A PHASE III MULTICENTRE DOUBLE BLIND RANDOMISED TRIAL OF CELECOXIB VERSUS PLACEBO IN PRIMARY BREAST CANCER PATIENTS (REACT – RANDOMISED EUROPEAN CELECOXIB TRIAL)

ICCG C/20/01, GBG 27, BIG 1- 03, ISRCTN NO: 48254013, EUDRACT NO: 2004-00004939

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GERMAN BREAST GROUP

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AN INTER COOPERATIVE GROUP STUDY

PROTOCOL – VERSION 39, 01.11.2016

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A PHASE III MULTICENTRE DOUBLE BLIND RANDOMISED TRIAL OF CELECOXIB VERSUS PLACEBO IN PRIMARY BREAST CANCER PATIENTS

and agree to conduct the trial in compliance with the study protocol and to ensure that all data are recorded, reported and maintained in accordance with the protocol. I agree to provide all research personnel involved with the study with copies of the protocol and medication information.

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INVESTIGATOR'S AGREEMENT

Ich habe den folgenden Prüfplan der German Breast Group gelesen:

EINE MULTIZENTRISCHE, DOPPELBLINDE, RANDOMISIERTE STUDIE DER PHASE III ZUM VERGLEICH VON CELECOXIB VERSUS PLACEBO BEI PATIENTINNEN MIT PRIMÄREM MAMMAKARZINOM (REACT – Randomised EuropeAn Celecoxib Trial) Prüfplan - Amendment 4 (Version 38, 29/09/2015)

und versichere, dass er alle notwendigen Angaben zur Durchführung der Studie enthält. Ich werde die Studie wie hierin vorgesehen durchführen. Ich werde allen an der Durchführung der Studie beteiligten Ärzten Kopien des Prüfplans und Arzneimittelinformationen zur Verfügung stellen. Ich versichere, dass eine ordnungsgemäße Dokumentation aller mit der Studie in Zusammenhang stehenden Daten erfolgt.

Leitender Klinischer Prüfarzt:

Datum: 01.11.2016 Unterschrift: 

Prof. Dr. G. von Minckwitz

Prüfärztin / Prüfarzt:

Datum: _____ Unterschrift: _____

Stempel oder Name in Blockschrift

Table of Contents

1 Abbreviations

ACE	Angiotensin Converting Enzyme
ADAPT	Alzheimer's Disease Anti-Inflammatory Prevention Trial
ALP	Alkaline Phosphatase
ANC	Absolute Neutrophil Count
APC	Adenoma Prevention with Celecoxib
AUC	Area Under Curve
CDC	Coordinating Data Centre
COX	Cyclo-oxygenase
CRF	Case Report Form
DCIS	Ductal Carcinoma In Situ
DFS	Disease free Survival
ECG	Electrocardiogram
ER	Oestrogen receptor
FISH	Fluorescent In Situ Hybridisation
GBG	German Breast Group
GnRH	Gonadotropin-releasing hormone
Hb	Haemoglobin
HER2	Human Epidermal growth factor Receptor
HR	Hormone Receptor
ICCG	International Collaborative Cancer group
ICR-CTSU	Instiute of Cancer Research Clinical Trials and Statistics Unit
IDMC	Independent Data Monitoring Committee
IEC	Institution Ethics Committee
IES	Intergroup Exemestane Study
IRB	Institution Review Board
NADH	Nicotinamide Adenine Dinucleotide Phosphate Hydrogen
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NYHA	New York Heart Association
OS	Overall Survival
PG	Prostaglandin
PgR	Progesterone receptor
PreSAP	Prevention of Spontaneous Adenomatous Polyps
QD	Once Daily
QOD	Every other day
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Event
TMG	Trial Management Group
TX	Thromboxane
WBC	White Blood Cells

2 TRIAL SUMMARY

Title	A phase III, multicentre, double blind, randomised trial of celecoxib versus placebo in primary breast cancer patients.
Study Objectives	The primary aim is to assess the disease free survival (DFS) benefit of two years adjuvant therapy with the COX-2 inhibitor celecoxib compared with placebo in primary breast cancer patients.
Study Design	A multicentre, phase III, randomised, double-blind, placebo-controlled trial. Patients are randomised between two years celecoxib and placebo in a 2:1 ratio in favour of celecoxib.
Sample Size	2590 patients
Main Eligibility Criteria	Completely resected breast cancer. Entry into the study must be within 4 months of day 1 of the last cycle of adjuvant chemotherapy or within 3 months of the end of surgery, or within 6 weeks of the end of radiotherapy. Patients can have radiotherapy concurrently with study drug. Node negative, T1, Grade 1 patients are excluded. Her 2 +++ or FISH positive patients are excluded. All HR negative patients MUST have received chemotherapy.
Treatment	400mg celecoxib/placebo once daily for a total of 2 years. HR positive patients will also receive endocrine therapy according to local practice.
Follow up in UK	Year 1 Baseline and months 3, 6 and 12 Year 2 & 3 6 monthly (months 18, 24, 30 & 36) Year 4 & 5 annually (months 48 & 60) Year 6 – 10* annual follow up
Follow up in Germany	On-treatment follow up: Year 1 Baseline and months 3, 6 and 12 Year 2 6 monthly (months 18, 24) Off-treatment follow up: Year 3 – 10* Information on the health status and late side-effects of the patient will be collected at least annually using a self-reporting system via a patient questionnaire, chart reviews at the sites or based on information deriving from the GBG registry of previous study participants * Should cost effective, reliable systems be in place, for example electronic methods of routine data collection, and at the discretion of the Trial Steering Committee, off-treatment follow up may continue beyond 10 years
Primary Endpoint	Disease free survival

Secondary Endpoints

- Overall survival.
- Toxicity associated with long term use of celecoxib in primary breast cancer patients.
- Cardiovascular mortality.
- Incidence of second primaries.
- Subgroup analysis based on HR status (HR+ve, HR-ve) will be performed using the same endpoints as in the analysis of all patients.

3 BACKGROUND AND INTRODUCTION

3.1 Celecoxib as adjuvant therapy for primary breast cancer

It has long been recognised that there is an association between chronic immune activation and cancer but the mechanisms behind this observation are not fully understood (O'Byrne and Dalgleish, 2001). The inflammatory process may provide an environment for development of malignant disease, with mediators of inflammatory response such as the cyclo-oxygenases playing an important role and providing a target for therapeutic intervention.

Prostaglandins (PGs) are synthesised from phospholipids by the action of phospholipase A2 and cyclo-oxygenases. Cyclo-oxygenase (COX) -1 differs from COX-2 in that the latter is inducible and its expression is induced by a large range of oncogenes and growth factors. Celecoxib is a selective COX-2 inhibitor that does not cause the effects of COX-1 inhibition, namely gastrointestinal ulceration (Emery et al, 1999; Waddell and Loughry, 1983). Celecoxib is currently available for clinical use in Europe and the US for the treatment of chronic arthritic conditions.

The key regulatory step in this process is the enzymatic conversion of fatty acids to PGG2 and PGH2 by COX. PGH2 is subsequently converted to one of several structurally related PGs including PGE2, PGD2, PGF2, and thromboxane A2 (TxA2), by the activity of specific PG synthases. PGs have important functions in every organ system and regulate a variety of physiological functions such as immunity, maintenance of vascular integrity and bone metabolism. COX-2 is not normally expressed in most tissues, but is induced by a wide spectrum of growth factors and pro-inflammatory cytokines in specific pathophysiological conditions. (Smith et al, 2000; Smith et al, 1996). The expression of COX-2 is highly induced in cells transformed with the oncogene v-src (Xie et al, 1991) or treated with phorbol esters. (Kujubu et al, 1991).

Several studies have suggested an association between non-steroidal anti-inflammatory drug (NSAID) consumption and decreased breast cancer risk. These include the studies of Friedman and Ury (1980) and Harris et al (1996), the latter showing a reduction to 66% in women who were treated with NSAIDs for more than one year. A further two studies also showed a reduction in incidence (Schreinemachers and Everson, 1994; Sharpe et al, 2000). There are a number of potential mechanisms that can be evoked to explain these findings, including the inhibition of procarcinogen activation and formation, tumour cell invasion and metastasis, induction of apoptosis, inhibition of angiogenesis and endothelial tube formation (Elder et al, 1996; Sheng et al, 1997).

Elevated COX expression in breast cancer was suggested some time ago by the finding of elevated PG production in breast tumours (Bennett et al, 1977); PGs are also known to be involved in invasion (Liu and Rose, 1996). COX-2 is expressed in breast cancers (Parrett et al, 1997) and can be detected by immunohistochemistry (Soslow et al, 2000). COX-2 overexpression in mice resulted in mammary tumour development in 85% of mice (Liu et al, 2001). COX-2 expression seems associated with c-erbB2 expression (Subbaramaiah et al, 1999) and with aromatase content (Brueggemeier et al, 1999). These observations suggest that COX-2 inhibition could have a role to play in enhancing treatment directed at either of these molecular targets.

Colorectal polyps may disappear in patients taking NSAIDs for pain relief (Waddell and Loughry, 1983; Giovanucci et al, 1994; Giovanucci et al, 1995; Thun et al, 1991; Labayle et al, 1991; Nugent et al, 1993; Giardiello et al, 1993). These studies used NSAIDs that inhibit both COX-1 and COX-2; encouraging results have also been obtained with the selective COX-2 inhibitor, celecoxib (Steinbach; 2000). There is pharmacological and genetic evidence to indicate that a significant component of the anticancer property of NSAIDs is due to their ability to inhibit the COX-2 enzyme. The role for COX-2 in promoting tumour–associated angiogenesis has been clarified by Dormond and co-workers (Dormond et al, 2001).

