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

(REACT – Randomised EuropeAn Celecoxib Trial)

Statistical Analysis Plan

Version 1.0

12/03/2014

STUDY NO: ICCG C/20/01, GBG 27, BIG 1- 03, ISRCTN No: 48254013

COORDINATING GROUPS: INTERNATIONAL COLLABORATIVE CANCER GROUP
GERMAN BREAST GROUP

SPONSOR: IMPERIAL COLLEGE OF SCIENCE, TECHNOLOGY AND MEDICINE, EXHIBITION ROAD, LONDON SW7 2AZ, U.K

AN INTER COOPERATIVE GROUP STUDY

This statistical analysis plan has been approved by the following personnel. All versions of this document and any subsequent approved amendments will be stored in the statistical section of the Trial Master File.

This statistical analysis plan is a framework guide to analysis and may be supplemented by additional analyses. Trial statisticians reserve the right to amend analysis methods as appropriate after discussion with the ICR-CTSU Scientific Lead.

Trial Statistician: Lucy Kilburn (Holly Tovey/James Morden providing cover during maternity leave)

Signed: Tovey

Date: 11/06/2014

ICR-CTSU Scientific Lead: Judith Bliss

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Signed:

Date: 16/04/2014

Document history

Version	Date	Changes made

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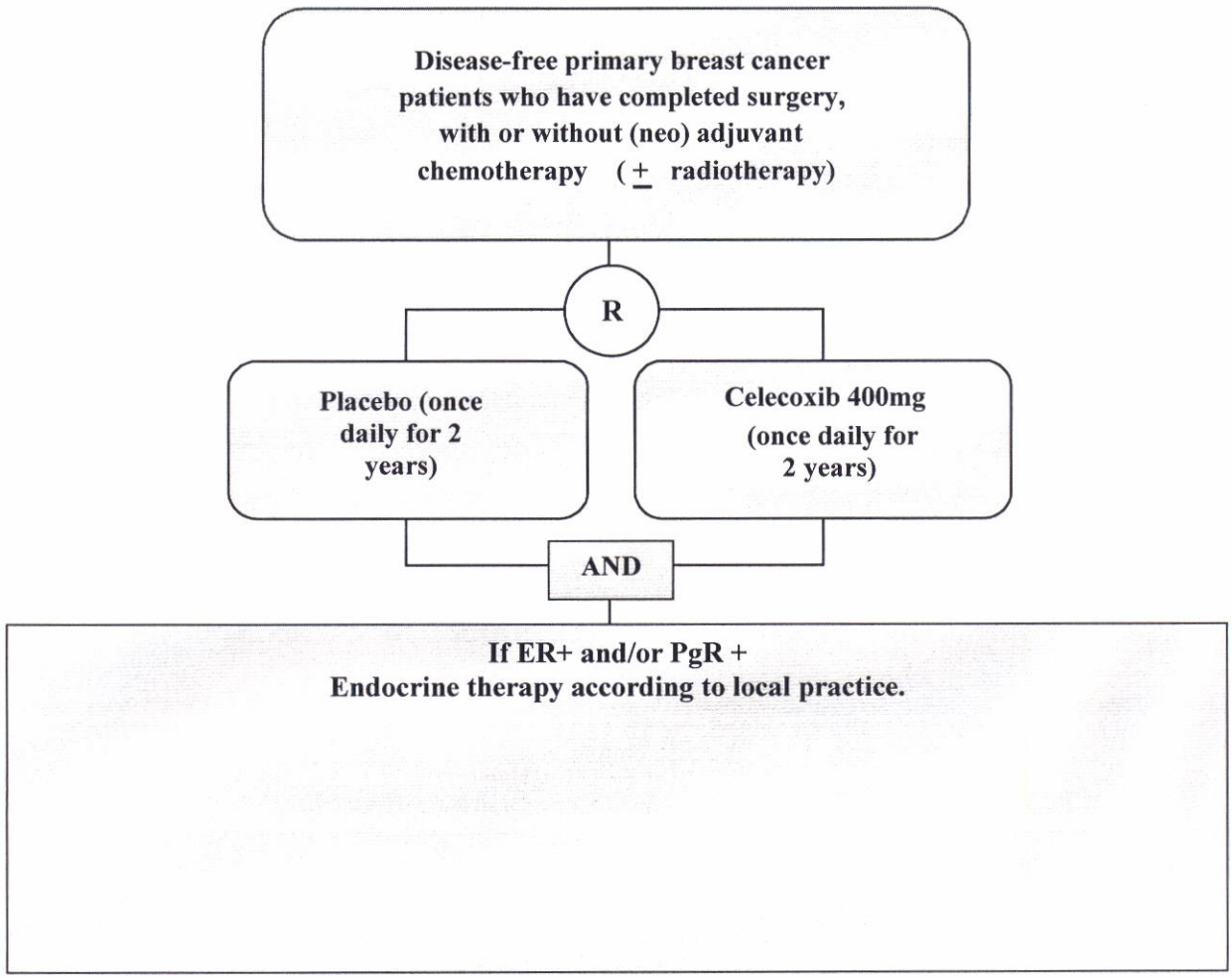
1.0 Introduction

