

**Neoadjuvant trial of pre-operative exemestane or  
letrozole +/- celecoxib in the treatment of ER positive  
postmenopausal early breast cancer**

**Protocol Version 2, 19<sup>th</sup> January 2007**

**EudraCT Number:2006-000436-27  
Protocol Number:BR3031  
ISRCTN09768535**



University Hospital Birmingham **NHS**  
NHS Trust





## INVESTIGATOR SIGNATURE PAGE

**Investigator Signature:**

I have read and agree to the protocol, as detailed in this document. I agree to adhere to the protocol as outlined and agree that any suggested changes to the protocol must be approved by the Trial Steering Committee prior to seeking approval from the Independent Ethics Committee.

I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP)<sup>1</sup>, the Declaration of Helsinki, local regulations (as applicable) and the study protocol and I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

**Investigator's Name:** \_\_\_\_\_

**Signature:** \_\_\_\_\_

**Name of Institution:** \_\_\_\_\_

**Date:** \_\_\_\_\_

**The Principal Investigator should sign this page and return a copy to the NEO-EXCEL Trial Office**

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<sup>1</sup>European Commission Directive (91/507/EEC), July 1991.

ICH Harmonised Tripartite Guideline E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Step 5, adopted by CPMP July 1996.

Food and Drug Administration Code of Federal Regulations for Good Clinical Practices Parts 50, 56, 312, 314.



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<b>Main REC Number:</b>	06/MRE07/31 (West Midlands MREC)
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<b>Protocol Code:</b>	BR3031

This clinical trial protocol is intended to provide guidance and information only for the conduct of the NEO-EXCEL trial in participating centres.  
It is not for use as a guide for the management of other patients outside of the trial.



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## Clinical Trial Supplies

**Drug Distribution:**  
**DHP Pharma Ltd.**  
**Elvicta Business Park, Crickhowell, Powys, NP8 1DF**

**For queries during the hours 9:00am-5:00pm:**  
**☎ NEO-EXCEL Study Office on 0121 414 3797**

**Refer to NEO-EXCEL Pharmacy File/Investigator Site File for full pharmacy instructions and codebreak procedure.**



## 2. TRIAL SUMMARY

### ACRONYM: NEO-EXCEL

**TITLE:** A neoadjuvant trial of pre-operative exemestane or letrozole +/- celecoxib in the treatment of oestrogen receptor (ER) positive postmenopausal early breast cancer.

### TRIAL OBJECTIVES

To determine if exemestane is superior to letrozole as primary neoadjuvant endocrine therapy for early stage ER positive breast cancer in postmenopausal women, and whether the activity of aromatase inhibitors in this setting may be enhanced by the addition of the selective COX 2 inhibitor celecoxib.

### TRIAL DESIGN

Prospective Phase III, multicentre, bifactorial (four-arm), randomised clinical trial, with both open label and placebo-controlled comparisons.

### OUTCOME MEASURES

#### Primary

- Objective clinical response (Complete Response, Partial Response) to neoadjuvant treatment

#### Secondary

- Objective ultrasound-determined response (CR, PR) to neoadjuvant treatment
- Type of surgery (mastectomy, breast conserving surgery)
- Axillary lymph node involvement at surgery
- Complete pathological response
- Local recurrence-free survival
- Progression-free survival
- Overall survival

#### Translational sub-study

- Biological profiling for prognostic and predictive indicators

### SAMPLE SIZE

1000 subjects

### MAIN SELECTION CRITERIA

Women with a histological diagnosis of early invasive breast carcinoma, meeting the following criteria:

- Postmenopausal
- ER positive
- Breast tumour >2cm by clinical evaluation
- No previous treatment for breast cancer
- Adequate haematological, renal and hepatic function
- ECOG performance status 0, 1 or 2