COX-2 inhibition plays a role in the prevention of a number of cancer types, in addition to breast, and may also have a role in treatment. Studies using twice daily celecoxib include:

- Phase III Neoadjuvant trial of pre-operative exemestane or letrozole +/- celecoxib in the treatment of ER positive postmenopausal early breast cancer [Neo-Excel] (A UK study, currently being initiated by P. Canney)
- NCI/MSKCC phase 2 study of celecoxib and herceptin in women with HER2+ metastatic breast cancer refractory to herceptin. Treatment continues until disease progression/toxicity.
- NCI phase 1 randomised study of 6 weeks neoadjuvant celecoxib for localised prostate cancer
- RTOG phase 1/2 study of external beam radiotherapy and brachytherapy, celecoxib,
- NCI/UCSF randomised phase 2 study of two years celecoxib for prevention of basal cell carcinoma in patients with basal cell naevus syndrome.

NSAIDs and specific COX-2 inhibitors can inhibit solid tumour cell proliferation both in vitro and in vivo. Two separate animal studies have shown that selective COX-2 inhibitors can prevent mammary tumour formation, reducing the incidence by up to 85% (Harris et al, 2000; Nakatsugi et al, 2000). Recently these results have been confirmed by Rozic et al (2001) who also observed the anti-angiogenic activity of COX-2 antagonists. COX-2 inhibition can reverse resistance to apoptosis (Tsujii et al, 1995) and has been implicated in growth factor production which stimulates angiogenesis (Tsujii et al, 1998).

A principal attraction of selective COX-2 antagonists is the lower incidence of side effects compared with other NSAIDs. Thus, in a study published in 2000 with more than 8000 patients with osteoarthrosis who received celecoxib 400mg twice daily for a period of 6 months , the incidence of gastrointestinal side-effects, including gastrointestinal bleeding and dyspepsia, was reduced (Silverstein et al, 2000).

3.2 Dosage and Duration of Celecoxib

Since COX-2 inhibitors do not inhibit COX-1, it is expected that they will not interfere with homeostatic prostanoid-dependent processes such as upper gastrointestinal tract mucosal protection and platelet aggregation. A recent randomised study (Simon et al, 1999) compares side effects of celecoxib in patients randomised to 100mg, 200mg or 400 mg (twice daily) with naproxen, 500mg (twice daily), in 1149 patients with rheumatoid arthritis. The overall incidence of gastrointestinal tract adverse effects was 19% for placebo, 28%, 25% and 26% for celecoxib at 200mg, 400mg, and 800mg/day respectively, compared with 31% for naproxen.

The long term use of celecoxib has recently been evaluated in two trials comparing celecoxib to placebo in subjects at risk for spontaneous adenomatous polyposis.In the Adenoma Prevention with Celecoxib (APC)

study, participants were randomly assigned to take either 200mg of celecoxib twice a day, 400mg of celecoxib twice a day, or placebo for 3 years. At the time of analysis 77% of the 2035 patients had completed the study and all of the remaining surviving patients had completed at least 2.8 years of follow up. A composite cardiovascular endpoint of death from cardiovascular causes, myocardial infarction, stroke or heart failure was reached in 7 of 679 patients in the placebo group (1%) as compared with 16 of 685 patients receiving 200mg of celecoxib twice daily (2.3%; hazard ratio, 2.3; 95% CI, 0.9 to 5.5 and with 23 of 671 patients receiving 400mg of celecoxib twice daily (3.4%; hazard ratio, 3.4; 95% CI, 1.4 to 7.8 (Soloman et al, 2005).

In contrast, preliminary results from the Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial showed no apparent increase in cardiovascular risk. Preliminary data released in December 2004 stated a 1.8% incidence (11 events) of cardiovascular events in the placebo group (n=628) in comparison to 1.7% incidence (16 events) of cardiovascular events in those taking celecoxib 400mg daily (n=933). The analysis performed on the findings in this trial and in the APC trial, which demonstrated an increased risk of events with celecoxib, were identical, having been performed by the same independent cardiovascular safety review committee. In the PreSAP trial, however, the review committee determined that those patients on celecoxib demonstrated no increased risk in cardiovascular events compared to those taking placebo. The difference in the dosing regimens between these two trials – twice daily in the APC study as compared with once daily in the PreSAP study supports the hypothesis that sustained inhibition of prostacyclin may contribute to the increase in cardiovascular risk. However other potential differences in the trials, including geographic differences, differences in the patient population, and differences in use of concomitant medications, may also have contriibuted to the disparity in the preliminary findings.

Another trial whose findings contrast with the APC study was the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), a study designed to assess the efficacy of celecoxib in the prevention of Alzheimer's disease. The study involved 750 patients of >70 years old, who were treated for up to 3 years with naproxen 220mg twice daily, celecoxib twice daily or placebo. Preliminary results from this study showed a 50% increased risk of cardiovascular events in patients who were on the naproxen regimen compared to placebo but not celecoxib relative to placebo.

In another study, arthritis patients were randomised to receive celecoxib 400mg twice daily, ibuprofen 800mg 3 times daily or diclofenac 75mg twice daily. The incidences of serious cardiovascular thromobembolic events were not significantly different (< 1.5% in all arms) between celecoxib and NSAID comparators.

In a meta-anaysis of randomised trials in patients receiving celecoxib, there was no increased cardiovascular risk with celecoxib relative to placebo and it demonstrated a comparable rate of cardiovascular events with celecoxib treatment compared with nonselective NSAIDS (White 2007).

A meta-analysis has shown a significant reduction in myocardial infarction in women treated with tamoxifen (Braithwaite 2003). Recent evidence from an epidemiological study using the General Practice Research Database also suggests that tamoxifen therapy reduces the risk of myocardial infarction and angina (Bradbury 2005) and in results from the EBCTG Overview 2005, patients who were treated with 5 years tamoxifen had no excess of CV deaths overall (death rate ratio = 0.968 [SE 0.11] NS) which was consistent with decreased risk of cardiac events (death rate ratio = 0.79 [SE =0.11] 2P =0.06) (EBCTCG 2005).

As regards concurrent administration of celecoxib with the other main class of endocrine therapies, the Aromatase Inhibitors, a recent review and analysis of patients with metastatic or locally advanced breast cancer has concluded that the combination of celecoxib and an AI (in this case, exemestane) had similar cardiac side- effects when compared to exemestane alone (Falandry et al, Ann Oncology, 2008). A more recent meta-analysis of all studies comparing AIs with placebo has concluded that there may be a slight increase in cardiac events (<1%) in those patients receiving up-front AI, but this was not observed in patients pre-treated with tamoxifen (Amir E etal, 2011. JNCI).

3.3 Pharmacokinetics of Celecoxib

The following has been obtained from the Investigator Brochure, December 2012 . Absorption: peak plasma levels of celecoxib occur approximately three hours after an oral dose. Under fasting conditions, both peak plasma levels (Cmax) and area under the curve (AUC) are roughly dose proportional up to 200mg BID; at higher doses, there are less than proportional increases in Cmax and AUC. Absolute bioavailability studies have not been conducted. With multiple dosing, steady state conditions are reached on or before day 5. The pharmacokinetic parameters of celecoxib in a group of healthy subjects are as follows: Cmax 705ng/ml; Tmax 2.8, t½ 11.2. In healthy subjects, ~97% celecoxib is protein bound within the clinical dose range. Celecoxib is eliminated predominantly by hepatic metabolism with <1% unchanged drug recovered in the urine. At higher doses (400mg twice daily) celecoxib should be administered with food.

3.4 Rationale for the use of Celecoxib

In summary, therefore, there are multiple reasons for initiating a randomised study to examine the impact of COX-2 inhibition in enhancing the adjuvant treatment of breast cancer - as follows:

- inhibition of angiogenesis
- inhibition of cell growth
- inhibition of tumour-associated inflammation
- inhibition of invasion
- promotion of apoptosis

The conventional way of evaluating a novel anti-cancer compound in the adjuvant setting would be to carry out a formal study in patients with metastatic disease of a variety of solid tumours and then proceed to phase 2 studies in patients with metastatic breast cancer. However, in this instance, this is not felt to be the appropriate way forward for two reasons: firstly, many thousands of patients have already received celecoxib at the proposed dose, and it is much less toxic than either conventional NSAIDs or chemotherapy, with a withdrawal rate of 2-4%, and no attributable deaths; secondly, there is a wealth of data to show that NSAIDs prevent tumour progression in animal models and carcinogenesis in humans. Furthermore, the mechanisms susceptible to COX-2 inhibition (see above) are likely to be operative in the micrometastatic situation, rather than in the context of advanced disease. For these reasons, we do not believe that the conventional route from metastatic to adjuvant therapy should necessarily be followed.

3.5 Risk Benefit Assessement

From completed studies to date, the following drug related adverse events are considered to be expected and common following treatment wit celecoxib: abdominal pain, diarrhea, dyspepsia, flatulence, peripheral edema, dizziness, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection and rash.

Cardiovascular Risk

Celecoxib may cause an increased risk of serious cardiovascular thrombotic events, myocardial infraction and stroke, which can be fatal. All NSAIDs may have similar risk. This risk may increase with the duration of use. Patients with cardiocasvular disease or risk factors for cardiovascular disease are at greater risk. A cardiovascular assessment is carried out during screening to exclude patients at risk. Patients on study treatment will be monitored and will have a cardiovascular assessment at 12 months visit and at end of treatment (normally 24 months).

Gastrointestinal Risk

Celecoxib as other NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach and intestines, which can be fatal. These events can occur at any time during use and without warning symtoms. Elderly patients are at greateser risk of serious gastrointestinal events. Patiens will need to be advised to be alert and to report any symtomps of stomach bleed.

Hepatic Effects

Borderline elevations of one or more liver-associated enzymes may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including Celecoxib. In controlled clinical trials of Celecoxib, the incidence of borderline elevations (greater than or equal to 1.2 times and less than 3 times the upper limit of normal) of liver associated enzymes was 6% for Celecoxib and 5% for placebo, and approximately 0.2% of patients taking Celecoxib and 0.3% of patients taking placebo had notable elevations of ALT and AST. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), Celecoxib should be discontinued.