1.1 Trial design

REACT is a phase III multicentre double blind randomised trial of celecoxib versus placebo in primary breast cancer patients. 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. Patients are randomised between two years celecoxib and placebo in a 2:1 ratio in favour of celecoxib. Additionally ER+ and/or PgR+ patients will receive endocrine therapy according to local practice. It is planned to accrue a total of 2590 patients.



Hormone receptor (ER and PgR) negative patients will not receive endocrine treatment.

1.2 Study population

This study is for resected node positive or high risk node negative breast cancer. All HR negative patients MUST have received chemotherapy. Entry into the study is within between 3 weeks and 4

months of day 1 of the last cycle of adjuvant chemotherapy, within 3 months of the end of definitive breast surgery, or within 6 weeks of the end of radiotherapy. Patients can have radiotherapy concurrently with study drug.

More detailed inclusion and exclusion criteria are:

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 and entry must be within 3 months of definitive breast surgery
4. Within 3 months of the end of definitive breast surgery (if no chemotherapy is to be given)
5. If adjuvant chemotherapy has been received* then the treatment must be finished and the patient must have received at least 4 cycles. Entry into the study must be within between 3 weeks and 4 months of day 1 of the last cycle.
6. Within 6 weeks of the end of radiotherapy
7. WHO Performance status 0 or 1
8. Pre-treatment haematology and biochemistry values within acceptable local limits:
   Haemoglobin
   WBC ≥ 3.0 · 109/l or ANC ≥ 1.5 x 109/l
   Platelets ≥ 100 · 109/l
   Serum bilirubin <1.5 UNL
   Alkaline phosphatase ≤ 1.5 x UNL
   Serum creatinine < 1.5 x UNL
9. Negative pregnancy test in premenopausal patients.
10. Normal baseline ECG and normal clinical cardiovascular assessment after completion of all (neo) adjuvant chemotherapy
11. No previous or current evidence for metastatic disease
12. Be accessible for and consent to long term follow-up
13. Written informed consent prior to commencement of specific protocol procedures must be obtained and documented according to the local regulatory requirements

* ER negative women must have received prior chemotherapy.

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

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, celecoxib, salicylates or sulphonamides
6. On current or planned chronic NSAIDs therapy (except low dose aspirin ≤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 (i.e. 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. Hormone receptor 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.
17. 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.
18. Psychiatric or addictive disorders which could preclude obtaining informed consent.

19. Clinical evidence of severe osteoporosis and/or history of osteoporotic fracture.

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

2.0 Trial objectives

There are several reasons for initiating a randomised study to examine the impact of COX-2 inhibition in enhancing the adjuvant treatment of breast cancer - COX-2 inhibition may result in inhibition of angiogenesis, inhibition of cell growth, inhibition of tumour-associated inflammation, inhibition of invasion and promotion of apoptosis.

2.1 Primary objectives

- 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.

2.2 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 the tolerability of celecoxib with hormone therapy.
- To assess acute and late toxicities after radiotherapy for each treatment group.

2.3 Tertiary objectives

To investigate COX2 level and other tumour-associated proteins in the tumour tissue and relate these findings to trial outcome.

3.0 Sample size and power

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 on-going the Independent Data Monitoring Committee (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 approximately ¼, ½, and ¾ of the required number of events.

4.0 Randomisation procedures

Patients confirmed as being eligible for the trial are randomised to receive either celecoxib or placebo in a 2:1 ratio in favour of celecoxib. The first patient was recruited on 19/01/2007, randomisation is performed using computer generated permuted blocks. Patients are stratified according to their treatment centre and hormone receptor status. Patients are randomised:

- Within 3 months of definitive breast surgery, (if no chemotherapy is to be given or already received neo-adjuvant chemotherapy). The patient can be given radiotherapy concurrently with the study medication.
- If adjuvant chemotherapy has been received then the treatment must be finished and the patient must have received at least 4 cycles. Entry into the study must be within between 3 weeks and 4 months of day 1 of the last cycle.
- Within 6 weeks of the end of radiotherapy.