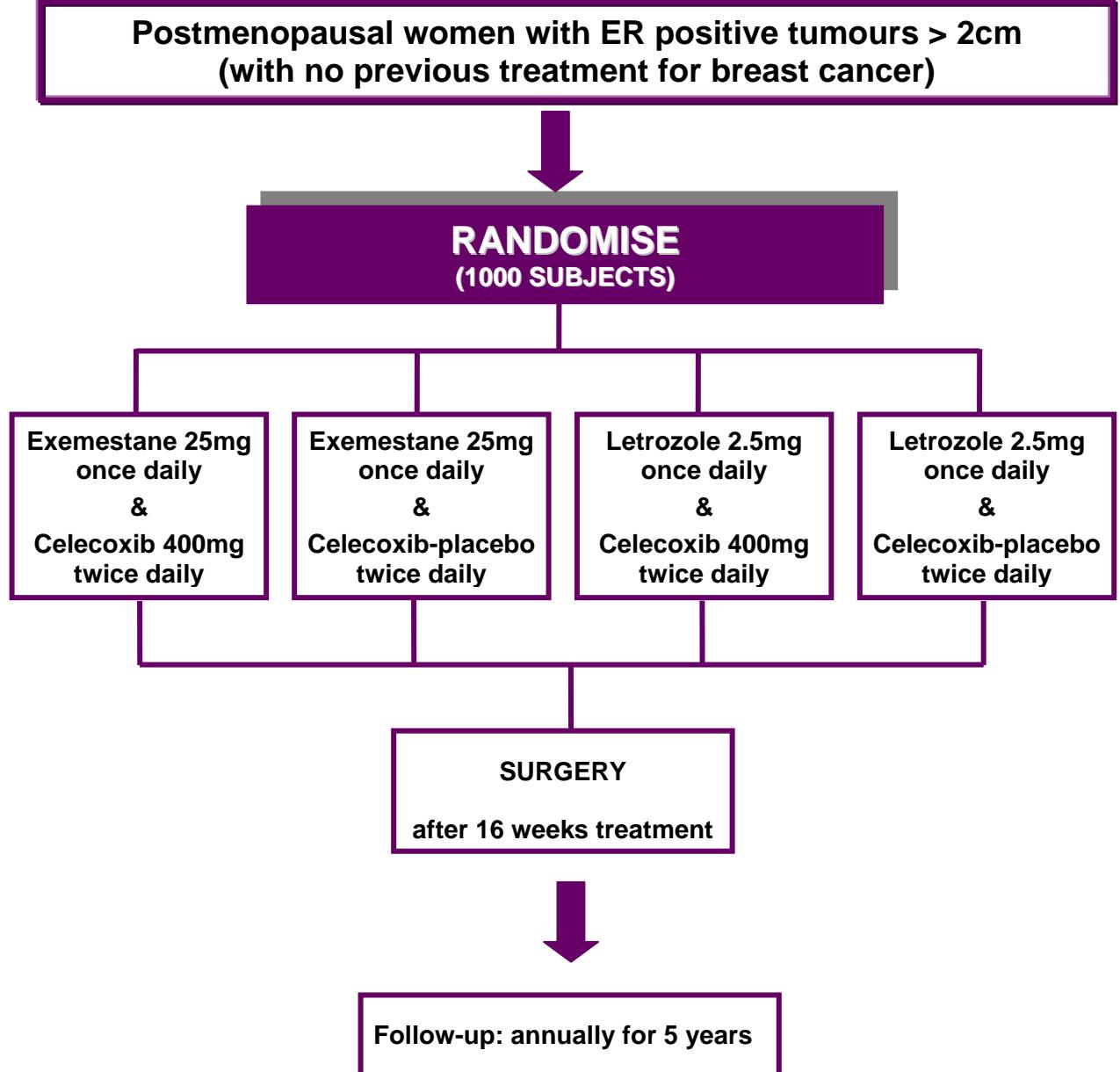
### RANDOMISATION

(9:00am till 5:00pm, Monday to Friday)

☎ 0800 371 969 or 0800 731 7625

📠 0800 328 6412

# Trial Schema



### 3. BACKGROUND AND INTRODUCTION

#### 3.1 Current surgical treatment for postmenopausal early breast cancer

The management of early stage breast cancer remains sub-optimal. Standard treatment is primary surgery and subsequent selective adjuvant radiotherapy, hormone therapy and chemotherapy. Larger tumours and those close to the nipple are usually treated by mastectomy whilst smaller more peripheral tumours are often suitable for breast conserving surgery. There is good evidence that body image is just as important to postmenopausal women as it is to younger patients<sup>1</sup>. Neoadjuvant chemotherapy, usually offered to younger patients, can achieve overall survival identical to post-operative chemotherapy but with the additional benefit of less radical surgery<sup>2-4</sup>. Postmenopausal patients are not routinely given the opportunity of neoadjuvant chemotherapy to downstage their tumours and allow less disfiguring surgery because of concerns about the associated toxicity. Furthermore the large majority of these patients have oestrogen receptor-positive tumours and may thus be less likely to respond well to chemotherapy. However, the proven ability of aromatase inhibitors to downstage these tumours<sup>5</sup> pre-operatively, without the toxicity of chemotherapy, is currently infrequently utilised and is the subject of this study.

