31% with anastrozole, tamoxifen, and combination therapy, respectively) (12).

In a third trial, the PROACT trial, anastrozole and tamoxifen yielded a similar response rate. In the subgroup of patients who did not receive concurrent chemotherapy, anastrozole produced a higher response rate (36.2% vs 26.5% p=.09) (13).

The aromatase inhibitor exemestane has been compared with tamoxifen in a randomized study including 151 postmenopausal women with ER and/or PgR-positive breast cancer (15). The aromatase inhibitor significantly increased the clinical response rate (76% vs 40% p=.05) and the rate of breast-conserving surgery (36.8% vs 20% p=.05) (14).

Endocrine therapy with aromatase inhibitors has been compared with four courses of doxorubicin and paclitaxel in a randomized study including 121 postmenopausal patients with ER-positive breast cancer. The preliminary results showed that four courses of chemotherapy yielded comparable response rate and pCR rate if compared with exemestane and anastrozole (15).

Conflicting results have been reported in the literature on the value of factors predictive of response in the neoadjuvant setting in particular in the subset of patients with ER-positive tumors.

The presence of elevated Ki67 before neoadjuvant therapy has been found to predict response to chemotherapy in locally advanced breast cancer. In particular higher Ki67 levels after preoperative chemotherapy significantly and independently correlate with poorer DFS (16,17).

Recent results indicate that Ki67 might represent a valid surrogate of outcome in patients with ER-positive breast cancer treated with neoadjuvant endocrine therapy. In fact tumor Ki67 levels determined during neoadjuvant endocrine treatment were found to be a marker of treatment efficacy and to have significant prognostic value.

Moreover, Ki67 data have been integrated into a post-treatment model (PEPI score) which also includes pathologic stage and ER levels. The model was found to be useful in identifying subsets of patients for whom adjuvant treatment without chemotherapy could be considered after a neoadjuvant endocrine treatment. In particular, in the IMPACT trial no relapses were recorded among patients with small node-negative tumors and a PEPI score of 0 (residual tumor with low Ki67 index and with maintained ER expression) (18).

The PEPI score (19) is based on a post neoadjuvant treatment model that integrates central pathology review (CPR) results of pathological features and biomarkers (tumor size, node status, Ki67 expression level and ER status by Allred score). The risk points associated with recurrence free survival (RFS) will be used in this trial to calculate the PEPI Score (see table below).

		RFS	
Pathology, biomarker status		HR	Points
Tumor size:			
T1/2			0
T3/4		2.8	3
Nodal status			
Negative			0
Positive		3.2	3
Ki67 level			
0 – 2.7%	(0 – 1 [a])		0
>2.7 – 7.3%	(1 – 2 [a])	1.3	1
>7.3 – 19.7%	(2 – 3 [a])	1.7	1
>19.7 – 53.1%	(3 – 4 [a])	2.2	2
>53.1%	(>4 [a])	2.9	3
ER status, Allred score			
0 – 2		2.8	3
3 – 8			0

[a]The natural logarithm interval corresponding to the per cent Ki67 values on the original percentage scale.

In the adjuvant setting, a body of evidence also suggests that the level of both ER and PgR may play a crucial role in predicting response to treatment. In a study of the Edinburgh group, 83 postmenopausal women were treated with neoadjuvant letrozole for 3 months. Tumors were subdivided according to their ER Allred scores and of these, 60 tumors were scored 8 while 23 were scored as Allred 6 or 7. Although response rates were similar in both groups, a significantly greater reduction in tumor volume was observed in patients whose tumors had the highest ER levels (20).

3.3. Primary endocrine therapy in premenopausal breast cancer patients

Limited data are available on neoadjuvant treatments administered in premenopausal patients. In a study focused on 13 premenopausal women with endocrine responsive disease, neoadjuvant therapy with a gonadotropin-releasing hormone (GnRH) analogue induced a 54% rate of clinical response after 3 months of treatment (21). Torrisi et al. analyzed the efficacy of letrozole in combination with GnRH analogues and revealed among its 32 evaluable patients a median duration of therapy of 5.2 months for letrozole. A single patient (3%) obtained a complete clinical response, which was confirmed as by pCR upon pathological examination, whereas 15 patients (47%) obtained a partial response that produced an overall response rate of 50%; no patients progressed during treatment (22).

The STAGE study randomized 204 premenopausal women with ER-positive, HER2-negative breast cancer to receive goserelin 3·6 mg/month plus either anastrozole and tamoxifen placebo or tamoxifen and anastrozole placebo for 24 weeks before surgery. More patients in the anastrozole group had a complete or partial response than did those in the tamoxifen group during the 24 weeks of neoadjuvant treatment (70.4% vs. 50.5%, respectively) (23).

3.4. GnRH agonist and GnRH antagonist

3.4.1. GnRH agonist

GnRH or LHRH (luteinizing hormone-releasing hormone agonist) analogues or agonists are synthetic peptide drugs modeled after the human hypothalamic gonadotropin-releasing hormone (GnRH). GnRH agonists are designed to interact with the GnRH receptor and modify the release of pituitary gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), for therapeutic purposes. Upon administration of GnRH agonists an initial stimulating action of the hypophysis occurs – termed a «flare» effect - which eventually causes a paradoxical and sustained drop in gonadotropin secretion. This second effect was termed «downregulation» and can be observed after about 10 days. While this phase is reversible upon stopping the medication, it can be maintained when GnRH agonist use is continued for a prolonged period of time. For some patients, there can be a delay of approximately 2-4 months until downregulation of the gonadotropins occurs.

3.4.2. GnRH agonist and antagonist in prostate cancer

Degarelix (tradename: Firmagon), a new GnRH receptor blocker (antagonist), was developed as a novel therapy for patients with prostate cancer. Degarelix binds to and blocks the GnRH receptors in the anterior pituitary gland, resulting in decreased secretion of both LH and FSH. This leads directly to a rapid decrease in the production of testosterone. Testosterone suppression to castration levels (≤0.5 ng/mL) (24) is achieved within 1–3 days of administration.

In two phase II dose-finding clinical trials, a starting dose of 240 mg degarelix and maintenance doses of 160 mg or 80 mg were shown to effectively suppress testosterone levels in patients with prostate cancer, with no evidence of testosterone surge or inducement of clinical flare (25,26).

In a dose-finding study CS07, patients were allocated to one of eight single doses. These were: 120 mg (40 mg/mL); 120 mg (20 mg/mL); 160 mg (40 mg/mL); 200 mg (40 mg/mL); 200 mg (60 mg/mL); 240 mg (40 mg/mL); 240 mg (60 mg/mL); and 320 (60 mg/mL). The single 240 mg (40 mg/mL) dose was identical to the starting dose being proposed for registration. Based on the results for the primary and secondary endpoints relating to serum testosterone suppression, doses of 200 mg (40 mg/mL) and 240 mg (40 mg/mL) were the most efficacious as measured by response rates ≥ 95%. The study provides supportive evidence for the efficacy of the proposed initial dose of 240 mg (40 mg/mL) (27).

A pivotal study compared the efficacy and safety of two s.c. degarelix treatment regimens and an i.m. leuprolide (L) 7.5 mg treatment regimen administered every 28 days for up to 12 months in patients with prostate cancer. The two degarelix regimens were both initiated with a dose of 240 mg (40 mg/mL) followed 28 days later by a maintenance dose of either 160 mg (40 mg/mL) or 80 mg (20 mg/mL) repeated every 28 days. The results for the primary analysis showed that both D240/160 and D240/80 treatment regimens were effective in suppressing testosterone from Day 28 to Day 364. The results also showed that both D240/160 and D240/80 treatment regimens were non-inferior to L7.5 in suppressing testosterone from Day 28 to Day 364 (28).

A phase III study was conducted to compare the efficacy of monthly administrations of the luteinizing hormone releasing hormone agonists triptorelin and leuprolide to induce and maintain castrate levels of serum testosterone in men with advanced prostate cancer. Men with advanced prostate cancer were randomly assigned to receive triptorelin 3.75 mg or leuprolide 7.5 mg. In all, 284 men received either triptorelin (140) or leuprolide (144). The percentage of men with castrate levels of serum testosterone was lower at 29 days for triptorelin than for leuprolide (91.2% vs 99.3%; point estimate - 8.0, 95% confidence interval - 16.9% to - 1.4%), but equivalent at 57 days (97.7% vs 97.1%). The mean (98.8% vs 97.3%) and cumulative (96.2% vs 91.2%) castration maintenance rates between 29 and 253 days were equivalent between the treatment groups (29).

3.4.3. GnRH agonist and antagonist in breast cancer

Triptorelin administered at a dose of 3.75 mg was shown to induce strong estradiol suppression among premenopausal patients with breast cancer (30). Moreover, letrozole in combination with triptorelin at the dose of 3.75 mg q 28 days induces a more intense estrogen suppression than tamoxifen + triptorelin in premenopausal patients with early breast cancer. Prospectively collected hormonal data were available in a study that included 81 premenopausal women, of whom 30 were assigned to receive tamoxifen + triptorelin whereas 51 were assigned letrozole + triptorelin +/- zoledronate with a median age of 44 years for both groups of patients. Letrozole + triptorelin (+/- zoledronate) induced stronger suppression of median E2 serum levels ($P = .0008$), LH levels ($P = .0005$), and cortisol serum levels ($P < .0001$) compared with tamoxifen + triptorelin (31).

It therefore seems reasonable to compare the GnRH agonist triptorelin at the dose of 3.75 mg every 28 days with the GnRH antagonist degarelix at the initial dose of 240 mg s.c., followed by 80 mg s.c. on day 1 of subsequent 28 day cycles.

3.5. Plasma estradiol levels during endocrine therapy with AI

The guidelines of Smith et al. for the use of adjuvant AIs after chemotherapy-induced amenorrhea (32) recommend caution in the situation where estradiol levels determined by highly sensitive/specific methods such as GC-MS/MS are >10 pmol/L (>2.72 pg/mL) while on an AI, because this indicates that the AI is not exerting its full effectiveness. Thus optimal suppression will be defined as E2 levels ≤2.72 pg/mL or ≤10 pmol/L.