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

Each patient is allocated a unique trial number which is used to identify the patient on all subsequent case report forms.

5.0 Endpoints

5.1 Primary

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.

5.2 Secondary

- 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+, HR-) will be performed using the same endpoints as

in the analysis of all patients. These analyses will be exploratory in nature as the trial is not powered to detect differential treatment effects within these subgroups.

6.0 Analysis methods

6.1 Efficacy Analysis

All patients will be evaluated for endpoints in the treatment group 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 patients randomised.

The principal analysis will be based on a log rank comparison of DFS (as defined below). 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, COX-2 status and chemotherapy regimen. Exploratory sub group analyses will be reported via Forest plots 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.

6.2 Safety Analysis

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. 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. "Other" toxicities specified by text will be coded according to the latest version of MedDRA available. The Chief Investigator may wish to group MedDRA codes further into more clinically meaningful groups for analysis and interpretation.

Incidence of cardiovascular events after randomisation will be compared between the two treatment groups and the absolute difference in incidence will be estimated (with associated confidence limits). Subgroup analysis based on HR status (HR+, HR-) 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.

6.3 Primary endpoint

Disease free survival (DFS) 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 recurrence, all patients must be followed up for distant recurrence, second malignancy and survival. Similarly in the case of second malignancy, patients should continue to be followed for distant recurrence and where possible the relation of any subsequent distant recurrence and/or death to the primary or second cancer should be established.

In the case of a second malignancy and subsequent distant recurrence, only distant recurrence attributable to the primary breast cancer will be included as a DFS event. In the event of uncertainty about the relation of the distant recurrence it will be assumed that the recurrence is related to the primary breast cancer.

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

Relapse will be categorised as follows:

- Ipsilateral breast,
- Axillary nodal relapse or relapse to the supraclavicular nodes (Loco-regional),
- Distant relapse (Distant),
- Contralateral breast disease (malignant) (2nd primary).

Any relapse requires 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 v7.

'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 protocol treatment after a second (non-breast) primary is diagnosed.

6.4 Secondary endpoints

Overall survival

Overall survival time will be calculated as date of randomisation until the date of death from any cause or censored at the date the patient was last seen alive. The Kaplan-Meier method will be used to estimate overall survival and differences between treatment groups will be compared using the log rank test. Multivariable analysis will be performed using the Cox proportional hazards model to adjust for known clinical prognostic factors. The proportional hazards assumption of the Cox model will be assessed using the *stphtest* command in Stata. The ITT population will be used for this analysis.

6.5 Baseline characteristics

All baseline characteristics will be tabulated by treatment group. No formal tests shall be made between the groups unless there appears to be a large difference between the treatment groups with regard to a particular baseline variable. In this case a test for difference may be considered.

6.6 Patient flow through trial

A CONSORT diagram will be presented to show the flow of patients through the trial.

6.7 Treatment compliance

Patients who deviate from their randomised treatment will be investigated. Numbers deviating and reasons for this will be tabulated by treatment group.

6.8 Exploratory analyses

Additional analyses other than those listed as primary and secondary above may be performed as appropriate.

7.0 Data monitoring and interim analyses

An Independent Data Monitoring and Committee (IDMC) has been set up to monitor the progress of the trial. They will meet at regular intervals as they see fit but at least annually. Following each

meeting, they will report their findings and recommendations to the chairs of the Trial Management Group and Trial Steering Committee. All interim analyses will be supplied in confidence by the trial statistician to the IDMC together with any other analyses the IDMC request. The IDMC will advise on the frequency of reviews of the data on the basis of accrual and event rates.

8.0 Procedures for monitoring data accuracy and data entry quality assurance

Data entry and management are conducted according to relevant SOPs at ICCG (Imperial) and GBG. Details of the data accuracy checking procedure can be found in the central statistical data monitoring plan, stored in the statistical TMF.

9.0 Analysis Programs

Analysis will be conducted using Microsoft Excel, SPSS and Stata version 10.0 (or subsequent versions). Programs will be in the relevant ANALYSES directory.

10.0 Analysis program locations

All programs will be stored in the analyses folder for REACT on the ICR-CTSU server (ANALYSES directory). Only the REACT trial statistician(s), ICR-CTSU IT staff and, if appropriate, Translational Analyst Scientist, Director and Deputy Directors of ICR-CTSU will be able to see the analysis folder. Programmes will be stored under the type of analysis e.g. IDMC meeting. All official analysis reports that are to be circulated externally of ICR-CTSU will be password protected. Hard copies of reports will be stored securely in the statistical section of the REACT trial master file held in a locked fire proof cupboard with restricted access.

11.0 References

None