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, ACE-inhibitors, angiotensin II receptor antagonists, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with Celecoxib have shown renal effects similar to those observed with comparator NSAIDs. No information is available from controlled clinical studies regarding the use of Celecoxib in patients with

advanced renal disease. Therefore, treatment with Celecoxib is not recommended in these patients with advanced renal disease.

Potential Benefit

Celecoxib has been widely used across the world and has a well-established safety profile. Studies have showed that COX-2 inhibition plays a role in the prevention of cancer and may also play a role in treatment as discussed in section 3.1.Therefore, the proposed study will assess the potential of COX-2 inhibitors as "maintenance therapy", following surgery with or without chemotherapy (+ or - radiotherapy), to improve disease free survival of patients with primary breast cancer.

Overall Risk Benefit

Although there can be no certainty of clinical benefit to patients, studies have showed that the use of NSAIDs and specific COX-2 inhibitors can inhibit tumour cell proliferation both *in vivo* and *in vitro*. It has been shown that patients exposed to selective COX-2 antagonists have fewer incidences of GI side effects when compared with other NSAIDs. In addition to this, clinical data for hormone receptor positive patients showed that the concomitant use of celecoxib and hormone treatment is considered to be safe. Thus, the risk-benefit assessment for this study supports the safe oral administration of celecoxib (400 mgs daily) for patients with primary breast cancer according to the proposed study design.

4 STUDY OBJECTIVES

4.1 Primary Objective

To assess the disease free survival (DFS) benefit of two years adjuvant therapy with the COX-2 inhibitor celecoxib compared with placebo in primary breast cancer patients.

4.2 Secondary Objectives

- To compare overall survival
- To define the safety of adjuvant therapy with celecoxib in this patient population
- To compare incidence of second primary breast cancers
- To assess tolerability of celecoxib with hormone therapy.
- To assess DFS benefit of two years adjuvant celecoxib compared with placebo in HR positive (i.e. ER positive and/or PR positive) and in HR negative (i.e. ER negative/PR negative) disease.

4.3 Tertiary Objectives

To investigate COX-2 level and other tumour-associated proteins in the tumour tissue and relate these findings to the trial outcome.

5 TRIAL ORGANISATION

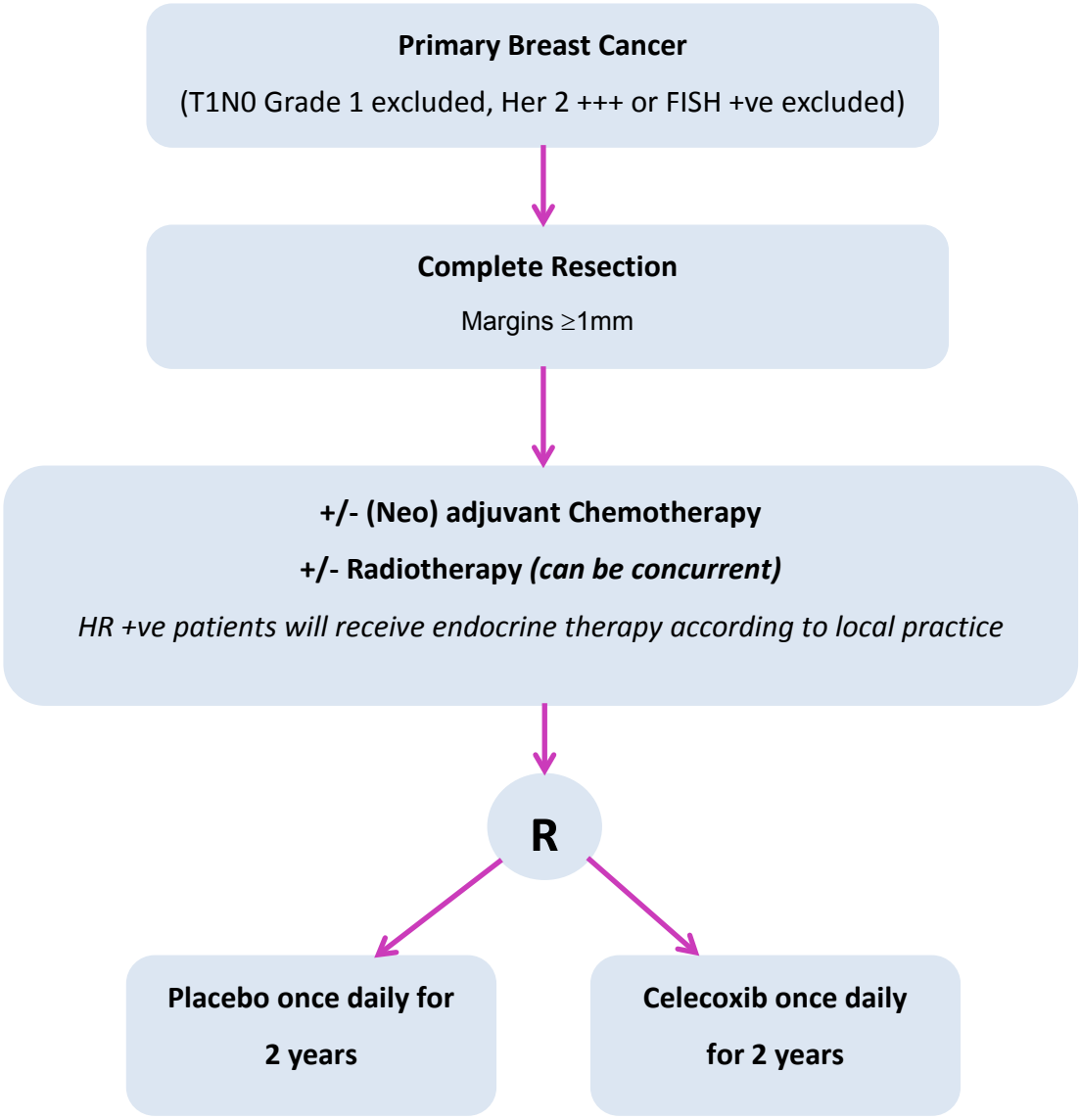
This is an intergroup co-operative multicentre, randomised, double blind, placebo-controlled trial.

This trial has been developed by the Steering Committee of the International Collaborative Cancer Group (ICCG) and the German Breast Group (GBG) and will be run under the auspices of the Breast International Group (BIG). The trial will be co-ordinated jointly by the ICCG Data Centre located at the Charing Cross campus of Imperial College London, with support from the Institute of Cancer Research Clinical Trials and Statistics Unit and by the GBG Forschungsgesellschaft mbH.

In this study, the two Coordinating Data Centres (CDCs) will be responsible for the overall conduct of the trial and the collection of data. An Independent Data Monitoring Committee (IDMC) will be appointed to review safety and efficacy data, in confidence, on a regular basis as they see fit, but at least annually.

6 TRIAL DESIGN

A phase III, multicentre, double-blind, placebo controlled, randomised trial. Patients are randomised between two years celecoxib and placebo in a 2:1 ratio in favour of celecoxib.



7 PATIENT SELECTION

7.1 Chemotherapy Treatment for Primary Disease

Prior to randomisation, patients may have received chemotherapy[1]. Any patients who have received chemotherapy should have finished their treatment at least three weeks prior to randomisation, and must have received at least 4 cycles. The schedule of preference is FEC 3-weekly for 6 courses, however, other dose schedules of FEC or FAC plus combinations that contain EC/AC followed by a taxane, or Epirubicin/Doxorubicin plus a taxane are permitted. CMF may be substituted for patients where Epirubicin is contraindicated. (See Appendix II for recommended chemotherapy regimens). All patients should have an electrocardiogram (ECG) and clinical cardio-vascular assessment before randomisation, at the 12 month visit and at the end of celecoxib/placebo therapy (normally at 24 month visit). If treatment is terminated early a cardiovascular assessment and ECG must be performed as soon as possible, but no further cardiac assessments are required by the protocol.

As the trial is open to patients who may or may not have received chemotherapy, it is recommended that eligible patients in the UK should be identified at the hospital multidisciplinary team meetings and referred to the local investigator. All patients will receive further information about the study, including the patient information sheet prior to consent.

7.2 Participation in Other Studies

Patients previously entered into interventional trials, regardless of endpoint, can only be entered into the study provided that the Trial's Steering Committee and/or Management Group (as applicable) approve participation in REACT. The treatment phase of any interventional trial should have finished before patients start taking celecoxib/ placebo. In addition, the REACT Trial Management Group (TMG) needs to be informed of this decision. Trials of neo-adjuvant chemotherapy where the primary endpoint is pathological tumour response are permitted with the prior consent of the REACT TMG.

7.3 Inclusion Criteria

All the following criteria must be fulfilled for study entry:

1. Completely resected (≥1mm), histologically or cytologically proven unilateral breast cancer.
2. Female ≥18 years of age, no upper age limit
3. If (neo)adjuvant chemotherapy has been received, then the patient must have received at least 4 cycles. Patients must have completed chemotherapy prior to study entry.
4. HR negative women must have received prior chemotherapy.
5. Study entry must be within **any** of the following timelines:
   - 3 months of the end of definitive breast surgery OR
   - Between 3 weeks and 4 months after day 1 of the last cycle of adjuvant chemotherapy OR
   - 6 weeks of the end of radiotherapy.
6. World Health Organisation (WHO) performance status 0 or 1
7. Pre-treatment haematology and biochemistry values within acceptable local limits:
   - Haemoglobin (as per local ranges)

[1] All HR negative patients MUST have received chemotherapy prior to study entry.