3.6. Rationale of the trial

Despite the advances achieved with primary therapy, novel treatment approaches are still necessary to increase disease control. Neoadjuvant endocrine therapy with a combination of GnRH agonist and AIs is effective for a select group of premenopausal patients.

Degarelix induces a fast and profound reduction in LH, FSH and in turn, testosterone suppression. Its activity in suppressing ovarian function of premenopausal women might therefore be faster than that of the GnRH agonists, and for some patients this might mean shortening time to ovarian suppression by several weeks. A difference in onset of action might have significant clinical value in patients who are candidates for short-term neoadjuvant endocrine treatment.

4. Trial objectives and endpoints

The primary objective is to compare the endocrine activity of neoadjuvant degarelix and triptorelin in premenopausal patients receiving letrozole for primary endocrine responsive breast cancer. The endocrine activity is measured by time to optimal ovarian function suppression.

4.1. Primary endpoint

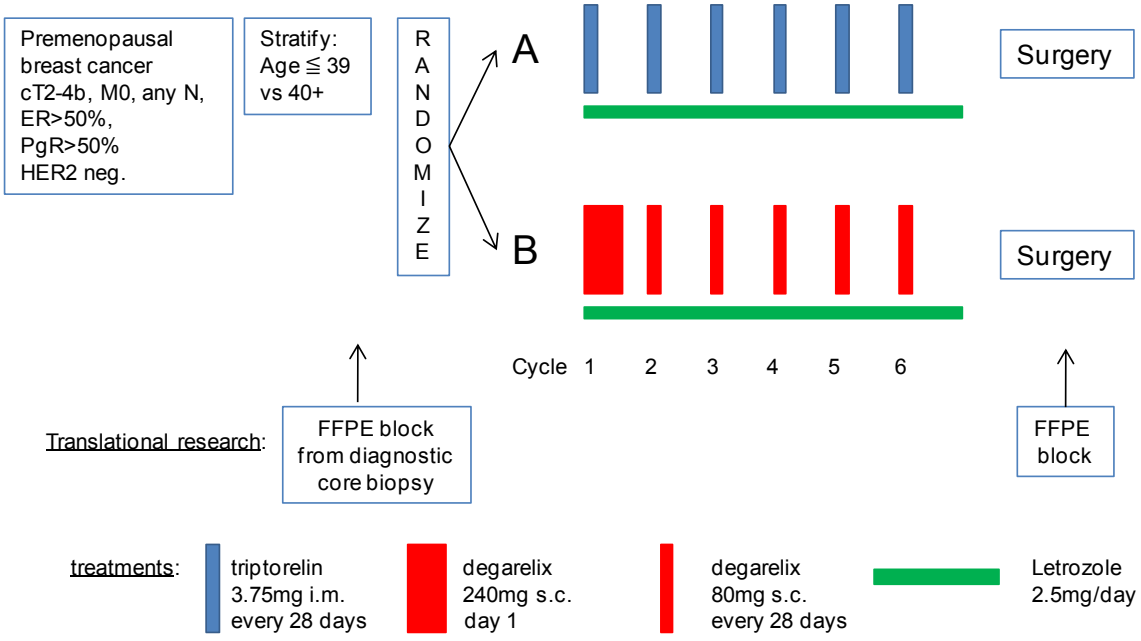
Time to optimal ovarian function suppression: time from the first injection of degarelix or triptorelin to the first assessment of centrally assessed 17-β-estradiol (E2) level in the range of optimal ovarian function suppression (≤2.72 pg/mL or ≤10 pmol/L) during the 6 cycles of neoadjuvant treatments. Time for patients who do not reach the targeted E2 level will be censored at the last E2 assessment date.

4.2. Secondary endpoints

- Tolerability: adverse events according to CTCAE version 4
- Ki67 proliferation marker changes
- The Preoperative Endocrine Prognostic Index (PEPI) score determined after completion of neoadjuvant therapy or at the time of surgery
- Best overall (disease) response: defined as best response recorded from the start of treatment across all time points until disease progression. Confirmation of partial or complete response by an additional scan is not required in this trial. Best overall response will be determined by a team consisting of the study chair, co-chair and IBCSG Head of Medical Affairs. Tumor assessment will use WHO response criteria.
- Node-negative disease at surgery
- Breast-conserving surgery (BCS) rate
- Patient-reported symptoms (PRS) outcomes (see Section 16.5)

5. Trial design, duration and termination

5.1. Trial schema



Randomization allocation 1:1 to one of the two arms

5.2. Sample size and trial duration

- Neoadjuvant endocrine therapy of letrozole with either degarelix or triptorelin in 28 days cycle for a total of 6 cycles.
- Total of 50 patients (Arm A: 25 and Arm B: 25) will be enrolled.
- Estradiol (E2) levels will be determined centrally from samples taken at day 1 of first treatment cycle before the administration of the first dose (baseline), thereafter at 24 and 72 hours, 7 days and 14 days after first injection, and on day 1 of cycles 2 to 6.
- Tumor evaluation will be at baseline (within 14 days prior to randomization) and at the end of 3rd and 6th cycles of treatment (denoted as day 1 of cycle 4 and prior to surgery).

The randomization of 50 patients is expected to occur over approximately 24 months. The treatment and post-surgery evaluation will occur within 7 months. Thereafter patients will have no further follow-up. The end of the trial therefore will be approximately 31 months after randomization of the first patient.

The trial will be conducted in 7 Centers in Italy.

6. Patient selection

6.1. Criteria for patient eligibility

6.1.1. Female gender

6.1.2. Premenopausal status determined locally:
Estradiol (E2) must be above 54 pg/mL (or above 198 pmol/L), measured within 14 days prior to randomization.

6.1.3. Age ≥ 18 years

6.1.4. Performance Status – Eastern Cooperative Oncology Group (ECOG) 0-1 (see chart at end of section*)

6.1.5. Histologically confirmed invasive breast cancer:
- Primary tumor greater than 2 cm diameter, measured by clinical examination and mammography or echography (cT2-4b)
- Any nodal stage
- No evidence of metastasis (M0)

6.1.6. Primary tumor must have ER and PgR >50% of the cells

6.1.7. Primary tumor must be HER2 negative (by IHC and/or ISH)

6.1.8. Hematopoietic status:
- Absolute neutrophil count ≥ 1.5×10^9/L
- Platelet count ≥ 100×10^9/L
- Hemoglobin ≥ 9 g/dL

6.1.9. Hepatic status:
- Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN). In the case of known Gilbert's syndrome, a higher serum total bilirubin (< 2 × ULN) is allowed
- AST and ALT ≤ 2.5 × ULN
- Alkaline phosphatase ≤ 2.5 × ULN

6.1.10. Renal status: Creatinine ≤ 1.5 ×ULN

6.1.11. Negative serum pregnancy test, within 2-weeks (preferably 7 days) prior to randomization. Pregnancy test has to be repeated before treatment start if treatment does not start within 15 days of the previous test.

6.1.12. The patient must be willing to use effective non-hormonal contraception (barrier method – condoms, diaphragm – also in conjunction with spermicidal jelly, or total abstinence) after the pregnancy test and up to surgery. Oral, injectable, or implant hormonal contraceptives or medicated IUD are not allowed within 2 months prior to randomization and during the trial.

6.1.13. Prior fertility treatment is allowed but must have been stopped at least 12 months before randomization

6.1.14. The patient has completed the baseline patient-reported symptoms questionnaire

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

6.1.16. The patient has been informed of and agrees to data transfer and handling, in accordance with national data protection guidelines

6.1.17. The patient accepts blood samples to be taken according to the schedule in section 17.4 for the determination of the primary endpoint

6.1.18. The patient agrees to make tumor (diagnostic core biopsy and surgical specimen) available for submission for central pathology review and to conduct translational studies as part of this protocol

NOTE: Central Pathology Review on the primary tumor is mandatory for this trial, but patients will be evaluated for eligibility according to tumor characteristics as determined by the local Pathologist. Both the diagnostic breast core biopsy specimen and the final breast surgical specimen must be submitted for Central Pathology Review.

* ECOG Performance Status:

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
PS 3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

6.2. Criteria for patient ineligibility

6.2.1. Postmenopausal patients

6.2.2. Any hormonal treatment (e.g., oral, injectable, implant, or medicated IUD) in the previous 2 months.

6.2.3. Presence of HER2/neu overexpression or amplification

6.2.4. Received any prior treatment for primary invasive breast cancer

6.2.5. Received any GnRH analog or SERM or AI within 12 months prior to randomization

6.2.6. A history of malignant neoplasms within the past 10 years, except for curatively treated
- Basal and squamous cell carcinoma of the skin

- Carcinoma in situ of the cervix
- Carcinoma in situ of the bladder

6.2.7. Previous ipsilateral breast cancer (invasive or in situ) at any time

6.2.8. Inflammatory breast cancer

6.2.9. Bilateral invasive breast cancer

6.2.10. Known history of uncontrolled or symptomatic angina, clinically significant arrhythmias, congestive heart failure, transmural myocardial infarction, uncontrolled hypertension (≥ 180/110), unstable diabetes mellitus, dyspnea at rest, or chronic therapy with oxygen

6.2.11. Concurrent disease or condition that would make the subject inappropriate for study participation or any serious medical disorder that would interfere with the subject's safety

6.2.12. Unresolved or unstable, serious adverse events from prior administration of another investigational drug

6.2.13. Active or uncontrolled infection CTCAE v.4 grade 2 or higher

6.2.14. Dementia, altered mental status, or any psychiatric condition that would prevent the understanding or rendering of Informed Consent

6.2.15. Treatment with an investigational agent must have stopped at least 30 days before randomization

6.2.16. Pregnant or lactating women; lactation has to stop before randomization.

7. Randomization and stratification

This trial will use a web-based randomization system. Specific details for randomizing are in the "IBCSG Registration/Randomization Procedures Manual" which is available on the IBCSG website (www.ibcsg.org).