#### 3.2 Aromatase inhibitors and breast cancer

Aromatase inhibitors are administered systemically to inhibit oestrogen synthesis in tissues by the aromatase enzyme which catalyses the conversion of androgens to oestrogens. Aminoglutethimide is a first-generation aromatase inhibitor and although effective as treatment for advanced disease and active as an adjuvant therapy in breast cancer,<sup>6</sup> it was poorly tolerated and was partially replaced by the better tolerated second-generation aromatase inhibitor formestane. However the drawbacks of this compound were that not only did it require parenteral administration, but it only suppressed oestradiol to 1/3 of baseline levels<sup>7,8</sup>. The current third-generation aromatase inhibitors fall into two categories, irreversible steroidal type I inhibitors such as exemestane and non-steroidal type II inhibitors such as letrozole and anastrozole. These drugs are far more potent than their predecessors in terms of oestradiol reduction, are orally administered, and are in many respects better tolerated than tamoxifen<sup>9,10</sup>.

There is increasing and compelling evidence to indicate that third-generation aromatase inhibitors are more effective than tamoxifen in the advanced and adjuvant setting. There is also accumulating evidence that aromatase inhibitors are superior to tamoxifen as pre-operative therapy.

Data from the Anastrozole, Tamoxifen Alone or in Combination (ATAC) trial demonstrate that anastrozole has a relapse-free survival benefit over tamoxifen in the adjuvant setting, with generally improved tolerability<sup>11-13</sup>. Exemestane has demonstrated superior efficacy compared to tamoxifen when introduced half way through a 5-year program of adjuvant hormone therapy<sup>14</sup>. Toxicity differences are similar but not identical to those seen in the ATAC study, with fewer gynaecological symptoms and a reduced incidence of endometrial cancer. However aromatase inhibitors are associated with a higher incidence of arthralgia and bone mineral density loss when used over long periods. Preliminary reports now indicate that letrozole is also more active than tamoxifen in the adjuvant setting with a similar hazard ratio. (B. J. Thurlimann, A. Keshaviah, H. Mouridsen, L. Mauriac, J. F. Forbes, R. Paridaens, M. Castiglione-Gertsch, R. D. Gelber, I. Smith, A. Goldhirsch abst 511. BIG 1-98: Randomized double-blind phase III study to evaluate letrozole (L) vs. tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer).

### 3.2.1 Neoadjuvant aromatase inhibitor use in breast cancer

Two randomised Phase III trials have compared pre-operative tamoxifen with an aromatase inhibitor. The P024 trial randomised 337 postmenopausal women with ER positive tumours to 16 weeks neoadjuvant letrozole (2.5mg/day) versus tamoxifen (20mg/day)<sup>15</sup>. The primary endpoint was to compare overall objective response (CR+PR). Secondary endpoints included rates of breast conserving surgery. Results clearly showed letrozole to be significantly more effective than tamoxifen in respect of objective response (55% versus 36%, p<0.001). Clinically determined complete response rates were 10% for letrozole and 4% for tamoxifen. Letrozole was at least as well tolerated (Table I). Letrozole permitted significantly more breast conserving surgery (45% versus 35%, p=0.022). Clinical response rate differences were confirmed by ultrasound and mammographic response assessments (35% versus 25% and 34% versus 16% respectively). In this study, pre-treatment biopsies were analysed and two potentially important correlations of response and molecular features have been reported<sup>16</sup>. Tumours expressing either HER-1 or HER-2 (ErbB-1/Erb-B2) or both markers were associated with poor response to tamoxifen, 4/19 (21%). This difference was statistically significant p=0.004 compared to 15/17 (88%). Response rates in tumours negative for both markers were 42/100 (42%) for tamoxifen and 55/101 (54%) for letrozole, which were not significantly different. The other observation was a higher response rate in tumours with higher levels of ER scored by Allred score, irrespective of treatment allocation. This appeared most striking for tamoxifen, with no responses seen with scores below 6, but responses were observed with letrozole in tumours with Allred scores as low as 3. This relationship was however not statistically different with small numbers of tumours in the low Allred score groups. In case series where only strongly positive tumours have been treated, no clear patterns of differential sensitivity between the aromatase inhibitors have emerged<sup>17</sup>. In any new large study of neoadjuvant therapy, central review of the quantitative steroid hormone receptor expression is therefore critical.