- WBC $\geq 3.0 \times 10^9$/l or ANC $\geq 1.5 \times 10^9$/l
- Platelets $\geq 100 \times 10^9$/l
- Serum bilirubin <1.5 x UNL
- Alkaline phosphatase $\leq 1.5 \times$ UNL
- Serum creatinine < $1.5 \times$ UNL

8. Negative pregnancy test in patients of child-bearing potential.
9. Normal baseline ECG and normal clinical cardiovascular assessment after completion of all (neo) adjuvant chemotherapy.
10. No previous or current evidence for metastatic disease.
11. Be accessible for and consent to long term follow-up.
12. Written informed consent prior to commencement of specific protocol procedures must be obtained and documented according to the local regulatory requirements.

A randomisation form detailing basic eligibility and identifying information must be received before the patient can be randomised.

7.4 Exclusion Criteria

Any patient with any of the following criteria will **not** be eligible for randomisation:

1. Patients with node negative, T1, Grade 1 breast cancer.
2. Unresectable, metastatic or bilateral breast cancer.
3. Active or previous peptic ulceration or gastrointestinal bleeding in the last year.
4. Active or previous history of inflammatory bowel disease.
5. A past history of adverse reaction/hypersensitivity to NSAIDs, including celecoxib and salicylates, or sulphonamides.
6. On current or planned chronic NSAIDs therapy (except low dose aspirin $\leq$ 100 mg QD or 325mg QOD). Chronic use of NSAIDs is defined as a frequency of 1 or more a day, for more than a total of 6 weeks per year.
7. Current or long-term use of oral corticosteroids.
8. Known or suspected congestive heart failure (>NYHA I) and/or coronary heart disease, previous history of myocardial infarction, uncontrolled arterial hypertension (ie BP >160/90mmHg) under treatment with two anti-hypertensive drugs, rhythm abnormalities requiring permanent treatment. ECG should be considered within normal limits by a clinician prior to starting trial therapy. Echocardiogram although not essential can be carried out if the investigator judges it to be necessary.
9. Patients with diabetes controlled by diet and oral medication are eligible for the study however patients with insulin dependent diabetes are excluded.
10. Past history of stroke/TIA, symptomatic peripheral vascular disease or carotid disease.
11. Previously entered into an adjuvant chemotherapy trial for which approval for entry into REACT has not been granted by the Steering Committee/Management Group of the other trial.
12. ER receptor status unknown.
13. HER2+++ or FISH positive, or HER 2 status unknown.
14. HR negative and not received (neo)adjuvant chemotherapy
15. Use of hormone replacement therapy within the last 6 weeks.

16. Pregnant or lactating women or women of childbearing potential unwilling or unable to use adequate non-hormonal contraception. No previous or concomitant malignancies except adequately treated squamous cell / basal cell carcinoma of the skin, in situ carcinoma of the cervix or DCIS/LCIS of the breast, unless there has been a disease-free interval of 10 years or more.
17. Psychiatric or addictive disorders which could preclude obtaining informed consent.
18. Clinical evidence of severe osteoporosis and/or history of osteoporotic fracture.

Note: Use of Bisphosphonates for clinical purposes is not an exclusion criterion.

7.5 Entry Procedure

Assessments required pre-randomisation:

- Complete history and physical examination (within 4 weeks before randomisation)
- WHO Performance Status assessment
- Clinical cardiovascular assessment including cardiac history, blood pressure, pulse, results for HDL and total cholesterol, smoking status and diabetes.
- Baseline ECG (standard 12 lead ECG) within three months of entry in the study to exclude any cardiac condition that would preclude entry into REACT. The ECG should be performed after completion of all (neo) adjuvant chemotherapy. A copy of the ECG obtained at each visit should be sent to the designated CDC. The ECGs and reports must have the identity of the patient protected. Only the patient's initials, trial ID number, date of birth, site number and date of assessment should be included on the report and on the ECG trace.

Note: The baseline ECG does not have to be sent to the CDC before a patient can be randomised.

- Haematology (Hb, WBC or ANC, platelets) & Biochemistry (serum bilirubin, creatinine, alkaline phosphatase), and cholesterol (within 4 weeks before randomisation).
- Pregancy Test (patients of child-bearing potential must have had a negative pregnancy test result within 7 days prior to randomisation. Pregancy test can either be urine or serum based.
- Mammogram at a maximum of 3 months prior to diagnosis of breast cancer. If mammography is part of the current practice in the participating centre or a mammographic screening program is in place, the program should continue and all patients participating in this program should have mammograms performed as scheduled. No additional mammograms (further to routine screening program) will be required as part of the REACT study. Imaging/Examinations, where clinically indicated metastatic disease should be excluded prior to randomisation using investigations according to local practice (i.e. Chest X-ray / CT, liver ultrasound, bone scan). However, it is recommended that in the case of node positive breast cancer with more than 3 positive nodes, that all three of these investigations are performed routinely to exclude metastatic disease.

Also to be recorded:

- Demography (date of birth & ethnic origin).
- Breast cancer history (date of surgery, surgical procedure, size and grade of primary tumour nodal status, ER status, radiotherapy and chemotherapy).
- Concomitant medication (description of classes of concomitant medication taken at the time of randomisation).
- Menopausal status:
  a) Postmenopausal:
     - >12 months since last menstrual period at time of diagnosis OR

- postmenopausal gonadotrophin levels (luteinizing hormone or follicle stimulating hormone levels >40 IU/L) or postmenopausal estradiol levels (<5ng/dL) OR
- prior bilateral oophorectomy OR
- radiation menopause (at least 3 months previously).
- NB Chemotherapy or GnRH induced amenorrhoea is not accepted

b) Perimenopausal:

- Women with irregular periods within 6 months or more prior to diagnosis.

c) Premenopausal

- With patient's specific consent, pathology information relating to tissue to be donated to the central tumour banks.
- With patient's specific consent, hospital and/or health service number.

7.6 Randomisation

Each participating centre should agree its affiliation to one of the CDCs prior to participating in the study. Randomisation will be carried out by one of the CDCs.
Patient randomisation will only be accepted from authorised investigators.
Patients may be randomised within any of these timelines:

- Within 3 months of definitive breast surgery OR
- Within 4 months of day 1 of the last cycle of adjuvant chemotherapy. Patients should have finished chemotherapy prior to randomisation and there should be a gap of at least three weeks between day 1 of the last cycle and the date of randomisation OR
- Within 6 weeks of the end of radiotherapy. Patients can have radiotherapy concurrently with study medication as long as this is not part of a radiotherapy trial.

No patients who have started and terminated chemotherapy before they have received 4 cycles, will be permitted to be randomised.

Centres affiliated to the ICCG will randomise patients by FAX to the ICCG. Centres affiliated to GBG will randomise patients using the MedCODES®-System. All centres will be required to complete a randomisation request form before randomisation.

Confirmation of randomisation will be provided within 24 hours on working days and all patients will be allocated a unique trial identification (ID) number and a box number for the first 12 months of study treatment.

The unique trial identification number consists of eight (8) characters - two letters for the country abbreviation, three digits for the Centre number (i.e. hospital) and three digits for the patient number (within each centre).

This number should be used on all Case Report Forms (CRFs) and all subsequent correspondence relating to that patient.

The CDC will contact the site with a new box number prior to patient resupply at 12 months. Each patient will be assigned unique box numbers and these should be recorded on the designated part of the CRFs.

Separate randomisation lists will be prepared for each participating centre. The randomisation list will provide the link between the patient's trial ID and the drug supply. Copies of the lists will be held by the randomising CDC. If a trial ID has been incorrectly allocated, no attempt should be made to rectify the error but details of the mistake should be recorded, including an appropriate explanation, and forwarded to the CDC immediately. The patient should continue with the number that has been allocated. Allocation of subsequent patients will continue using the first unallocated number from the randomisation list.

8 TREATMENT

Treatment must begin within 14 days after randomisation. Radiotherapy should be given according to local policy (concomitant trial treatment and radiotherapy is permitted provided patients are not receiving treatment as part of a radiotherapy trial). Patients will be randomised 2:1 (in favour of celecoxib) to receive:

Placebo: Two capsules once daily with food **OR**
Celecoxib: Two 200mg capsules once daily (400mg per day) with food

The duration of celecoxib/placebo treatment is 2 years.

Since the trial is double-blind, the patient's specific treatment will not be indicated on the trial supplies or mentioned during the randomisation process. The unique box number allocated at the time of randomisation allows the tracing of each patient's treatment to their allocated treatment code in the case of unblinding (see separate section 8.6 for information on code breaking).

In addition all HR+ve patients will receive endocrine therapy according to local practice. Patients who are eitherHR+ve (both ER+ve/PgR-ve and ER+ve/PgR+ve) or PgR+ve (e.g. ER-ve/PgR+ve) are considered to be HR+ve for the purposes of this study.

8.1 Source of Drug

Pfizer Inc. manufactures celecoxib 200 mg capsules and matching placebo capsules.

8.2 Celecoxib / placebo Packaging and Labels

Pfizer Inc. will supply celecoxib or placebo in white plastic bottles. Drug will be distributed to each participating centre and will be used solely for the treatment of patients in the REACT trial. Each bottle will contain 140 celecoxib 200 mg capsules or matching placebo with a child resistant cap and tamper-evident seal. The box that will be assigned at dispensing will contain 6 bottles of celecoxib/placebo representing a 1 year supply.

The box will be labelled in accordance with Annex 13 and will have a two-part tear-off label, which will contain minimally, the protocol number, a blank for the unique trial identification number, a blank for the investigator name, and the box number. The bottles will also be labelled in accordance with Annex 13 and will contain minimally, the protocol number, a blank for the unique trial identification number, a blank for the investigator name, box number, storage instructions and administration instructions.All blanks on the box and bottle labels should be completed prior to dispensing.

At the time of dispensing the right side of the box tear-off label will be removed and attached to the dispensing records to verify correct box number as well as to provide details for unblinding (in the case of an emergency only). Other site personnel should not have access to this information. Celecoxib / placebo will be resupplied at one year following the allocation of a new box number from the CDC. It is the responsibility of the Principal Investigator (PI) to ensure that drug is available for the duration of treatment.

It should be noted that during the course of the study each patient will be allocated one unique trial identification number. However, to aid drug supply, each patient will be allocated a different box number each time they are dispensed medication.