7.1. Protocol requirements before randomization

7.1.1. Pathology material from the diagnostic breast biopsy of the primary tumor has to be available for submission for central review as part of the quality control measures for this protocol.

NOTE: Central Pathology Review (CPR) on the primary tumor is mandatory for this trial, but patients may be included based on tumor characteristics as determined by the local Pathologist.

NOTE: An FFPE block with a specimen of the final breast surgery will have to be submitted for CPR as well. Please notify the pathologist of this requirement in advance.

7.1.2. Check current and concomitant medications

NOTE: Additional hormonal treatments (oral or transdermal) including estrogen, progesterone, androgens, aromatase inhibitors, hormone replacement therapy, oral or other types of hormonal contraceptives (including implants and depot injections and medicated IUD), 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. 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®).

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).

Concomitant medication needs to be documented on the Form 41-CCM for the 14 days prior to randomization and throughout the trial until 30 days after surgery.

7.1.3. Patient needs to complete baseline PRS questionnaire.

7.2. Registration and randomization procedures

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

7.2.1. Verify eligibility (see section 0)

7.2.2. Make sure that the information needed for registration is available:

- E2 level used to determine premenopausal status
- Type of surgery intended to be performed upon completion of neoadjuvant treatment
- Patient age in years
- Prior fertility treatment yes/no, date of last such treatment
- Date of most recent pregnancy test

7.2.3. Obtain written Informed Consent both for the clinical trial and biological material submission, signed and dated by the patient and Investigator. Informed consent must be obtained prior to any trial-specific screening procedure or intervention.

7.2.4. Directly access the IBCSG Registration/Randomization System and provide the requested information as indicated on the Confirmation of Registration (41-A) Form. The date the Informed Consent Form and the Biological Material Consent was signed by the patient and the date signed by the Investigator are both required to complete randomization.

The IBCSG Registration/Randomization System will provide the following information via e-mail:

- Patient ID (randomization number)
- Treatment assignment
- Date of randomization

7.2.5. Submit the Confirmation of Registration (41-A) electronic case report form (eCRF) via iDataFax. The patient binder of eCRFs will be available in iDataFax within 24 hours of successful randomization.

7.3. Randomization Help Desk

The IBCSG Data Management Center (located at Frontier Science and Research Technology Foundation (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: 00:00-18:00 US Eastern Time Monday through Friday

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
E-mail: bc.helpdesk@fstrf.org

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

7.4. Randomized arms

Randomization (1:1) to 2 arms; cycles last 28 days:

Arm A: Triptorelin 3.75 mg i.m. on day 1 of every cycle + letrozole 2.5 mg/day orally for 6 cycles

Arm B: Degarelix 240 mg s.c. given as two subcutaneous injections of 120 mg on day 1 of cycle 1, followed by 80 mg s.c. on day 1 of cycles 2 to 6 + letrozole 2.5 mg/day orally for 6 cycles

7.5. Stratification

For randomization, patients will be stratified by age (in years): less than or equal to 39 vs 40 or more.

Dynamic institution balancing will be used in order to balance randomized assignments within institutions.

8. Study drugs formulation and handling

Triptorelin, degarelix and letrozole are the investigational drugs used in this trial; all will be supplied.

Complete details of the study drug logistics, distribution, packaging, labeling and handling are described in a separate drug supply manual.

8.1. Triptorelin

Triptorelin is a synthetic decapeptide analogue of the natural gonadotropin-releasing hormone (GnRH). GnRH is a decapeptide synthesized in the hypothalamus and regulates the biosynthesis and release of the gonadotropins: LH (luteinizing hormone) and FSH (follicle stimulating hormone) by the pituitary. The increase of LH and FSH levels will

initially lead to an increase of the serum estrogen concentration in women, however chronic administration results in an inhibition of pituitary LH- and FSH-secretion. This inhibition leads to a reduction in steroidogenesis, through which the serum estradiol concentration in women fall into the postmenopausal range.

Dose: 3.75 mg i.m. every 28 days for 6 cycles.

In Italy, triptorelin has marketing authorization for the use in breast cancer, presurgical treatment before myomectomy/hysterectomy, uterine fibromyomas, and endometriosis.

8.1.1. Packaging and labeling

Both the box label and vial label will fulfill all requirements specified by governing regulations.

8.1.2. Storage and handling

Instructions for proper handling and disposal of triptorelin should be followed. All drugs will be stored as per the current version of the product's SPC's (Summary of Product Characteristics) and the standard hospital procedures. Pharmacy will maintain temperature logs of all storage conditions and comply with hospital pharmacy standard operating procedures.

8.2. Degarelix

Degarelix (Firmagon®) is a gonadotropin releasing hormone (GnRH) receptor blocker and the chemical structure is a linear decapeptide amide containing seven unnatural amino acids, five of which are D-amino acids.

Degarelix is a selective gonadotropin releasing-hormone (GnRH) antagonist that competitively and reversibly binds to the pituitary GnRH receptors, thereby rapidly reducing the release of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH).

Degarelix is registered in the European Union for treatment of adult male patients with advanced hormone-dependent prostate cancer. In women, degarelix has been safely administered for the treatment of infertility.

Degarelix is supplied as a powder and solvent for solution for injection. The reconstitution procedure needs to be carefully followed.

Dose: 240 mg s.c. given as two subcutaneous injections of 120 mg on day 1 of trial treatment, followed by 80 mg s.c. every 28 days for cycles 2-6.

8.2.1. Packaging and labeling

Both the box label and vial label will fulfill all requirements specified by governing regulations.

8.2.2. Storage and handling

Instructions for proper handling and disposal of degarelix should be followed. All drugs will be stored as per the current version of the product's SPC's (Summary of Product Characteristics) and the standard hospital procedures. Pharmacy will maintain temperature logs of all storage conditions and comply with hospital pharmacy standard operating procedures. This medicinal product does not require any special storage conditions.

8.3. Letrozole

Letrozole is a potent, orally active non-steroidal competitive inhibitor of the aromatase enzyme system. As a non-steroidal aromatase inhibitor, letrozole effectively inhibits the conversion of androgens to estrogens both in vitro and in vivo.

Letrozole is registered for the following indications:

- Treatment of advanced breast cancer in postmenopausal women with disease progression following anti-estrogen therapy
- First-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer
- Extended adjuvant treatment of early breast cancer in postmenopausal women who have received 5 years of adjuvant tamoxifen therapy
- Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer
- Pre-operative therapy in postmenopausal women with localized hormone receptor positive breast cancer, to allow subsequent breast-conserving surgery for women not originally considered as appropriate surgical candidates.

Letrozole is supplied as film-coated tablet containing 2.5 mg letrozole.

Dose: 2.5 mg / day orally.

8.3.1. Packaging and labeling

Both the box label and blister label will fulfill all requirements specified by governing regulations.

8.3.2. Storage and handling

Procedures for proper handling and disposal of letrozole should be followed. All drugs will be stored as per the current version of the products SPC's (Summary of Product Characteristics) and the standard hospital procedures. Pharmacy will maintain temperature logs of all storage conditions and comply with hospital pharmacy standard operating procedures.

Do not store above 30°C or outside original package.

9. Treatment

9.1. Trial treatments

Six cycles of 28 days each:

Arm A: Triptorelin 3.75 mg i.m. on day 1 of every cycle + letrozole 2.5 mg/day orally for 6 cycles

Arm B: Degarelix 240 mg s.c. given as two subcutaneous injections of 120 mg on day 1 of cycle 1, followed by 80 mg s.c. on day 1 of cycles 2 to 6 + letrozole 2.5 mg/day orally for 6 cycles

Letrozole 2.5 mg/day orally should be started on day 1, concurrently with triptorelin or degarelix.

Trial treatment should start as soon as possible, and no later than 14 days after randomization.

NOTE: Treatment can be started at any time during the menstrual cycle.

Trial treatment stops at surgery.

If the patient has to continue endocrine treatment with an LHRH analogue after surgery, she should wait at least 6 weeks from the date of last administration of degarelix in order to avoid drug interactions.

9.2. Criteria for stopping neoadjuvant treatment

In the following cases neoadjuvant treatment should be stopped, and the patient should undergo surgical intervention:

- If ovarian function suppression is not achieved within 56 days after start of treatment according to local laboratory limits
- In the case of an adverse event grade ≥ 3, judged by the Investigator to be at least possibly related to study drugs.

9.3. Timing of surgery

Definitive surgery should be performed within 2 to 3 weeks after the last administration of triptorelin or degarelix.

9.4. Dose modifications and delays

No dose modifications are allowed for the drugs used in this trial (triptorelin/degarelix and letrozole).

Compliance with the protocol endocrine treatment should be strictly observed.

- Delays in the administration of triptorelin/degarelix should not exceed 2 days.
- Interruptions in the administration of letrozole should not exceed 2 days.

In the case of adverse event(s) grade ≥ 3, judged by the Investigator to be at least possibly related to study drugs, treatment will be stopped and patient will undergo surgical intervention.

10. Determination of objective response

Objective response will be assessed using the **WHO tumor measurement and response criteria.**

10.1. Tumor measurements

Bilateral mammography and breast ultrasound are required at baseline, after 3 treatment cycles and prior to surgery.

Breast ultrasound and mammography are mandatory.

The technique(s) used for measurement of the tumor will be left to the discretion of the Investigator, however, for each patient the same technique(s) should be used throughout the study treatment period. Whenever possible, measurements should be made by the same Investigator or reporter for all assessments for each patient.

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

In the case of multifocal or multicentric disease, only the lesion with the largest dimensions will be considered.

Primary tumor diameters as well as nodal status must be reported in the appropriate sections of the eCRF.

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

10.2. Response criteria

To determine response, changes in tumor size from baseline to the assessments after 3 and after 6 cycles as measured physically by caliper or ruler and as measured by breast tumor imaging will be used and the WHO criteria will be followed.