The IMPACT trial randomised 330 women and compared 12 weeks of anastrozole with 12 weeks of tamoxifen and the combination of both agents as neoadjuvant therapy<sup>18</sup>. The overall response rate was 37.2 % for anastrozole, 36.1% for the combination and 39.4% for tamoxifen. In larger tumours where pre-treatment mastectomy was thought to be required anastrozole was associated with a higher probability of downstaging to permit breast conservation. HER-2 expression was observed to predict low response to tamoxifen, with maintained response to anastrozole. However the sample size was small and statistically unreliable. As the P024 and IMPACT studies involved different treatment durations and different inclusion criteria it is not possible to make any firm conclusions from cross comparisons, but the clear difference in response rates between tamoxifen and letrozole is encouraging.

Another study, the PROACT trial, randomised 451 women to receive 12 weeks of anastrozole or tamoxifen treatment before surgery in a double-blind trial in which some patients also received chemotherapy. While the presence of chemotherapy has somewhat complicated the interpretation of this study, anastrozole use was associated with a higher rate of breast conserving surgery over tamoxifen.

Exemestane has been less extensively evaluated as a neoadjuvant therapy. Recently reported studies include a multicentre French trial in which 38 ER positive postmenopausal women requiring mastectomy pre-treatment were treated with exemestane 25 mg/day for 16 weeks. The overall response rate was reported as 70.6%, with 45.2% of women able to undergo breast conserving surgery<sup>19</sup>.

The Edinburgh group have reported a single centre randomised Phase II trial comparing tamoxifen with exemestane<sup>20</sup>. They report an 83% response rate (10/12 patients). More extensive experience is reported by the Russian group who have conducted a randomised Phase II trial. Here 73 postmenopausal women with ER positive tumours were randomised to tamoxifen or exemestane for 12 weeks. Exemestane was reported to have an overall response rate of 69.4% and tamoxifen 40.5%. The rate of breast conservation was 38.7 % for exemestane and 10.8 % for tamoxifen<sup>21</sup>. This group has also reported a further randomised Phase II trial comparing neoadjuvant chemotherapy, using doxorubicin and paclitaxel, against neoadjuvant endocrine therapy using anastrozole or exemestane. 146 postmenopausal women with ER or PgR positive large primary breast tumours were randomised. Overall response was similar in all three groups; chemotherapy 76%, anastrozole 75.6% and exemestane 81.5%. Breast conserving surgery was more common in the endocrine treated group, 34% versus 23.934%,  $p=0.058$ . Endocrine therapy was clearly better tolerated in this study, and low toxicity has been observed in all studies of neoadjuvant exemestane<sup>22</sup>.

### 3.3 COX 2 inhibitors and breast cancer

The potential for cyclo-oxygenase (COX) inhibition in cancer prevention and treatment is founded on epidemiology (reduction of colorectal cancers in aspirin users), animal experiments and molecular genetics. Non-steroidal anti-inflammatory drugs (NSAIDS) block endogenous prostaglandin synthesis from arachidonic acid through inhibition of cyclo-oxygenase enzyme activity, primarily that of COX 2. COX 2 is frequently overexpressed in tumours and is inducible by various agents such as growth factors and tumour promoters.

The role of COX 2 in carcinogenesis is thought to be related to its abilities to increase production of prostaglandins, convert pro-carcinogens to carcinogens, inhibit apoptosis, promote angiogenesis, modulate inflammation and immune function and increase tumour cell invasiveness<sup>23</sup>. The advent of specific COX 2 inhibitors which do not interfere with the cytoprotective constitutive COX I enzyme has opened up new therapeutic possibilities. A review of the role of COX 2 inhibitors in breast cancer<sup>24</sup> provides overwhelming evidence from molecular, animal and cell line studies supporting the ability of COX 2 inhibitors to prevent the development of breast tumours. Administration of increasing doses of the COX 2 inhibitor celecoxib inhibited mammary tumour incidence and multiplicity as well as tumour volume in a dose dependant manner in female Sprague-Dawley rats. The control rats had a higher incidence of tumours ( $p<0.001$ ), higher tumour volume ( $p<0.001$ ) and more tumours ( $p<0.001$ ) than animals receiving celecoxib<sup>25</sup>. The effect of cyclo-oxygenase inhibition on tumour growth has also been studied in breast cancer cells in BALB/c mice. Microvessel density was reduced and tumour cell apoptosis was increased in primary tumours of mice treated with cyclo-oxygenase inhibitors. In vitro, cyclo-oxygenase inhibition decreased vascular endothelial growth factor production and increased apoptosis of cells<sup>26</sup>.