The left side of the label that will remain on the bottle at dispensing will contain minimally, the protocol number, a blank for the unique trial identification number, lot number, storage instructions and administration instructions. The right side of the label will contain minimally, the protocol number, lot number and a blank for the unique trial identification number. At the time of dispensing the right side of the label will be removed and attached to the dispensing records.

8.3 Drug Distribution

Celecoxib / placebo for the duration of the study will be supplied by Pfizer Inc. and will be distributed to the participating centres by Almac Clinical Services. Celecoxib / placebo will be dispensed through the hospital pharmacy or investigator upon receipt of the unique trial identification number and box number allocated by the CDC.

Randomisation lists for each Centre will be generated by the ICR-CTSU, with a copy sent to each CDC. An agreed number of allocations will be sent to the Centre pharmacy or investigator. The CDC will be responsible for informing ALMAC when further supplies are required.

8.4 Drug Dispensing

The person at the investigator Centre responsible for dispensing will dispense study medication. The unique trial identification number will be written on the box label. Prior to dispensing, the tear-off section of the label should be removed and attached to the appropriate dispensing records. For centres affiliated to the GBG, patients will be provided with a patient-passport where the next visit date, box number(s) and contact information will be noted. Celecoxib/placebo will be dispensed at baseline and at the 12 month visit.

8.5 Storage

The study drug must be stored at room temperature at 25°C (77°F); excursions permitted to 15-25°C (59-77°F). The investigator will be responsible for ensuring that the study medication is stored in a secured area, such as a pharmacy or locked cabinet. The study product may not be used outside the context of the protocol. Under no circumstances should the PI or Centre personnel supply product to other investigators or clinics, or allow the drug supplies to be used other than as directed by this protocol without prior authorization of study management.

8.6 Code Breaking

Unblinding is restricted to emergency situations and should only be used under circumstances where knowledge of the treatment is necessary for the proper clinical care of the patient. The blinded code will be broken on the occasion of a Serious Adverse Event (SAE) only if a relationship between the reaction and the double blind medication is definite, probable or possible AND the event is unexpected i.e. SUSAR. Unblinding can also be carried out if a study participant becomes pregnant while on treatment with celecoxib/placebo or within 30 days after the end of treatment. In this case the pregnancy and the baby will need to be followed up for a period of 18 months to assess any congenital anomaly or birth defect. If the pregnancy occurs after 30 days of the end of treatment, it will no longer need to be reported to the sponsor and no further follow up is necessary.

If the blinded treatment code needs to be broken, the relevant code break card should be retrieved. This can be identified from the tear-off label attached to the dispensing records. It is the responsibility of the PI to ensure that code break cards are stored in a secure area and that only appropriate personnel have access to them.

An 'Unblinding Request' must be completed and the CDC informed immediately. The reason for unblinding and date should be recorded on the Unblinding Request and signed by the PI. The request should be sent to the person or department responsible for storing the code break envelopes.

An 'End of Blinded Study Drug' form must be sent to the CDC if treatment is discontinued prematurely for any reason.

8.7 Drug Interactions/Precautions

Celecoxib should not be given to patients who have demonstrated allergic type reactions to sulphonamides or who have experienced asthma, urticaria or allergic type reactions after taking aspirin or other NSAIDs. Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit 2C9 should be carried out with caution. *In vitro* studies indicate that celecoxib although not a substrate is an inhibitor of cytochrome P450 2D6. Therefore, there is a potential for an *in vivo* drug reaction with drugs that are metabolised by P450 2D6.

Clinical studies have identified potentially significant interactions with fluconazole and lithium. Experience with nonsteroidal anti-inflammatory drugs NSAIDs also suggests the potential for interactions with furosemide and ACE inhibitors (see Appendix III).

The following medications are not permitted while patients are receiving celecoxib/placebo:

- Chronic use of other NSAIDs (chronic use is defined as a frequency of 1 or more a day, for more than a total of 6 weeks per year)
- Oral corticosteroids
- Hormonal replacement therapy
- Hormonal contraception methods (birth control pill or implants).

These medications should not be given concomitantly with celecoxib/ placebo. A treatment break of up to one month is allowed. If a patient requires a longer break from celecoxib/ placebo the patient should be withdrawn from study medication but should continue on follow-up.

A more detailed list of drug interations and precautions can be found in Apendix III.

8.8 Drug Accountability

Patients must be asked to bring their trial medication with them every time they attend the clinic, for purposes of drug accountability. Every effort should be made to encourage patients to return the unused medication and empty packs/bottles. The unused capsules should be collected by the investigator/study nurse and returned to pharmacy for destruction according to local practices. Drug accountability and destruction will be recorded on study specific forms.

9 FOLLOW UP SCHEDULE

9.1 Routine follow-up visits

During the course of the trial, all patients will be followed-up as follows:

UK:

Year 1	Baseline and months 3, 6 and 12
Year 2 & 3	6 monthly (months 18, 24, 30 and 36)
Year 4 & 5	Annually (months 48 & 60)
Year 6 – 10*	Annual follow up

Germany:

Year 1	Baseline and months 3, 6 and 12
Year 2	6 monthly (months 18, 24)
Year 3 – 10*	Annual follow up via a self reporting questionnaire, chart reviews at the sites or based on information deriving from the GBG registry of previous study participants.

* Should cost effective, reliable systems be in place, for example electronic methods of routine data collection, and at the discretion of the Trial Steering Committee, off-treatment follow up may continue beyond 10 years

9.2 On-treatment assessments

- Patient and disease status
- Physical examination
- WHO performance score
- Blood pressure

  If BP>140/90 is detected during follow-up then the patient should be referred to the GP for further assessment of blood pressure and treatment as per National Guidelines
- Clinical cardiovascular assessment (including cardiac history, blood pressure, pulse, results for HDL and total cholesterol and smoking status) and ECG 12 months after randomisation and at the end of celecoxib/placebo therapy (normally at 24 months). If treatment is terminated early a cardiovascular assessment and ECG must be performed but no further cardiac assessments are required. A copy of the ECG obtained at each visit should be sent to the designated CDC

  If at 12 months and at the end of celecoxib/placebo (normally at 24 months) the ratio between Total and HDL cholesterol is equal or higher than 6, patients should be recommended to see their primary

care physician with a view to being offered dietary advice and/or lipid lowering therapy as per National Guidelines

- Safety relevant concomitant medication
- Endocrine treatment details – name of treatment, date of first intake, treatment compliance (if applicable)
- Bisphosphonates (if applicable) – start and end date
- Imaging/Examinations– additional tests/investigations (e.g. Bone/liver scan etc) to detect metastatic disease are at the investigators' discretion if clinically indicated
- Compliance of trial medication
- Adverse events assessment. Only AEs assessed as CTCAE grade 2 or above should be reported on the relevant CRFs. All other AEs should be treated and followed-up as per normal local practice

9.3 UK Off-treatment Follow-up assessments

- Patient and disease status
- Other cancer treatment details (if applicable):
  - Endocrine therapy – Name of treatment
  - Bisphosphonates – Start and end date
- Adverse events that occurred within 30 days after discontinuation of celecoxib/placebo. Only AEs assessed as CTCAE grade 2 or above should be reported on the relevant CRF
- In the off-treatment follow up period following the 30 days after discontinuation of celecoxib/placebo, only PI assessed Cardiac and GI side effects/ illnesses assessed as CTCAE grade 2 or above should be reported on the relevant CRF
- Serious Adverse Events (if in the opinion of the Investigator the event is related to celecoxib/placebo)
- Imaging/Examinations – additional tests/investigations (e.g. Bone/liver scan etc) to detect metastatic disease are at the investigators' discretion if clinically indicated

9.4 Germany Off-treatment follow up

Post-treatment data will be collected annually using a self-reporting system via a patient questionnaire, chart reviews at the sites or based on information deriving from the GBG registry of previous study participants:

- Patient and disease status
- Other cancer treatment details (if applicable):
  - Endocrine therapy – Name of treatment / Start and end date
  - Bisphosphonates intake
- CTCAE grade 2 or above Adverse events relating to GI surgery and Myocardial infarction

9.5 Schedule of Assessments

Months from Randomisation	0 (Baseline)	3	6	12	18	24	30	36	48	60 – 120
Demography, breast cancer history, menopausal status[1]	X									
WHO Performance	X	X	X	X	X	X				
Pregnancy Test	X									
Physical Examination	X	X	X	X	X	X				
Blood Pressure	X	X	X	X	X	X				
Haematology and Biochemistry	X									
Safety Relevent Concurrent Medication	X	X	X	X	X	X				
Mammogram	X									
Clinical Cardiovascular Assessment / ECG	X			X		X				
Dispense Celecoxib/ placebo	X			X						
Patient and disease status		X	X	X	X	X	X	X	X	X
Study Treatment Compliance		X	X	X	X	X				
Endocrine Treatment (if applicable)		X	X	X	X	X	X	X	X	X
Bisphosphonate Treatment (if applicable)		X	X	X	X	X	X	X	X	X
Adverse Events[2]		X	X	X	X	X	X			
Cardiac and GI Ilnesses and side effects							X	X	X	X
Tumour Block Collection (optional)	X									
Chest X-ray /Liver ultrasound /Bone scan	X									
Imaging/examinations	X									

9.6 Follow-up upon relapse

Upon relapse, patients should have the appropriate clinically indicated tests as determined by local practice, but which must include as a minimum those described in section 9.3 and 9.4. Follow-up after relapse should be according to the routine follow-up schedule defined above unless otherwise indicated clinically.

9.7 Premature discontinuation of treatment

Patients will be withdrawn from trial treatment if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the patient. Any patient who is found to have developed new Q-waves, indicative of myocardial infarction on routine ECG, will be removed from the celecoxib/placebo therapy immediately. The

[1] As detailed in section 7.5.