No confirmatory assessment will be required.

10.2.1. Complete response (CR)

The disappearance of all known disease.

10.2.2. Partial response (PR)

A 50% or more decrease in total tumor size, i.e., the sum of the products of the maximal diameter (MD) and the corresponding largest perpendicular diameter (LPD) of the lesions which have been measured to determine the effect of therapy. In addition, there can be no appearance of new lesions or progression of any lesion.

10.2.3. Stable disease (SD)

Neither a 50% decrease in total tumor size (i.e., the sum of the products MD*LPD of lesions), nor a 25% increase in the size of one or more measurable lesions has been determined.

10.2.4. Progressive disease (PD)

An increase of least 25% in total tumor size relative to the smallest size measured during the trial (i.e. the sum of the products MD*LPD of lesions), and/or the appearance of one or more new lesions.

10.3. Best overall response

Best overall response is defined as best response recorded from the start of treatment across all time points until disease progression. Confirmation of partial or complete response by an additional scan is not requested in this trial. Best overall response will be determined by a team consisting of the Study Chair, Co-chair and IBCSG Head of Medical Affairs.

10.4. Treatment in case of progression

Patients with evidence of complete response, partial response, or no change will remain on treatment for the full 6 cycles of endocrine treatment.

Patients with progressive disease confirmed by imaging will undergo surgery.

11. Clinical and laboratory evaluations

11.1. Before randomization

11.1.1. Breast palpation with tumor measurement and nodal status – caliper or ruler measurements preferred

11.1.2. Bilateral mammography and breast ultrasound (mandatory)

11.1.3. Chest X-ray; not required in patients who have undergone a PET scan

11.1.4. Abdominal ultrasound or CT scan is required if alkaline phosphatase or AST is >2.5 x ULN; not required in patients who have undergone a PET scan

11.1.5. Bone scan is required if alkaline phosphatase is >2.5 x ULN or if the patient has unexplained bone pain; not required in patients who have undergone a PET scan

11.1.6. Tumor measurements according to WHO criteria for determination of response (see section 10) by mammography and breast ultrasound

11.1.7. Physical examination, ECOG Performance Status, and body weight

11.1.8. Hematology: Hemoglobin, platelet count, white blood cell count including differential (absolute neutrophil count)

11.1.9. Blood chemistry: blood urea nitrogen, creatinine, alkaline phosphatase, AST and ALT, total bilirubin, calcium, urea, total cholesterol, LDL and HDL cholesterol, triglycerides

11.1.10. CEA and CA 15.3

11.1.11. Menopausal status

11.1.12. Serum pregnancy test; has to be repeated before treatment start, if treatment does not start within 15 days of the previous test

11.1.13. Medical history including details of malignancy: date of diagnosis, primary tumor type characteristics (histology, grade, stage)

11.1.14. The determination of the estradiol level is mandatory within 4 days prior to randomization in order to check eligibility,

11.1.15. Patient must complete baseline PRS questionnaire.

11.2. During first cycle of trial treatment

11.2.1. For estradiol level determination by central laboratory (for primary trial endpoint): Take a blood sample on day 1 of treatment **before the administration of the first dose**, thereafter at 24 and 72 hours, 7 days and 14 days after first injection; extract serum and store at -80°C. Please consult the Manual for Blood Sample Logistics for details.

11.3. Day 1 of every treatment cycle

11.3.1. Physical examination, ECOG Performance Status, and body weight

11.3.2. Collection of any adverse event and assignment of appropriate adverse events grade according to the NCI CTCAE Version 4

11.3.3. Record all concomitant medication

11.3.4. Breast palpation with tumor measurement and nodal status (caliper or ruler measurements preferred)

11.3.5. For estradiol level determination by central laboratory (for primary trial endpoint): Take a blood sample **before the administration of the next dose of the GnRH agonist or antagonist**; extract serum and store at -80°C.

11.3.6. Local determination of estradiol level

11.3.7. The patient must complete a PRS questionnaire **on day 1 of cycles 2 and 4**

11.4. After three cycles of trial treatment

11.4.1. Hematology: Hemoglobin, platelet count, white blood cell count including differential (absolute neutrophil count)

11.4.2. Blood chemistry: blood urea nitrogen, creatinine, alkaline phosphatase, AST and ALT, total bilirubin, calcium, urea, total cholesterol, LDL and HDL cholesterol, triglycerides

11.4.3. CEA and CA 15.3

11.4.4. Breast palpation with tumor measurement and nodal status (caliper or ruler measurements preferred)

11.4.5. Bilateral mammography and breast ultrasound (mandatory)

11.4.6. Tumor measurements according to WHO criteria for determination of response (see section 10) by mammography and breast ultrasound

11.5. At visit prior to surgery

11.5.1. Physical examination, ECOG Performance Status and body weight

11.5.2. Hematology: Hemoglobin, platelet count, white blood cell count including

differential (absolute neutrophil count)

11.5.3. Blood chemistry: blood urea nitrogen, creatinine, alkaline phosphatase, AST and ALT, total bilirubin, calcium, urea, total cholesterol, LDL and HDL cholesterol, triglycerides

11.5.4. CEA and CA 15.3

11.5.5. Local determination of estradiol level

11.5.6. Collection of any AE and assignment of appropriate adverse events grade according to the NCI CTCAE Version 4

11.5.7. Record all concomitant medication

11.5.8. Breast palpation with tumor measurement and nodal status (caliper or ruler measurements preferred)

11.5.9. Bilateral mammography and breast ultrasound (mandatory)

11.5.10. Tumor measurements according to WHO criteria for determination of response (see section 10) by mammography and breast ultrasound

11.5.11. Patient has to complete PRS questionnaire

11.6. At visit 30 days after surgery

11.6.1. Collection of any AE and SAE and assignment of appropriate adverse events grade according to the NCI CTCAE Version 4

11.6.2. Record all concomitant medication

12. Safety

12.1. Adverse effects of degarelix

The following adverse reactions have been reported in clinical trials in male patients:

(**NOTE:** Only partly categorized according to CTCAE version 4.)

Very common (≥ 10%):

Vascular disorders: hot flushes

General disorders and administration site conditions: injection site adverse events

Common (1 – 10%):

Blood and lymphatic system disorders: anemia

Metabolism and nutrition disorders: weight increase

Psychiatric disorders: insomnia

Nervous system disorders: dizziness, headache

Gastrointestinal disorders: diarrhea, nausea

Hepatobiliary disorders: liver transaminases increased

Skin and subcutaneous tissue disorders: hyperhidrosis (including night sweats), rash

Musculoskeletal, connective tissue and bone disorders: musculoskeletal pain and discomfort

Reproductive system and breast disorders: gynecomastia

General disorders and administration site conditions: chills, pyrexia, fatigue, influenza-like illness.

Uncommon (0.1 – 1%):

Immune system disorders: hypersensitivity

Metabolism and nutrition disorders: hyperglycemia/diabetes mellitus, cholesterol increased, weight decreased, appetite decreased, changes in blood calcium

Psychiatric disorders: depression, libido decreased

Nervous system disorders: mental impairment, hypoesthesia

Eye disorders: vision blurred

Cardiac disorders: cardiac arrhythmia (incl. atrial fibrillation), palpitations

Vascular disorders: hypertension, vasovagal reaction (incl. hypotension)

Respiratory, thoracic and mediastinal disorders: dyspnea

Gastrointestinal disorders: constipation, vomiting, abdominal pain, abdominal discomfort, dry mouth

Hepatobiliary disorders: bilirubin increased, alkaline phosphatase increased

Skin and subcutaneous tissue disorders: urticaria, skin nodule, alopecia, pruritus, erythema

Musculoskeletal, connective tissue and bone disorders: osteoporosis/osteopenia, arthralgia, muscular weakness, muscle spasms, joint swelling/stiffness

Renal and urinary disorders: pollakiuria, micturition urgency, dysuria, nocturia, renal impairment, incontinence

Reproductive system and breast disorders: breast pain, pelvic pain, genital irritation

General disorders and administration site conditions: malaise, peripheral edema

Changes in laboratory parameters:

Changes in laboratory values seen during one year of treatment in the confirmatory phase III study (N=409) were in the same range for degarelix and a GnRH-agonist (leuprorelin) used for comparison. Markedly abnormal (>3×ULN) liver transaminase values (ALT, AST and GGT) were seen in 2%-6% of patients with normal values prior to treatment, following treatment with both medicinal products. Marked decrease in haematological values, hematocrit (≤0.37) and hemoglobin (≤115 g/l) were seen in 40% and 13%-15%, respectively among those patients with normal values prior to treatment, following treatment with both medicinal products. It is unknown to what extent this decrease in haematological values was caused by the underlying prostate cancer and to what extent it was a consequence of androgen deprivation therapy. Markedly abnormal values of potassium (≥5.8 mmol/l), creatinine (≥177 µmol/l) and BUN (≥10.7 mmol/l) in patients with normal values prior to

treatment, were seen in 6%, 2% and 15% of degarelix treated patients and 3%, 2% and 14% of leuprorelin treated patients, respectively.

Changes in ECG measurements:

Changes in ECG measurements seen during one year of treatment in the confirmatory phase III study (N=409) were in the same range for degarelix and a GnRH-agonist (leuprorelin) used as comparator. Three (<1%) out of 409 patients in the degarelix group and four (2%) out of 201 patients in the leuprorelin 7.5 mg group, had a QTcF ≥ 500 msec. From baseline to end of study the median change in QTcF for degarelix was 12.0 msec and for leuprorelin was 16.7 msec.

12.2. Drug interactions with degarelix

No drug-drug interaction studies were conducted.

Since androgen deprivation treatment may prolong the QTc interval, the concomitant use of degarelix with medicinal products known to prolong the QTc interval or medicinal products able to induce torsades de pointes such as class IA (e.g., quinidine, disopyramide) or class III (e.g., amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, cisapride, moxifloxacine, antipsychotics, etc., should be carefully evaluated.