Epidemiological evidence shows that long-term use of NSAIDS appears to reduce the risk of developing breast cancer, with a risk reduction of nearly 25% in the most recent studies<sup>27-29</sup>. Celecoxib has been licensed by the FDA for the prevention of colorectal carcinoma in the USA.

COX 2 inhibition enhances the apoptotic effect of chemotherapy<sup>30</sup> and the combination of the two treatments is currently under investigation in Phase III trials in several tumour types. Linkage between the COX 2 and aromatase enzyme systems in malignancy suggest that COX 2 inhibition with aromatase inhibition may also be more effective than either therapy alone.

In a previously reported case controlled study (BMC Cancer 2006) a significant reduction in the risk of human breast cancer due to intake of selective COX 2 inhibitors has been observed. Chemopreventive effects against breast cancer were associated with recommended daily doses of celecoxib (median dose=200 mg) or rofecoxib (median dose=25 mg) for an average duration of 3.6 years. Nevertheless, even in the short window of exposure to these compounds, the selective COX 2 inhibitors produced a significant (71%) reduction in the risk of breast cancer, underscoring their strong potential for breast cancer chemoprevention.

### 3.4 Aromatase inhibitors with COX 2 inhibitors in breast cancer

COX 2 expression and aromatase expression have been found to correlate in breast cancer tissue<sup>31</sup>. The COX 2 product prostaglandin E2 (PGE2) and cytokines such as interleukin-6 (IL6) can up regulate aromatase expression through interaction with the 1.3 promoter of the aromatase gene<sup>32</sup>, with the resulting possibility that aromatase inhibition and COX 2 inhibition treatments may be more effective when prescribed together. Reviewed in Annals of Oncology, 2002 (Davies G et al).

The Glasgow group has reported good tolerability and encouraging activity in a Phase II feasibility study of the combination of exemestane and celecoxib in postmenopausal women with ER positive advanced breast cancer<sup>33</sup>. The CAAN trial reported at San Antonio 2003 that exemestane plus celecoxib is well tolerated in patients with locally advanced breast cancer. However, evidence of the therapeutic superiority of this combination compared to exemestane alone as anticancer treatment is currently lacking.

### 3.5 Celecoxib: clinical pharmacology

Celecoxib is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of celecoxib is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of COX 2 and at therapeutic concentrations in humans, celecoxib does not inhibit the COX 1 isoenzyme. In animal colon tumour models, celecoxib reduced the incidence and multiplicity of tumours (Pfizer data on file).

#### 3.5.1 Pharmacokinetics

**Absorption:** Peak plasma levels of celecoxib occur approximately 3hrs after an oral dose. Under fasting conditions, both peak plasma levels (Cmax) and area under the curve (AUC) are roughly dose proportional up to 200 mg 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.

**Distribution:** In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose range. In vitro studies indicate that celecoxib binds primarily to albumin and, to a lesser extent,  $\alpha$ 1-acid glycoprotein. The apparent volume of distribution at steady state (Vss/F) is approximately 400L, suggesting extensive distribution into the tissues. Celecoxib is not preferentially bound to red blood cells.

**Metabolism:** Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX 1 or COX 2 inhibitors. Patients who are known or suspected to be P450 2C9 poor metabolisers based on a previous history should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

**Excretion:** Celecoxib is eliminated predominantly by hepatic metabolism with little (< 3%) unchanged drug recovered in the urine and faeces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the faeces and 27% was excreted into the urine. The primary metabolite in both urine and faeces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making terminal half-life ( $t_{1/2}$ ) determinations more variable. The effective half-life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500mL/min (Pfizer data on file).

### 3.5.2 Cardiovascular safety of celecoxib

At the end of 2004, as a result of a small but statistically significant excess of myocardial and cerebrovascular events, in a trial using the COX 2 inhibitor rofecoxib versus placebo as secondary prophylaxis in patients with colorectal polyps, rofecoxib was voluntarily withdrawn from sale. The increased risk did not emerge until patients had been exposed to the drug for more than 18 months and the risk appears to be a chronic effect. The aetiology of the increased cardiovascular risk is as yet unclear and the magnitude of the increased risk is small. The clinical data which prompted the withdrawal of rofecoxib relates specifically to rofecoxib.