[2] Adverse events (CTC grade 2 or above) that occur within 30 days after discontinuation of celecoxib/placebo (normally at 24 months) should be reported at the 30 MFU visit using the current AE Reporting forms. In case of premature discontinuation of celecoxib/placebo, AEs that occur within 30 days after discontinuation should be reported at the next visit. All reported AEs need to be followed-up until resolution.

development of new Q-waves on ECG should be reported as a Serious Adverse Event within the guidelines stated in Section 11.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document the patient outcome, if possible. If a patient requests withdrawal from the trial (as distinct from premature withdrawal from treatment), the patient must be asked whether she accepts that her clinical data will continue to be used for trial purposes (particularly details of disease related events and follow-up).

Patients will discontinue study treatment in the case of any relapse. Patients treatment after relapse is at the discretion of the investigator. Other reasons for a patient to discontinue study treatment include; the occurrence of an SAE, which is considered to be related to treatment and unexpected and which necessitates a change in treatment, the withdrawal of consent, or the experience of unacceptable toxicity. There will be no dose modification and the patient will be discontinued from study treatment should any unacceptable event occur. An End of Treatment with Blinded Study Drug 'form must be completed, and the CDC informed if treatment is discontinued prematurely for any reason. CDC should be notified as soon as possible in this instance.
All patients will continue to be followed-up, irrespective of whether they have discontinued study treatment prematurely, unless, in exceptional circumstances, they withdraw their consent to be followed up.

9.8 Treatment Breaks

Treatment breaks up to one month are permitted; however, the overall treatment duration should not be extended past 2 years to account for such breaks.

Note: There is no evidence of delays in wound healing if celecoxib/placebo is used in the perioperative period**.**

9.9 End of Trial

The end of trial will be last patient's last data capture.

10 ADVERSE EVENT REPORTING

10.1 Definition of an Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient administered a drug; the event does not necessarily have a causal relationship with the treatment or usage.

10.2 Procedure for collecting Adverse Events

All adverse events assessed by the PI as NCI-CTCAE grade 2 or above will be collected from the time of the randomisation until 30 days after the discontinuation of celecoxib/ placebo and should be reported on the AE reporting Form. Whenever one or more signs and/or symptoms correspond to a disease or a well-defined syndrome only the main disease/syndrome should be reported. The severity of adverse events will be

graded according to the current NCI-CTCAE criteria. For each sign/symptoms, the highest grade observed since the last visit should be reported.
During off treatment follow-up only Cardiac and GI side effects/ illnesses assessed as NCI-CTCAE grade 2 and above should be reported.

11 SERIOUS ADVERSE EVENTS AND SERIOUS ADVERSE REACTIONS

11.1 Definition of a Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is defined as any of the following, whether or not considered related to the trial treatment:

- Death
- Life-threatening condition (i.e. immediate risk of death)
- In-patient hospitalisation, excluding elective surgery, or prolongation of existing hospitalisation.
- Persistent or significant disability/incapacity
- Permanent impairment of function or permanent damage to body structure or if an intervention is required to prevent permanent impairment or damage.
- Cancer*
- Congenital anomaly/birth defect
- Overdose (excluding asymptomatic overdose)
- Development of new Q-waves on ECG

[*other than breast cancer recurrence, the patient having had breast cancer and relapse with breast cancer being a study end-point].

Any other adverse event that the investigator or company judges to be serious or which is defined as serious by the regulatory agency in the country in which the adverse event occurred.

If a serious adverse event occurs during the follow-up period, it must be reported if in the investigator's judgement there is a relationship to any study medication.

11.2 Procedures for reporting SAEs

In the event of a SAE the investigator must:

- Complete a Serious Adverse Event Report Form and fax to the designated CDC within 24 hours of awareness of the event. This should contain all information known at the time of the report.
- The initial report should then be followed by the completed (with full information) Serious Adverse Event Report Form within 5 days of the event.
- Follow up of patients who have experienced an SAE should continue until recovery is complete or the condition has stabilised.

All SAEs will be centrally reviewed to confirm relatedness and expectedness as defined in 11.3.

11.3 Definition of a Serious Adverse Reaction (SAR)

A SAR is defined as a SAE (see section 11.1) that is judged by the local Investigator to have a definite, probable or possible causal relationship with the use of one or other of the study drugs.

The expectedness of a SAR should be assessed in accordance with the information in the current Celecoxib Investigator Brochure and/or UK/German SmPC Expected SARs should be reported as per the SAE reporting guidelines (section 11.2) and followed up until recovery is complete or the condition has stabilised.

11.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Suspected Unexpected Serious Adverse Reactions (SUSARs) are those events which

- meet the criteria of 'serious' (see section 11.1), AND
- are judged to have a definite/probable/possible causal relationship with one or other of the study drugs (section 11.3), AND
- are NOT consistent with the information listed in the current IB or SmPC.

SUSARs should be reported to the relevant CDC as per the SAE reporting guidelines (section 11.2). In addition they should be reported to the appropriate Ethics Committee by the relevant CDC, according to local regulations.

The CDCs are responsible for circulating information on SUSARs to participating centres and notifying both the Safety Department of Pfizer Inc. and the Health Authorities.

Follow up of patients who have experienced a SUSAR should continue until recovery is complete or the condition has stabilised.

12 STUDY ENDPOINTS

12.1 Primary end-points

The primary aim is to assess the disease-free survival (DFS) benefit of two years adjuvant therapy with the COX-2 inhibitor celecoxib compared with placebo in primary breast cancer patients.

12.2 Secondary end-points

Secondary endpoints will determine:

- overall survival (OS)
- the toxicity associated with long term use of celecoxib in primary breast cancer patients
- cardiovascular mortality
- the incidence of second primary cancers

Subgroup analysis based on HR status (HR+ve, HR-ve) will be performed using the same endpoints as in the analysis of all patients.

12.3 Definition of disease related events

Disease free survival is defined as time from randomisation to the date of first event; with events contributing to the analysis defined as loco-regional and distant breast cancer recurrence, new primary breast cancer (ipsilateral or contralateral) and death without disease relapse (intercurrent death).

First local recurrence and first distant recurrence will be recorded on separate parts of the CRF. In the event of local progression, all patients must be followed up for distant recurrence, second malignancy and survival. Similarly in the case of second malignancy, the appropriate CRF should be completed and patients should

continue to be followed for disease progression and where possible the relation of any subsequent disease progression and/or death due to the primary or second cancer should be established.

Date of suspicion of relapse, action taken to confirm relapse and date relapse confirmed will all be recorded on the CRF.

Any relapse requires study treatment to be stopped, and thus is included as an event. Any malignant contralateral breast disease will be included as a second primary, and relapse with supraclavicular disease will be included as local relapse according to TNM classification v6.

'Breast cancer' deaths will be all deaths with breast cancer specified as a cause of death and deaths from any cause following a distant relapse.

Patients may continue to receive the study treatment after a second (non-breast) primary is diagnosed; the final decision is at the Investigator's discretion.

12.4 Safety Evaluation

A potential increase in cardiovascular rates has been suggested with selective COX-2 inhibitors (Mukherjee et al, 2001). Cardiovascular events will therefore be closely monitored and will be a primary safety consideration.

13 STATISTICAL ISSUES

13.1 Stratification

At randomisation, patients will be stratified by centre and hormone receptor status (ER and/ or PgR positive versus ER/PgR negative).

13.2 Sample Size

In order to detect a 20% reduction in risk of recurrence in the five year DFS (e.g. from 70% to 75.2%), 2590 patients (709 events) are required (hazard ratio=0.8). This number is based on a 2:1 randomisation (celecoxib vs. placebo) with 80% power and α=0.05 (two-sided). The figure of 70% DFS at five years in the control group is based on an estimation of more than 40% of the patients randomised being HR negative.
Once recruitment is ongoing the IDMC may be asked to consider an increase in sample size. Formal interim analysis of efficacy based on log-rank comparison and an estimate of the hazard ratio will be conducted after ¼, ½, and ¾ of the required number of events (see section 13.1).

13.3 Analysis

13.3.1 Efficacy Analysis

All patients will be evaluated for endpoints in the arm to which they were randomised, irrespective of the treatment they actually receive. No patient will be removed from the analyses irrespective of whether she is found to have violated the eligibility criteria after randomisation or to have been withdrawn from trial medication prematurely, except in the case that she withdraws her consent to use of data already collected in the trial. Thus, analysis will be by intention to treat including all consenting patients randomised.

The principal analysis will be based on a log rank comparison of DFS. DFS is defined as time from randomisation to date of diagnosis of first local or distant metastases at any site or second breast primary confirmed by an appropriate method (see 12.3). Probabilities of DFS and OS will be presented as Kaplan-Meier survival curves with fixed term survival estimates. Hazard ratios will also be calculated. Cox regression techniques will be used to adjust for important factors likely to influence prognosis or confound any treatment effect. These factors may include ER, menopausal and COX-2 status, and chemotherapy regimen. Exploratory sub group analyses will be reported by hormone status, menopausal status, nodal status, and previous use of chemotherapy (or not). Baseline characteristics will be described by randomised treatment group. All statistical tests will be two-sided and 95% confidence intervals will be used.

13.3.2 Safety Analysis

There will be a sequential monitoring of toxicity and it is likely that the first analysis will be carried out when the first 100 patients have completed the first 6 months of assessment.

Toxicity and the frequency and nature of adverse events will be compared between the randomised groups. Summary measures and non-parametric tests will be used as necessary. In particular, the proportion of patients experiencing toxicity of CTC grade 3 or 4 and the maximum CTC toxicity grade will be compared. An analysis of safety endpoints by treatment received will be performed.

Incidence of cardiovascular events after randomisation will be compared between the two arms and the absolute difference in incidence will be estimated (with associated confidence limits).

Subgroup analysis based on HR status (HR+ve, HR-ve) will be performed using the same endpoints as in the analysis of all patients. The trial is not powered to detect differences within these subgroups thus these analyses will be descriptive in nature unless changes are made to the design of the trial or there is an increase in sample size (see 14.1 for details of this possibility).