Degarelix is not a substrate for the human CYP450 system. Degarelix is not an inducer or inhibitor of the CYP450 system in vitro. Therefore, clinically significant CYP450 pharmacokinetic drug-drug interactions are unlikely.

12.3. Adverse effects of triptorelin

The following adverse reactions have been reported in clinical trials and from post-marketing surveillance (gonapeptyl depot 3.75mg, Ferring):

(**NOTE:** Only partly categorized according to CTCAE version 4.)

Common (1 – 10%):

Endocrine: depressive mood, irritation

Gastrointestinal: nausea

Musculoskeletal system: myalgia, arthralgia

Body as a whole – general: tiredness, sleep disturbances, hypersensitivity reactions (itching, skin rash, fever)

Application site disorders: temporary pain at injection site

Uncommon (0.1 – 1%):

Metabolic and nutritional: elevated enzyme levels (LDH, yGT, SGOT, SGPT); slight rise in serum cholesterol

Central and peripheral nervous system: visual disturbances, paresthesia

General: aching of back

Body as a whole – general: anaphylaxis

Application site disorders: foreign body reaction at injection site

12.4. Adverse effects of letrozole

The following adverse reactions have been reported in clinical trials and from post-marketing surveillance:

(**NOTE:** Only partly categorized according to CTCAE version 4.)

Very common (≥ 10%):

Musculoskeletal and connective tissue disorders: arthralgia

General disorders and administration site conditions: hot flushes

Common (1 – 10%):

Metabolism and nutrition disorders: general edema

Psychiatric disorders: depression

Nervous system disorders: headache, dizziness

Gastrointestinal disorders: nausea, vomiting, dyspepsia, constipation, diarrhea

Skin and subcutaneous disorders: alopecia, increased sweating, rash

Musculoskeletal and connective tissue disorders: myalgia, bone pain, osteoporosis, bone fractures

General disorders and administration site conditions: fatigue, peripheral edema

Investigations: weight increase

Uncommon (0.1 – 1%):

Infections and infestations: urinary tract infection

Neoplasms, benign, malignant and unspecified (including cysts and polyps): tumor pain

Blood and lymphatic system disorders: leucopenia

Metabolism and nutrition disorders: general edema

Psychiatric disorders: anxiety

Nervous system disorders: somnolence, insomnia, memory impairment, dysesthesia, taste disturbance, cerebrovascular accident, carpal tunnel syndrome

Eye disorders: cataract, eye irritation, blurred vision

Cardiac disorders: palpitations, tachycardia

Vascular disorders: thrombophlebitis, hypertension, ischemic cardiac events

Rare (0.01 – 0.1%):

Vascular disorders: pulmonary embolism, arterial thrombosis, cerebrovascular infarction

Respiratory, thoracic and mediastinal disorders: dyspnea, cough

Gastrointestinal disorders: abdominal pain, stomatitis, dry mouth

Hepatobiliary disorders: increased hepatic enzymes

Skin and subcutaneous disorders: toxic epidermal necrolysis, erythema mutiforme

Musculoskeletal and connective tissue disorders: arthritis

Renal and urinary disorders: increased urinary frequency

Reproductive system and breast disorders: vaginal bleeding, vaginal discharge, vaginal dryness, breast pain

General disorders and administration site conditions: pyrexia, mucosal dryness, thirst

Investigations: weight loss

13. Adverse event and serious adverse event reporting

13.1. Adverse event reporting

The main criterion for tolerability is the occurrence of toxicities and adverse events. The severity and causality will be classified according to the NCI CTCAE Version 4. The CTCAE is available for downloading on the internet at http://evs.nci.nih.gov/ftp1/CTCAE/About.html. An interactive version can be found at http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx.

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.

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

An overdose, accidental or intentional, whether or not it is associated with an AE, of an investigational product should be reported as an SAE.

13.1.1. Severity / intensity

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

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

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death – the event results in death

The term “severe” is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as

"serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

13.1.2. Causality

The Investigator must determine the relationship between the administration of trial drug(s) and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	The temporal relationship of the adverse event to trial drug(s) administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	The temporal relationship of the adverse event to trial drug(s) administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

13.1.3. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

13.1.4. Action taken

The Investigator will report the action taken with trial drug(s) as a result of an AE or SAE, as applicable (e.g., discontinuation of trial drug(s)) and in case of an SAE report if concomitant and/or additional treatments were given for the event.

13.2. Targeted adverse events

The presence or absence of any of the following adverse events will have to be indicated on each occasion that an Adverse Event Form (Form 41-AE) is completed.

Adverse events should be graded using the NCI CTCAE version 4.0. The following list provides targeted adverse events (ordered by System Organ Class) that should be recorded on the eCRF at any time. Treatments to alleviate these should be recorded on the 41-CCM Form:

Reproductive system and breast disorders:

Vaginal dryness

Dyspareunia

Psychiatric disorders:

Libido decreased

Depression

Anxiety

Insomnia

Renal and urinary disorders:

Urinary incontinence

Vascular disorders:

Hot flashes

Hypertension

Thromboembolic event

Musculoskeletal and connective tissue disorders:

Osteoporosis

Myalgia

Arthralgia

Injury, poisoning and procedural complications:

Fracture

Nervous system disorders:

Stroke

Transient ischemic attacks

Intracranial hemorrhage

Cardiac disorders:

Acute coronary syndrome

Myocardial infarction

Ventricular arrhythmia

Ventricular fibrillation

Gastrointestinal disorders:

Nausea

General disorders and administration site conditions:

Fatigue

Injection site reaction

Immune system disorders:

Allergic reaction

Metabolism and nutrition disorders:

Glucose Intolerance

Hyperglycemia

Investigations:

Aspartate aminotransferase (AST) increased

Alanine aminotransferase (ALT) increased

Blood bilirubin increased

Electrocardiogram QT corrected interval prolonged

13.3. Abnormal Laboratory Values

An abnormal laboratory value grade 3 or higher is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of trial drug(s) dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

13.4. Serious adverse event (SAE) reporting

13.4.1. Definition

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

- fatal (any cause)
- life-threatening
- requires or prolongs inpatient hospitalization
- persistent or significant disability/incapacity
- congenital anomaly or birth defect
- secondary (non-breast) malignancy
- constitutes an important medical event
- neonatal deaths within 28 days of birth

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

All serious adverse events must also be reported for the period in which the trial protocol interferes with the standard medical treatment given to the patient. After completion of trial treatments, report all SAEs that are considered at least possibly related to previous trial treatment. Cases of second (non-breast) malignancies and congenital abnormalities are to be regarded as SAEs, regardless of whether they occur during or after study treatment. These events should be reported on the Serious Adverse Event eCRFs (SAE-A and SAE-B).

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

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

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

13.4.2. Exceptions to the definition

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

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

13.4.3. 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 eCRFs (SAE–A and SAE-B).

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

- The Investigator/MD responsible for the patient must complete a Serious Adverse Event (SAE-A) eCRF in English within 24 hours via iDataFax. A copy is automatically forwarded to the IBCSG Safety Office for medical review.
- Follow-up information should be completed, via iDataFax, on the Serious Adverse Event (SAE-B) eCRF within 15 days of the initial report, even if the event reported in the SAE-A eCRF is not yet resolved. If the event is not resolved within 15 days, revise the original Serious Adverse Event (SAE-B) eCRF in iDataFax to report the final resolution.
- All SAEs that have not resolved upon discontinuation of the subject's participation in the trial must be followed until recovered, recovered with sequelae, not recovered (death due to another cause) or death (due to the SAE).
- If a non-serious adverse event becomes serious, this and other relevant follow-up information must also be provided within 24 hours.
- Photocopies of all examinations carried out with the dates on which they were performed should be sent by fax into the DataFax system. Care should be taken to ensure that the patient's identity is protected and the patient's Randomization ID Number is properly included on ALL pages of any reports. For laboratory results, include the laboratory normal ranges.
- In the event the eCRF system is not working, the SAE Forms can be sent via fax into the DataFax system.

If a Serious Adverse Event (SAE-A and SAE-B) was submitted by fax, the original forms and the fax confirmation sheet(s) must be kept at the Participating Center.

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

The IBCSG will record the SAE and prepare a monthly SAE report. 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).

13.5. Pregnancy

Pregnancies and suspected pregnancies of a patient occurring during trial treatment, or within 30 days of the last dose of trial drug(s), are considered immediately reportable events. Trial drug(s) are to be discontinued immediately and the patient instructed to return any unused portion of the trial drug(s) to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported within 24 hours of the Investigator's knowledge using the Pregnancy Form (Form 41-PREG) to the IBCSG who will inform Ferring immediately.

The patient should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the patient until completion of the pregnancy, and must notify IBCSG immediately about the outcome of the pregnancy by completing the corresponding section on the Pregnancy Form (41-PREG).

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to trial drug(s) should also be reported within 24 hours of the Investigator's knowledge of the event using the SAE Forms.

13.6. Safety review of degarelix

Every six months the adverse events observed during trial treatment will be summarized in a safety report. Investigators should document treatment and adverse events immediately at the end of each cycle by completing the appropriate eCRFs.

The safety reports will be reviewed by the Data and Safety Monitoring Committee (see section 19.3).

14. 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:

14.1. Case report forms schedule

Registration/Randomization		***ALL data should be submitted in iDataFax (iDF) (unless otherwise specified)***
Informed Consent Form	Consent to participation in clinical trial including consent for biomaterial submission	Obtain before randomization and keep with patient records as documentation (hard copy only).
41-A	Confirmation of Registration Form	Complete in iDF after you or your Randomization Center has randomized the patient in the IBCSG Reg./Rand. System.
41-PRS	Patient-Reported Symptoms	Patient to complete prior to randomization and fax into DataFax after randomization.
Baseline		
41-H	History Form	Complete in iDF within 1 week of randomization.
Pathology Report	Pathology Report on diagnostic biopsy	Fax Report to DataFax System within 1 week of randomization.
41-PBx	Pathology Form for diagnostic core biopsy	Complete in iDF within 1 week of randomization.
41-BS	Baseline Symptoms Form	Complete in iDF within 1 week of randomization.
41-CCM	Concomitant Medications Form	Complete in iDF each time a medication is started, amended, or ended, including within 14 days of starting treatment, during treatment, and during follow-up.
41-TEV-B	Baseline Tumor Evaluation Form	Complete in iDF within 1 week of randomization.
During trial treatment		
41-AE	Adverse Events Form	Complete in iDF at the end of each 28 day cycle.
41-TEV	Tumor Evaluation Form	Complete in iDF at the end of cycle 3 and prior to surgery.
41-PRS	Patient-Reported Symptoms	Complete at day 1 of cycle 2 and 4 (i.e. after 4 and 12 weeks), and prior to surgery.
41-CCM	Concomitant Medications Form	Review the original CCM Form at the end of each cycle. Update in iDF any current medications if needed and add new medications taken.
41-PT (Cycle 1)	Protocol Therapy Form (including lab values)	Complete in iDF at the end of cycle 1.
41-PT (Cycles 2-6)	Protocol Therapy Form (including lab values)	Complete in iDF at the end of cycles 2-6.
Surgery		
41-C	Surgery Form	Complete in iDF 30 days after surgery.
41-P	Pathology Form	Complete in iDF 30 days after surgery.
Pathology Report	Pathology Report for definitive surgery	Fax report to DataFax System within 30 days after surgery.
End of treatment, after surgery		
41-AE	Adverse Events Form	Complete in iDF 30 days after surgery.
41-CCM	Concomitant Medications Form	Update in iDF any current medications if needed and add new medications taken.
Event Driven		
41-SAE-A	Serious Adverse Event initial report	Complete within 24 hours of the SAE in iDF. If iDF is not available, fax the form within 24 hours to DataFax.
41-SAE-B	Serious Adverse Event B follow-up report	Complete in iDF within 15 days of initial report (42-SAE-A). If event is not resolved in 15 days, complete 42-SAE-B again at time of resolution.
41-PREG	Pregnancy Form	Complete in iDF if a patient becomes pregnant on trial treatment. Complete the second section of the form at the end of pregnancy.
42-SM	Second Malignancy Form	Complete in iDF if a patient has a second (non-breast) malignancy while on trial treatment.
42-Death	Death Form	Complete in iDF if a patient dies while on trial treatment.
42-COC	Change of Consent Form	Complete in iDF if a patient withdraws consent for further trial participation.

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

14.2. Signing and submitting forms

An Authorization Log (see section 14.5) should be completed at each Participating Center to identify the persons who are authorized to complete eCRFs.

eCRFs should be completed on-line in iDataFax. PRS Forms, reports (lab, pathology, etc.) and any other non-eCRF data will need to be faxed to the DataFax system. Full instructions on submitting forms will be available on the IBCSG website (www.ibcsg.org). Also available on the website is a list of fax numbers that are available for faxing CRFs.

14.3. 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.

14.4. Investigators' file

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

- Protocol and appendices
- Amendments
- Signed Protocol Signature Pages
- Sample CRFs including blank SAE Forms
- Data Managers' Manual
- Obvious Corrections Document and Signature Page
- Randomization Manual
- iDataFax (iDF) Manual
- Drug Supply Manual
- Manual for Blood Sample Logistics
- Patient information and Informed Consent templates approved by Ethics Committee
- Investigator's Brochure and updates
- Ethics Committee (and Health Authority, if applicable) approval of protocol, Patient Information Sheet and IC, amendments
- Ethics Committee review of SAE, Investigators' alert, and other documents
- Correspondence with Ethics Committee and Health Authority (if applicable)
- Certificate of clinical trial insurance
- Agreement with IBCSG
- Center Activation e-mail from DMC
- Correspondence with IBCSG Coordinating Center, Data Management Center
- SAE Reports sent from IBCSG Data Management Center
- Normal laboratory values/reference ranges
- Laboratory Certifications
- CV of Principal Investigator and Co-Investigators, GCP certificates

- Trial Training Certificates issued by IBCSG
- Authorization Log
- Patient identification log (see section 14.6)
- Drug accountability log (including certificates of destruction if applicable)
- Temperature logs
- ICH GCP guidelines/Declaration of Helsinki and updates
- Audit certificates / monitoring reports

14.5. 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 eCRFs, queries, etc. Instructions for completing the Authorization Log can be found in the Authorization Log Manual, posted on the IBCSG website.

14.6. Patient identification log

No patients' names should be used in CRFs or any other documentation transmitted to IBCSG central offices. The only item used to identify a patient is the randomization number. It is therefore imperative that the local data manager keep an identification log for all patients entered in this trial including:

- Patient's name
- Patient ID (Randomization number)
- Date of birth

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

15. Statistical considerations

The primary objective of this randomized phase II trial is to compare the endocrine activity of neoadjuvant degarelix and triptorelin in premenopausal patients receiving letrozole. The endocrine activity is measured by time to optimal ovarian function suppression with the hypothesis that degarelix will achieve faster ovarian suppression than triptorelin. Patients will be randomized equally (1:1 ratio) between the two treatment arms with stratification based on age ($\leq$39 vs. $\geq$40 years).

15.1. Primary endpoint

The primary endpoint of time to optimal ovarian function suppression will be assessed in the two treatment arms and is defined as time from the first injection of degarelix or triptorelin to the first assessment of E2 $\leq$2.72 pg/mL or $\leq$10 pmol/L during the 6 cycles of neoadjuvant treatment. E2 levels will be determined centrally from samples taken at day 1 of the first treatment cycle before the administration of the first dose of degarelix or triptorelin (baseline), and thereafter at 24 and 72 hours, 7 days and 14 days after the first injection, and on day 1 of cycles 2 to 6 before the administration of degarelix or triptorelin.

The primary endpoint will be compared between the two treatment arms using a stratified log-rank test. The type I error will be controlled at a two-sided 0.05.

15.1.1. Sample size justification

The following table provides the assumption on the cumulative percent of patients who are anticipated to reach optimal ovarian function suppression (E2 level ≤2.72 pg/mL or ≤10 pmol/L) during the 6 cycles of neoadjuvant treatment.

	Percent (%) of patients with E2 ≤2.72 pg/mL or ≤10 pmol/L				
Treatment arms	2 weeks	4 weeks	8 weeks	12 weeks	16 weeks
Triptorelin+Letrozole (control)	30	60	75	90	100
Degarelix+Letrozole (experiment)	60	95	100	100	100

With 23 patients in each treatment arm and based on the assumption in the table above, the study has 90% power to detect a difference in time to optimal ovarian function suppression (E2 ≤2.72 pg/mL or ≤10 pmol/L) between the two treatment arms, using a two-sample log-rank test at a two-sided significance level of 0.05. Calculations were performed using nQuery Advisor® (logrank test of survival in two groups, simulation with percentages specified in above table).

To allow for missing data, the study plans to enroll 25 patients to each treatment arm for a total of 50 patients. The accrual is expected to be 2 patients per month with an accrual period of approximately 24 months and additional 7 months of follow up after the last patient is enrolled.

15.1.2. Analysis of the primary endpoint

Primary analysis will use the modified intent to treat principle. Randomized patients who receive at least one injection of triptorelin or degarelix will be included in the primary analysis. The primary endpoint will be compared between the two treatment arms using a stratified two-sample log-rank test, with age as stratification factor. The distribution of the primary endpoint will be summarized using the method of Kaplan-Meier and the two-sided 95% confidence interval (CI) for the difference in proportion of patients who achieve optimal ovarian function suppression (defined as E2 level ≤2.72 pg/mL or ≤10 pmol/L) between the two treatment arms at the end of the 1st, 2nd and 4th cycle will also be provided.

Cox proportional hazards model will also be used to assess the difference in time to optimal ovarian function suppression between the treatment arms adjusting for selected covariates including baseline E2 level, body mass index (BMI), smoking history, and recent oral contraceptive usage.

15.2. Secondary objectives

Secondary objectives include evaluation with respect to several secondary endpoints as defined in section 4.2. Analyses of the secondary endpoints will be descriptive. Tests of significance, whenever applicable, will not be controlled for multiple comparisons. Due to the limited sample size, the tests will largely be underpowered except in cases where differences between treatment groups are substantial. Randomized patients who received at least one dose of study treatment are included in the analysis unless otherwise indicated.

15.2.1. Tolerability (Safety of combined neoadjuvant therapy):

Tolerability will be evaluated in each treatment arm separately. Randomized patients who received at least one dose of the trial treatment will be included in the tolerability analyses.

The frequencies of adverse events (AE) according to CTCAE 4 by type and worst grade experienced while on the neoadjuvant treatments will be summarized and tabulated by treatment arms. Two-sided 90% confidence interval (CI) for the difference in proportion of patients with each type of grade 3 or higher targeted adverse event (see section 13.2) between the treatment arms will be assessed.

15.2.2. Changes in Ki67 expression levels

Patients who received at least one dose of study treatment and who have biospecimen available will be included in the analysis.

- The percentage change in Ki67 expression (geometric means*) from pre-treatment to surgery will be summarized for each treatment arm and two-sided 90% CI for the change will be calculated.
- The percentage changes in Ki67 expression (geometric means*) between the treatment arms at baseline and surgery are assessed using a two-sided 90% CI and explored using a two-sample Wilcoxon Rank Sum test.
- Other descriptive summary such as boxplots for the marker data will be provided.

** Due to the approximate lognormal distribution of the data*

In cases with no residual invasive tumor detected at surgery, the percentage change in Ki67 will be recorded as 100%.

15.2.3. The Preoperative Endocrine Prognostic Index (PEPI) score at the time of surgery

Patients with available central pathology review results will be included in the assessment. See section 3.2 for the calculation of the PEPI score.

Descriptive statistics will be used to summarize the PEPI score by treatment arm. Two-sided 90% CI for the difference in the PEPI scores between the two arms will also be assessed.