14 STUDY LOGISTICS

14.1 Role of Independent Data Monitoring Committee (IDMC)

An IDMC has been formed to review safety and efficacy data, in confidence, on a regular basis as they see fit, but at least annually. Following each meeting, the IDMC will report their findings and recommendations to the TMG. Interim analysis of side-effects, tolerability, disease-free and overall survival for all randomised patients will be supplied in strict confidence by the trial statistician to the IDMC together with any other analyses that the IDMC may request.

The main criterion for early release of efficacy data from the trial by the TMG upon suggestion from the IDMC will be that evidence from the trial and from other sources suggests a) proof beyond reasonable doubt that for all, or for some types of patient, one treatment regimen is clearly indicated or contra-indicated in terms of a net difference in DFS or OS, and b) evidence that might reasonably be expected to influence routine clinical practice. Criteria for the above will usually be a difference in DFS or OS at any stage significant at $p < 0.001$ by overall log-rank analysis. Particular consideration will also be given to cardiovascular event rates and, in addition to early reporting on the basis of efficacy, a stopping rule based on excess toxicity in the celecoxib arm will be employed. No results on survival or recurrence will be made available to participants or the sponsor until the IDMC considers the results to be clinically and statistically informative.
Once recruitment is ongoing the IDMC may be asked to consider:

a) An increase in sample size.

Factors dictating this would be:

i) a review of the absolute size of detectable benefit in the light of any new emerging data (as was the case with the Intergroup Exemestane Study)
ii) if the withdrawal rate from celecoxib/placebo treatment was substantial and sensitivity analyses indicated that the observed withdrawal rate (if it were to continue) was likely to impact on the trials ability to detect the hypothesised treatment effect.
iii) consideration of endocrine subgroup specific analyses
iv) consideration of a randomisation in HR+ patients between exemestane and non-steroidal aromatase inhibitor

b) Extending the celecoxib treatment to between 3-5 years or a further randomisation at 2 years of treatment to stop versus continue (to a total of 3-5 years).

Any of these amendments would require a full re-definition of the statistical considerations for each of the specific hypotheses.

Should the original expected event rates used to calculate the sample size be different from those observed in the maturing data the IDMC may advise an alternative timing for the principal analysis of the primary endpoint based on maturity of follow-up, rather than after 709 events have been obtained.

The TMG will make the final decision based on the recommendations of the IDMC and other factors, such as patient accrual.

The IDMC will reserve the right to release any data on outcome or side-effects through the Chairman to the TMG to participants if it determines at any stage that the combined evidence from this and other studies

justifies it. This includes the circulation of unblinded toxicity data if the IDMC believes that this may lead to improvement in patient care.

14.2 Analyses for Publication

Unless the IDMC advises otherwise, it is expected that the first analyses for publication/presentation will be performed when the required number of events is reached. All trial data are owned by the TMG which will have representation from ICCG and GBG and investigators participating in the trial.

14.3 Publishing policy

All publications and presentations relating to the trial will be authorised by the trial Steering Committee. Authorship will be determined by the REACT TMG, but will include the Chief Investigators and statisticians. A writing committee may be appointed. Further authorship will be determined by centre accrual and/or TMG membership and/or direction of sub-studies depending on the publication policy of the chosen journal. The REACT TMG will have the final decision as to which individuals are the named authors in the light of the above considerations. The trials offices who have undertaken the data management and all participating centres will be acknowledged in the final manuscript according to patient accrual.

Participants may only present data separately to the total data available, with the permission of the TMG, and not less than 6 months after publication of the main results.

Pfizer Inc. has the right to review all abstracts, papers, or other research communications prior to their submission to journals, meetings, or conferences. Pfizer Inc. may request removal of propriety information and may suggest editorial changes in the papers to the TMG. The TMG has final authority over the content of all publications.

15 SUB PROTOCOLS

A pathology study is taking place. The consent form for the main trial will give patients the opportunity to participate.

The aim is to investigate modulators of celecoxib response. A request for a representative formalin fixed paraffin embedded (FFPE) tumour block from the patient's definitive breast cancer surgery will be sent by the CDC to the investigator for any patients who consent to the sub-study.

16 TRIAL ADMINISTRATION AND DATA MANAGEMENT

Each collaborative group will be responsible for the day-to-day conduct of the trial for their collaborating hospitals.

The responsibilities will include some or all of the following:

- initiation visits to selected centres (it is important that the investigator and their relevant personnel are available during these visits and that sufficient time is devoted to the process).
- communication with/submission to local ethics committee
- randomising patients

- receipt or collection of CRFs from the hospitals
- raising and resolving queries with local investigators
- performing an initial data clean
- monitoring of centres
- requesting drug supply, circulating SAEs and safety reports to centres

16.1 Case Report Forms (CRFs)

CRFs should be completed for each subject and should not be made available to third parties.

CRFs will either be in the form of a booklet (if you are affiliated to the ICCG) or as an electronic document (if you are affiliated to GBG).

CRF documents will be supplied by the CDCs. CRF booklets will contain forms in triplicate. The top two copies must be sent to the CDC undertaking the data management as soon as they are due. The bottom copy must be retained in the booklet and held by the investigator. All sections are to be completed on the form before sending or submitting to the CDC. If information is not known it must be clearly stated.

The electronic version of the CRF is suited for online documentation through MedCODES® only.

To enable evaluations and/or audit from Health Authorities the investigator must agree to keep records, including the identity of all participating subjects (sufficient information to link records, e.g. CRFs and hospital records), all original signed Consent Forms, copies of CRFs and drug dispensing.

16.2 Liability/Indemnity/Insurance

This study is an investigator-led trial designed by the ICCG at Imperial College London and the GBG. The study is sponsored by Imperial College London and is being supported by Pfizer Inc. Imperial College, as sponsor of the study, maintains a "No Fault" Compensation Scheme through its public liability insurance policy. If patients suffer any harmful effects as a result of participation in this study, compensation may be claimed through this scheme. The GBG will provide insurance for all patients recruited in Germany according to the requirements of German Law.

16.3 Patient Confidentiality

The personal data recorded on all documents will be regarded as confidential, and to preserve each subject's anonymity, only their initials and date of birth will be recorded on the CRF. The investigator must ensure the patient's confidentiality is maintained.

The investigator must keep a separate log of patients' trial number, names, addresses and hospital numbers. The investigator must maintain in strict confidence trial documents which are to be held in the local hospital eg patients' written consent forms.

The ICCG/GBG will maintain the confidentiality of all subject data and will not reproduce or disclose any information by which subjects could be identified, other than reporting of SAEs as required by law.

Representatives of the trial team will be required to have access to patient notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

In the case of special problems and/or regulatory audit queries, it may also be necessary for authorised representatives of the appropriate regulatory authority to have access to the complete study records. Patient confidentiality will be protected at all times.

16.4 Ethics Issues

The study described in this protocol will be conducted in compliance with guidelines for Good Clinical Practice and applicable regulatory regulations.

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical assembly, Helsinki, Finland, 1964 and any later revisions.

It is the responsibility of the PI to obtain approval of the trial protocol and any subsequent amendment from the IRB/IEC. All correspondence with the IRB/IEC should be filed by the investigator. Copies of the IRB/IEC approval should be forwarded to the CDC.

It is the responsibility of the investigator to give each patient, prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. The patients must be informed about their right to withdraw from the trial and the possible risk involved. The patient information sheet is written according to national guidelines and must be given to each patient before enrolment. It is the responsibility of the investigator to obtain signed informed consent from all patients prior to inclusion in the trial.

All amendments and translations to the patient information sheet must be agreed prior to trial commencement. The trial sites may be subject to inspection by appropriate regulatory authorities.

Patient identification data will be required at randomisation to assist with long term follow-up.

16.5 Monitoring Strategy

This study will take a Risk-Based, ‘fit for purpose’ approach to the initiation and monitoring of this study consistent with the principles of GCP. Monitoring procedures and requirements will be documented in a Monitoring Plan. The appropriate level and nature of monitoring required for the trial will be assessed by undertaking a formal risk assessment of the study.

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APPENDIX I: Study Contacts

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APPENDIX II: Acceptable Chemotherapy Regimes

Completion of a minimum of 4 cycles of a chemotherapy is required for eligibility.

The recommended regimen is FEC.

In all cases, the maximum cumulative allowable dose of epirubicin is 720mg/m².

All preferred dosages correspond to the first starting dose. Dose reductions due to toxicity in the following cycles do not compromise eligibility of the patient.

Epirubicin in combination with Cyclophosphamide +/- 5-Fluorouracil (FEC or CEF or EC)

The minimum dose for Epirubicin is 50 mg/m² given on days 1 and 8 q day 28 or 75 mg/m² given on day 1 q day 21 or 60 mg/m² given on day 1 q day 21 for at least 5 cycles. 5-Fluorouracil and Cyclophosphamide should be given both at a dosage of at least 500 mg/m².

If Epirubicin is given in combination only with Cyclophosphamide the minimal dose should be 90 mg/m² every 3 weeks.

Epirubicin given in combination with a taxane (+/- Cyclophosphamide)

The minimal allowable dose for Epirubicin is 75 mg/m². Paclitaxel should be given at a minimal dose of 175 mg/m² and Docetaxel at a minimal dose of 75 mg/m². The dose of Cyclophosphamide should not be less than 500 mg/m². The regimen should be given every 14 to 21 days. Bevacizumab is allowed with EC for patients on the Gepar-5 trial.

Epirubicin given in sequence with a taxane

The minimum dose of Epirubicin is 90 mg/m² given alone or in combination with Cyclophosphamide (minimum dose 600 mg/m²) every 2 to 3 weeks. The dosage of Docetaxel should be 100 mg/m² every three weeks or 75mg/m² every two weeks or 80mg/m² every week. The dosage ofPaclitaxel should be 175 mg/m² over 3 hours or 80 mg/m² weekly for 12 cycles, RAD001 is allowed with Paclitaxel for patients on the Gepar-5 trial.