For example, a patient with pathologically node-negative T1 or T2 disease, Ki67 level ≤2.7% (or ≤1% on a natural log scale) and persistent ER expression after completion of neoadjuvant therapy is assigned a PEPI score of 0 (best prognostic group). Logistic regression modeling will be used to explore whether the PEPI score of 0 differs from PEPI score >0 with respect to disease characteristics at baseline.

15.2.4. Best overall (disease) response (defined in Section 4.2)

Descriptive summaries of the best overall response rate by the treatment arms and two sided 90% CI for the difference in best overall response rate will be provided. Tumor assessment is scheduled at the end of 3rd and 6th cycle of treatment. Clinical responses including complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) as defined in Section 10.2 will also be descriptively summarized by treatment arms.

15.2.5. Node negative disease at surgery

The percentage of patients with node-negative disease at surgery will be descriptively summarized by treatment arm. Two sided 90% CI for the difference in percentage of patients with node-negative disease between treatment arms will be assessed.

15.2.6. Breast-conserving surgery (BCS) rate

The proportion of patients undergoing BCS is evaluated in two analyses. First, considering all patients enrolled, the percent of patients in each treatment arm who had a breast-

conserving surgery will be presented, and the difference between the treatment arms assessed using a two-sided 90%CI. Second (i.e., rate of conversion), considering only patients who are reported at baseline not to be candidates for BCS, the percent in each treatment arm who had a BCS after neoadjuvant therapy will be presented, and the difference between the arms assessed using a two-sided 90% CI.

15.2.7. Patient-reported symptoms (PRS) outcomes (menopausal symptoms)

The PRS Study is described in section 16.

15.3. Stopping Rules and Data Monitoring

No formal stopping rule regarding the primary efficacy endpoints is planned.

Adverse events and safety monitoring are important for this study, as there are currently no safety data for degarelix used in high dose and in combination with letrozole for premenopausal women with invasive breast cancer. This study will implement detailed toxicity monitoring as described in section 13.

Adverse event reports are to be submitted within 28 days of each clinic visit. All relevant adverse events will be reviewed by the DSMC every 6 months (twice a year). The DSMC will make recommendation to the study management team if it notes any concerns regarding patient safety or if further action needs to be taken based on the safety monitoring review results. Formal assessment of targeted adverse events will also be included in statistical analysis for secondary objectives as detailed in section 15.2.1.

15.4. Accrual

The overall accrual goal of this trial is 50 patients. We anticipate that the accrual rate will be approximately 2 patients per month and the accrual will be completed within approximately 24 months, with additional 7 months of follow up after the last patient is enrolled.

16. Patient-reported symptoms (PRS)

16.1. Introduction

In clinical trials, toxicities and tolerability profiles are usually derived from a physician-recorded grading of adverse events (e.g. CTCAE). However, there is some evidence that these proxy ratings do not adequately reflect the burden of symptoms experienced by patients. Rates of symptoms related to endocrine therapy are suggested to be higher when self-reported compared to physician-recorded as shown in two studies, each comparing rates of patient-reported symptoms in their own sample to the prevalence rates published in pivotal trials (33,34). Several randomized trials in the adjuvant setting evaluated patient-reported symptoms related to endocrine therapy in postmenopausal women with breast cancer (35,36,37). These studies revealed no major effect on overall quality of life by the different endocrine agents, yet different profiles with regard to specific symptoms. To date, the ZIPP trial (Zoladex in Premenopausal Patients trial;38) is the only trial with published results on patient-reported side-effects of adjuvant endocrine treatment in premenopausal breast cancer patients. In this trial patient-reported side-effects were compared between women receiving goserelin (a GnRH agonist), goserelin plus tamoxifen, or tamoxifen alone. The treatment with goserelin was the most burdensome with similar symptom levels reported during previous chemotherapy, while side effects of tamoxifen alone were milder,

except for vaginal discharge. Two studies compared chemotherapy (i.e. cyclophosphamide, methotrexate, fluorouracil (CMF)) to goserelin treatment in pre- and perimenopausal women with lymph node-negative (39) or lymph node-positive (40) breast cancer. Both studies showed that patients receiving goserelin reported worse endocrine symptoms during the goserelin treatment period. This difference was reversed after cessation of goserelin treatment (after 3 years), then endocrine symptom scores were worse in those patients who had received chemotherapy.

With respect to degarelix one study assessed self-reported symptoms in patients with prostate cancer (41). A more rapid onset of self-reported hot flushes was seen in patients receiving degarelix compared to those receiving leuprolide, with a higher median hot flushes score during the first 3 months, but no differences in overall median hot flush scores over the entire 12 months of treatment.

16.2. PRS Objectives

The primary objective is to assess the differences in patient-reported symptoms (PRS) measurements between the two treatment arms over time. The PRS scores are measured at baseline, day 1 of cycle 2 and cycle 4 of triptorelin or degarelix administration and prior to surgery.

Secondary objectives are:

- To correlate estradiol levels with the total PRS score measured on day 1 of cycle 2 and day 1 of cycle 4 of triptorelin or degarelix administration.
- To summarize each of the 18 individual (endocrine symptom) items of the FACT-ES descriptively over time as the proportion of patients with “clinically significant” symptoms (those scoring 3 or 4).

16.3. PRS Patient selection

All patients randomized into this trial are required to complete Patient-Reported Symptoms Form 41-PRS. Patients must complete a baseline PRS Form prior to randomization. There will be no patient selection within Participating Centers. The only exceptions are physical impairment that interferes with any assessment.

16.4. PRS design

A longitudinal assessment is used to evaluate the differential effects of the randomized treatments on patients’ PRS. Patients are asked to complete a PRS Form at baseline (prior to randomization), day 1 of cycle 2 and cycle 4 of triptorelin or degarelix administration and prior to surgery.

16.5. PRS assessment

Patient-reported symptoms will be assessed using the Functional Assessment of Cancer Therapy Endocrine Subscale (FACT-ES). The FACT-ES (42) comprises 18 items, with a maximum possible sum score of 72. Each item or question has response choices ranging from 0 (‘‘not at all’’) to 4 (‘‘very much a problem’’). FACIT guidelines (www.facit.org) will be used for scoring and interpretation of the FACT-ES total score. To provide clinically useful information regarding treatment side effects, patient responses to each ES question can be labeled as ‘‘clinically significant’’ if they scored 3 or 4 (corresponding to ‘‘quite a bit’’ or ‘‘very much’’ a problem, respectively, on the questionnaire) and as ‘‘not clinically

significant'' for scores of 0, 1, or 2 (''not at all'', ''a little bit'', or ''somewhat'' a problem, respectively) (34). The questionnaire is completed before any subsequent procedures or treatment and refers to the past 7 days.

16.6. PRS statistical considerations

16.6.1. Primary analysis

The differences in PRS measurements between the two treatment arms over time will be assessed. We hypothesize that the PRS may change over time and that women receiving degarelix will experience a more rapid onset of PRS symptoms related to endocrine therapy than those receiving triptorelin. Repeated measures analysis based on generalized estimating equation (GEE) model will be used to investigate the differences in PRS between treatment arms, controlling for the stratification factor of age. All patients who receive at least one dose of study treatment and with at least one PRS assessment will be included in the analysis. This model will describe the effects of two neoadjuvant treatments (letrozole plus either degarelix or triptorelin) on PRS for the observation period. The analysis will be exploratory, given the limited sample size (maximum 25 patients per treatment arm). The power of the repeated measure test is likely to be low except if treatment differences are substantial.

16.6.2. Analysis for secondary objectives

- Correlation between the E2 levels and total PRS score measured on day 1 of cycle 2 and cycle 4 of triptorelin or degarelix administration will be assessed by treatment arms using Spearman' rank correlation coefficient.
- Each of the 18 (endocrine symptom) items of the FACT-ES will also be summarized descriptively over time by treatment arms as the proportion of patients with "clinically significant" symptoms (those scoring 3 or 4). Two sided 90% CI for the difference in the proportion will also be assessed.

Missing assessments may be due to stopping treatment, not completing the PRS assessments, and other reasons. Information on reasons why the patient did not complete the PRS Form will be collected.

16.7. PRS Timing requirements

All PRS Forms are to be completed during the patients' visits in the clinic. The schedule of PRS assessment time points must be followed as closely as possible. Timing effects have an impact on patients' self-estimation of PRS (43). It is important that the questionnaire is completed before any diagnostic procedures or communication of diagnostic information to the patient (exception: baseline assessment) and before any administration of treatment. If, for administrative reasons, the form has not been presented to the patient, it may be filled in at home and mailed.

16.8. PRS data collection and local data management

For the first assessment, the PRS Form has to be explained to the patient, with particular emphasis on making sure the patient understands the categorical response format. All questions must be answered. The completed questionnaire is to be checked while the patient is still present. If necessary, the patient should be asked to fill in missing answers. If the patient does not complete a scheduled PRS assessment, an empty PRS Form should be

faxed with the Patient ID number, the date the questionnaire was meant to be filled in, and the reason for not completing the questionnaire.

Questions regarding PRS assessment should be addressed to ibcsg41_TREND@fstrf.org.

17. Additional protocol-specific evaluations

17.1. Pathology and pathology material banking

The work of the pathologist is basic to the success of all studies. Each Participating Center should identify a pathologist responsible for study patients. The pathologist determines the diagnosis, classification, and grading of the primary tumor and evaluates the non-tumor breast tissue and local or regional spread as found in the diagnostic biopsy and definitive surgery 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.

NOTE: Central pathology review on the primary tumor is mandatory for this trial, but patients will be evaluated for eligibility by tumor characteristics as determined by the local pathologist.

Both the breast diagnostic biopsy specimen and a final breast surgery specimen have to be submitted for Central Pathology Review.