E-CMF (or Epi-CMF)

The minimum dose of Epirubicin is 100mg/m2 i.v. given on day 1 and repeated every 21 days for 4 cycles, followed by 4 cycles (28 days) Classical / Bonadonna CMF:

The minimum dose of cyclophosphamide is 100mg/m² if given orally on days 1-14 and 600mg/m² if given intravenously on day 1 and 8. The recommended dose of methotrexate is 40mg/m² and of 5-Fluorouracil is 600mg/m² given on day 1 and 8. The cycle should be repeated on day 29.

Doxorubicin in combination with Cyclophosphamide +/- 5-Fluorouracil (FAC or CAF or AC)

The minimum dose for Doxorubicin is 50 mg/m² intravenously given on day 1 q day 21 or 30mg/m2 days 1 and 8 q day 28 for at least 6 cycles. Cyclophosphamide should be given 500mg/m2 on day 1 and 8 or 100mg/m2 day 1-14 respectively and 5-Fluorouracil should be given at a dosage of at least 500 mg/m² i.v.

If doxorubicin is given in combination only with cyclophosphamide the doses should be doxorubicin 45-60 mg/m² i.v. and cyclophosphamide 400-600 mg/m2 i.v. every 3 weeks for at least 4 cycles.

Doxorubicin given in combination with a taxane (+/- Cyclophosphamide) The minimal allowable dose for doxorubicin is 50mg/m². Paclitaxel should be given at a minimal dose of 175 mg/m² and docetaxel at a dose

of 75 mg/m². The dose of Cyclophosphamide should not be less than 500 mg/m². The regimen should be given every 21 days.

Doxorubicin given in sequence with a taxane

The minimum dose of doxorubicin is 60mg/m² given alone or in combination with Cyclophosphamide (minimum dose 600 mg/m²) every 3 weeks for 4 cycles. This should be followed by 100 mg/m² docetaxel be for 4 cycles.

A-CMF (or Adria-CMF)

The minimum dose of doxorubicin is 75mg/m2 i.v. given on day 1 and repeated every 21 days for 4 cycles, followed by 8 cycles (28 days) Classical / Bonadonna CMF. The minimum dose of Cyclophosphamide is 100mg/m² if given orally on days 1-14 and 600mg/m² if given intravenously on day 1 and 8. The recommended dose of Methotrexate is 40mg/m² and of 5-Fluorouracil is 600mg/m² given on day 1 and 8. The cycle should be repeated on day 29.

CMF

The use of the CMF regimen alone is only allowed in patients where Epirubicin and doxorubicin are contraindicated, e.g. in cases where there is abnormal cardiac function (see above). The minimum dose of Cyclophosphamide is 100mg/m² if given orally on days 1-14 and 600mg/m² if given intravenously on day 1 and 8. Patients on the ICE2 trial will receive only 500 mg/m² of Cyclophosphamide. The recommended dose of Methotrexate is 40mg/m² and of 5-Fluorouracil is 600mg/m² given on day 1 and 8. The cycle should be repeated on day 29.

Docetaxel given in combination with Cyclophosphamide

The combination of Docetaxel 75 mg/m2 and Cyclophosphamide 600 mg/m2 intravenously every three weeks for 4-6 cycles. i.e. anthracycline free

5-Fluorouracil, Epirubicin and Cyclophosphamide followed by Docetaxel (FEC – T) and Docetaxel followed by 5-Fluorouracil, Epirubicin and Cyclophosphamide +/- Bevacizumab (4 cycles only)

The minimum dose of Epirubicin should be 60 mg/m². 5-Fluorouracil and Cyclophosphamide should be given both at a dosage of at least 500 mg/m². Each should be given on day 1 and this should be repeated every three weeks up to a total of 3 or 4 cycles. Docetaxel should be given at a minimum dose of 75mg/m² on day 1 every three weeks up to a maximum of 8 cycles in total. This sequence can be reversed so that Docetaxel is given prior to FEC. Bevacizumab may be given in combination with Docetaxel for patients participating in the ARTEMIS trial.

Weekly nab-paclitaxel in combination with capecitabine (ICE II trial). Nab-Paclitaxel (100mg / m²) on days 1, 8 and 15 repeated every three weeks with no infusion every six weeks plus Capecitabine (2000mg / m²) on days 1 to 14 repaeted every three weeks to a total of 6 cycles.

Some of the above regimens are only applicable in the context of chemotherapy trials.

Other regimens are only allowed after acceptance by the Trial Management Group.

APPENDIX III: Drug Interactions/ Precautions

Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver. Co administration of celecoxib with drugs that are known to inhibit 2C9 should be administered with caution. *In vitro* studies indicate that celecoxib, although not a substrate is an inhibitor of CYP2D6. Therefore, there is a potential for an *in vivo* interaction with drugs that inhibit CYP2D6.

Clinical studies have identified potentially significant interactions with fluconazole and lithium. Experience with nonsteroidal anti inflammatory drugs NSAIDs suggests the potential for interactions with furosemide and ACE inhibitors.

Angiotensin-converting enzyme (ACE) inhibitors - concurrent use with celecoxib may decrease the antihypertensive effects of ACE inhibitors; also, risk of renal failure is increased in patients taking these medications.

Antacids, aluminum- or magnesium-containing - the administration of celecoxib with an aluminum– or magnesium–containing antacid has been reported to result in a 37% decrease in the peak plasma concentration and a 10% decrease in the area under the plasma concentration–time curve [AUC] of celecoxib

Diuretics, thiazide or Furosemide - nonsteroidal anti-inflammatory drugs may decrease the natriuretic effects of diuretics, possibly by inhibiting renal prostaglandin synthesis; also, risk of renal failure is increased in patients taking these medications

Fluconazole - in clinical trials, concurrent administration of fluconazole 200 mg daily resulted in a two-fold increase in plasma concentration of celecoxib; the increase in plasma concentration of celecoxib was due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole; therefore, if celecoxib is coadministered with fluconazole, it is recommended that the dose of celecoxib should be initiated at the lowest recommended dose,. As it is not possible to adjust the dose of celecoxib in this study we do not recommend the concurrent administration of fluconazole and celecoxib in this trial.

Lithium - a 17% increase in the plasma concentration of lithium has been reported in patients receiving lithium 450 mg twice a day with celecoxib 200 mg twice a day compared with patients receiving lithium alone; therefore, monitoring of lithium concentrations is recommended when treatment is initiated and when treatment with celecoxib is discontinued.

Anticoagulants – Anticoagulant activity should be monitored particularly in the first few days of initiating celebrex activity in patients receiving warfarin or other similar agents, since these agents are at increased risk of bleeding complications.

Bevacizumab - Common toxicities associated with bevacizumab include hypertension, bleeding episodes and thrombotic events, however at the current time there is limited information concerning drug interactions with bevacizumab and other medication. Until such information is available the concurrent use of celecoxib and bevacizumab is not recommended in this trial.

Precautions

Celecoxib should not be given to patients who have demonstrated allergic type reactions to sulphonamides or who have experienced asthma, urticaria or allergic type reactions after taking aspirin or other NSAIDs.

APPENDIX IV – Protocol Amendment History

Protocol Version 30.0, December 2003 amended to Version 31.0, 29 July 2005

Substantial amendment

Amended to allow trial to re-start and incorporate additional patient safety checks

Protocol Version 31.0, 29 July 2005 amended to Version 32.0, 24 May 2006

Substantial amendment

Incorporationg additional patient safety checks

Protocol Version 32.0, 24 May 2006 amended to Version 32.1, 19 July 2007

Non-substantial amendment

Administrative changes

Protocol Version 32.1, 19 July 2007 amended to Version 33.0, 14 December 2007

Substantial amendment

Extension of endocrine therapy treatment to include AIs

Protocol Version 33.0, 14 December 2007 amended to Version 34.0, 28 September 2009

Substantial amendment

Change to inclusion criteria to include perimenopausal women

Protocol Version 34.0, 28 September 2009 to version 35.0 23 March 2011

Substantial amendment

Change to inclusion / exclusion citeria to exclude all patients with node negative, T1, grade 1 tumours.

Removal of reference to St. Gallen criteria

Removal of menopausal status from eligibility criteria

Administrative changes

Protocol Version 35.0, 23 March 2011 to Version 36.0, 31 August 2012

Substantial Amendment

Removal of Exemestane as an IMP and clarification that HR+ve patients should receive endocrine therapy according to local practice

Change to inclusion criteria to specify that all patients of child-bearing potential must have a negative pregnancy test in order to be eligible. Previously this was specified for premenopausal patients only

Clarification that patients should not take other NSAIDs, corticosteroids or HRT while on study treatment

Follow-up assessments have been divided into on-treatment follow-up assessments and off-treatment follow-up assessments and the schedule of assessments has been updated

Updated SAE definition to exclude hospitalisation due to symptoms of breast cancer recurrence/progression

Change to end of trial definition

Administrative changes

Protocol Version 36.0, 31 August 2012 to Version 37.0, 30 January 2014

Substantial Amendment

Clarification on Advserse Events (AE) reporting procedures

Guindance for Investigators on how to manage High levels of Cholesterol and BP during patient follow up

Removal of the expected Adverse Reactions (ARs) summary table. Investigators should refer to the current celecoxib Investigators Brochure for assessing ARs

Clarification of study assessements at study entry and during follow-up

Adminstrative changes

Protocol Version 37.0, 30 January 2014 to Version 38.0, 29 September 2015

Substantial Amendment

Clarification on REACT Post treatment follow-up procedures in Germany

Change to ICCG address

Clarification regarding unblinding and reporting of pregnancies

Administrative Changes

Protocol Version 38.0, 29 September 2015 to Version 39.0, 01 November 2016

Subtantial Amendment

Replacement of inadvertent deletion of text in section 11.1