17.2. Submitting pathology material to IBCSG

The following items are required for all patients:

1. Pathology Report (including steroid hormone receptor, HER2 and Ki67) of the diagnostic core biopsy
2. Pathology Report (including steroid hormone receptor, HER2 and Ki67) of the definitive surgery
3. Tumor block for banking from diagnostic core biopsy
4. Tumor block for banking from definitive surgery. This should include at least 5mm invasive tumor and a minor component of normal breast tissue (whenever it is available). Please notify the pathologist of this requirement in advance.
5. Representative H & E sections of the above blocks

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

All Pathology Reports, and FFPE blocks must be marked with the IBCSG Patient ID number. Please erase or black out any other identifiers like name or date of birth. Refer to the IBCSG website for additional FFPE specimen shipping recommendations.

Mailing address for the FFPE blocks, H&E slides and Pathology Reports:

IBCSG Central Pathology Office
European Institute of Oncology, EIO
Division of Pathology
Via Ripamonti 435
20141 Milano, Italy E-mail: pathology.ibcsg@ieo.it

Both Pathology Reports should also be submitted by Fax to DataFax.

17.3. Banking biological material

All FFPE blocks will be banked in the IBCSG Tissue Bank, to have available for Translational Research. If the return of the block is requested, cores (2-4 cores, 1mm thick) for tissue microarray (TMA) construction and cores (2-3 cores, 1mm thick) for banking for future translational research will be taken. DNA will be extracted.

All biological material will be logged in the IBCSG Pathology Material Tracking System /Translational Research System and banked in the IBCSG Tissue Bank.

The use of the biological material 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 Ethics Committee. As part of the Informed Consent process, patients are asked to indicate whether they agree to donate their sample for unspecified future research. The patient's decision is recorded on the IBCSG Confirmation of Registration (41-A) Form.

17.4. Blood samples

For determination of FSH, LH, E2 by the central laboratory, serum samples have to be taken and stored at -80°C at day 1 of treatment **before the administration of the first dose**, thereafter at 24 and 72 hours, 7 days and 14 days after first injection, and on day 1 of cycles 2 to 6, **before the administration of the next dose**. Serum has to be extracted and stored at -80°C locally at the Participating Center. At the end of the trial, samples will be collected by courier and sent to:

Harriet Johansson
Lab Senior Assistant
Division of Cancer Prevention and Genetics
European Institute of Oncology

Via Ripamonti 435, 20141 Milan, Italy,

Samples will be analyzed for FSH and LH. Then they will be batch shipped to the laboratory of Prof. Frank Stanczyk for the determination of E2 levels (primary endpoint of the trial):

Prof. Frank Stanczyk
Reproductive Endocrine Research Laboratory
USC Keck School of Medicine
Women's & Children's Hospital
1240 N. Mission Rd., Room 1M2
Los Angeles, CA 90033, USA

Please consult the Blood Sample Logistics Manual for details.

18. Ethical aspects, regulatory approval, and patient informed consent

The Investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997) or with local law if it affords greater protection to the patient. For studies conducted in the EU/EEA countries, the Investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC).

18.1. Ethical Review Board/Ethics Committee

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

Any modifications made to the protocol will be reviewed by the IBCSG Ethics Committee and must also be submitted to the appropriate ERB/IRB for information or approval in accordance with local procedures and regulatory requirements and to Health Authorities if required.

Once approved or acknowledged by the appropriate ERB/IRB and by the Health Authorities (if required), the Investigator shall implement the protocol modifications. Protocol modifications for urgent safety matters may be directly implemented following the instructions of IBCSG.

18.2. Regulatory approval procedures

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

18.3. Protection of human subjects

The IBCSG has an Office for Human Research Protection (OHRP) Federal Wide Assurance (FWA00009439) and follows all of the policies and procedures that are part of that assurance. All potential subjects for this trial will receive a full explanation of the trial, its purpose, treatments, risks, benefits, and all of the other items listed in Section 18.4. Additional institution-specific sections should be added to Appendix I as described in section 18.4.

The medical record must be available for review by the IBCSG audit team and regulatory authorities as described in section 19.5.

Serious Adverse Event (SAE) Reports are distributed monthly. In addition they are available on the IBCSG website (www.ibcsg.org) for participating Centers.

18.4. Informed Consent

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

The "Declaration of Helsinki" recommends that consent be obtained from each potential patient in biomedical research trials after the aims, methods, anticipated benefits, and potential hazards of the trial, and discomfort it may entail, are explained to the individual by

the physician (http://www.wma.net/en/30publications/10policies/b3/index.html). The potential patient should also be informed of her right to not participate or to withdraw from the trial at any time. The patient should be told that material from her tumor will be stored and potentially used for additional studies not described in this protocol.

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

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

18.5. Premature withdrawal

18.5.1. Withdrawal from trial treatment

Patients have the right to refuse further trial treatment at any time during the trial. Patients may also be withdrawn at any time from trial treatment at the discretion of the Investigator due to an adverse event, or based on any other relevant medical condition. Such patients will remain in the trial and will proceed to surgery. The patient will continue to be documented according to protocol.

18.5.2. Change of consent

Patients have the right to withdraw consent for further trial participation at any time without having to specify the reason. The data recorded up to the time point of withdrawal will continue to be evaluated in the trial. The Investigator should ask the patient for her consent to continue to be documented according to protocol.

It should be documented in both the medical records and in the eCRF (Form 41-COC) whether it is acceptable for the patient to be documented according to protocol despite her withdrawal of study consent.

19. Governance and Administrative Considerations

19.1. Insurance

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

19.2. Steering Committee

A Steering Committee will be constituted for this trial. The primary responsibilities of the Steering Committee are twofold. First, the Steering Committee is responsible for maintaining the scientific integrity of the trial, for example, by recommending changes to the protocol in light of emerging clinical or scientific data from other trials. Second, the Steering Committee is responsible for the translation of recommendations of the IBCSG Data and Safety Monitoring Committee into decisions. Membership will include IBCSG officials, study chair and co-chairs, trial statisticians, representatives from some Participating Centers, and representatives from Ferring Pharmaceuticals.

General partition of responsibilities:

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

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

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

19.3. Data and Safety Monitoring Committee (DSMC)

The trial will be presented for review to the IBCSG Data and Safety Monitoring Committee (DSMC) at each of their semi-annual meetings. Accrual and safety will be monitored.

19.4. Premature discontinuation of the trial

The trial may be discontinued early in parts or completely if the information on the trial treatment leads to doubt as to the benefit/risk ratio.

19.5. Quality Assurance

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

The Investigator should ensure that source documents are made available to appropriately qualified personnel from IBCSG or its designees, or to health authority inspectors after appropriate notification.

Ferring-designated staff and quality assurance auditors may audit the conduct of any site and shall be granted reasonable access to facilities during normal business hours. Such auditors shall not be entitled to access, make copies of the source documents and/or to take them away.

At regular intervals during the clinical trial, the Center will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient Informed Consent, patient recruitment and follow-up, SAE documentation and reporting, AEs with pre-specified monitoring documentation and reporting, AE documentation, trial treatment administration, patient

compliance with the regimens, drug accountability, concomitant therapy use and quality of data.

19.6. Data protection

A unique Patient Identification Number (ID) will be assigned by the IBCSG Registration/ Randomization System to each patient randomized into the trial. The names of the patients will not be disclosed to the IBCSG.

Only the Patient ID will be used to identify a patient on the eCRF. Identification of patients must be guaranteed at the Participating Center. In order to avoid identification errors, Centers should keep a Patient Identification Log containing the patients' name, year of birth, hospital number and the Patient ID allocated by IBCSG.

Regulatory authorities and the pertinent Ethics Committee (ERB/IRB) may have access to patient data on-site. IBCSG audit or monitoring personnel will also have access to such data on-site.

19.7. Record Retention

The Center must retain all essential documents according to ICH GCP. This includes copies of the patient trial records, which are considered as source data, patient Informed Consent statement, laboratory printouts, drug inventory and destruction logs, and all other information collected during the trial. These documents are to be stored until at least 15 years after the termination of the trial. IBCSG guarantees access and availability of the data entered into iDataFax for at least 15 years after the termination of the trial.

Longer retention may be required for Participating Centers according to national regulations.

In the event that the Principal Investigator retires or changes employment, custody of the records may be transferred to another competent person who will accept responsibility for those records. Written notice of such transfer has to be given to IBCSG and the local Ethics Committee at least one month in advance.

20. Confidentiality

The protocol, eCRFs and other protocol-related documents are confidential and are the property of the IBCSG.

21. References

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22. List of abbreviations

AE	Adverse event
CI	Confidence interval
CR	Complete response
CRF	Case report form
NCI CTCAE	National Cancer Institute common toxicity criteria for adverse events
DMC	Data Management Center (IBCSG)
DSMC	Data and Safety Monitoring Committee
ECOG PS	Eastern Cooperative Oncology Group Performance Status
E2	17-β-estradiol
eCRF	Electronic case report form
ER	Estrogen receptor
FFPE	Formalin fixed paraffin embedded
FSH	follicle-stimulating hormone
FSTRF	Frontier Science and Technology Research Foundation
GCP	Good clinical practice
GnRH	Gonadotropin-releasing hormone
H&E	Hematoxylin and eosin
HER2	Human epidermal growth factor 2
HR	Hazard ratio
i.m.	intramuscular
IBCSG	International Breast Cancer Study Group
IC	Informed Consent
ICH	International conference on harmonization
iDF	iDataFax
INN	International Non-proprietary Name
IUN	Intra-Uterine Device
LH	luteinizing hormone

LHRH	luteinizing hormone-releasing hormone
OS	Overall survival
PFS	Progression-free survival
PgR	Progesterone receptor
PD	Progressive disease
PEPI	Preoperative Endocrine Prognostic Index
PR	Partial response
PRS	Patient-reported symptoms
s.c.	subcutaneous
SAE	Serious adverse event
SD	Stable disease
SERM	selective estrogen receptor modulator
SPC	Summary of product characteristics
ULN	Upper limit of normal
USAN	United States Adopted Name
WHO	World Health Organization