There is however a substantial body of evidence supporting the safety of celecoxib:

A pooled analysis of 30,000 patients who completed arthritis trials (including the CLASS and SUCCESS trials) indicates that celecoxib did not increase the incidence of thromboembolic events versus placebo, or in comparison with traditional NSAIDS<sup>34</sup>. In the CLASS trial, a long-term (12 month) prospective study, celecoxib, even at 2-4 times the approved dose for arthritis and pain, was not associated with an increased risk for serious cardiovascular events such as heart attack, stroke or unstable angina compared to non-specific NSAIDS<sup>35</sup>.

A recent FDA funded retrospective analysis of 1.4 million patients who were treated with COX 2 inhibitors or traditional NSAIDS showed that celecoxib demonstrated no increase in the relative risk of acute cardiac events when compared with those who had not taken any NSAID for at least 60 days<sup>36</sup>.

In a cohort analysis of over 138,000 people aged 65 or over, patients on celecoxib had a significantly less chance of being hospitalised for congestive heart failure than users of traditional NSAIDS and rofecoxib<sup>37</sup>.

A retrospective study of more than 54,000 elderly patients published in the journal, Circulation, showed that celecoxib was not associated with an increased risk for acute myocardial infarct compared with rofecoxib, traditional NSAIDS and no NSAID therapy<sup>38</sup>.

In December 2004 important safety information was reported from the Independent Data Safety Monitoring Boards (IDSMB) of the US National Cancer Institute monitoring the Adenoma Prevention with Celebrex (APC) and the Prevention of Spontaneous Adenomatous Polyps (PreSAP) trials. Results from a third long-term celecoxib study, a US National Institutes Aging



of Alzheimer's Prevention trial (ADAPT), were also recently reported. The results of these 3 studies are summarized below.

The cancer prevention studies used the same cardiovascular review board (commissioned by the Data Safety Monitoring Boards of the two respective trials) to adjudicate the results and used the same analysis methods. Patients in the studies were treated for up to 4 years.

### **APC**

In the Adenoma Prevention with Celecoxib (APC) Trial, celecoxib demonstrated a statistically significant increased cardiovascular risk over placebo. The doses of celecoxib in this trial were 400-800mg per day. These findings were unexpected and not consistent with other reported findings from the PreSAP trial. Patients taking 400 and 800mg of celecoxib daily had an approximately 2.5-fold increase in their risk of experiencing a major fatal or non-fatal cardiovascular event compared to those taking placebo.

### **PreSAP**

In the Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial there has been no increased risk for celecoxib patients taking 400mg daily compared with placebo. The two studies, which are following patients for 5 years, have enrolled a total of about 3,600 patients.

### **ADAPT**

The third trial (ADAPT) compared celecoxib to either naproxen sodium or placebo in a group of patients at risk for Alzheimer's disease treated for up to 3 years. Preliminary safety results (not yet adjudicated) from that study indicate an increased cardiovascular risk with naproxen sodium but not celecoxib relative to placebo.

As a result of this new data, in February 2005 the CSM issued the following advice for all selective COX 2 inhibitors (celecoxib, etoricoxib, valdecoxib and parecoxib) which has been entirely incorporated into the NEO-EXCEL protocol:

'Patients with established ischaemic heart disease or cerebrovascular disease should be switched to alternative treatment: in addition the existing contraindication for severe heart failure is now extended to include moderate heart failure (NYHA class II-IV). For all patients the balance of gastrointestinal and cardiovascular risk should be considered before prescribing a COX 2 inhibitor, particularly in those with risk factors for heart disease and those taking low dose aspirin, for whom gastrointestinal benefit has not been clearly demonstrated. The lowest effective dose of COX 2 inhibitor should be used for the shortest necessary period. Periodic re-evaluation is recommended, especially for osteoarthritis patients who may only require intermittent treatment.'

There is a wealth of data supporting gastrointestinal safety and the tolerability profile of celecoxib. In a retrospective observational study of 144,000 elderly patients, celecoxib demonstrated a reduced risk of hospitalisation due to upper GI haemorrhage versus traditional NSAIDS, misoprostol plus diclofenac and rofecoxib<sup>39</sup>.

## 3.6 Letrozole / Exemestane: clinical pharmacology

### 3.6.1 Letrozole

Letrozole is a highly potent, orally active non-steroidal competitive inhibitor of the aromatase enzyme system. It effectively inhibits the conversion of androgens to oestrogens in both *in vitro* and *in vivo*. It is currently approved for use in women with locally advanced and metastatic breast cancer as first-line use and after anti-oestrogen failure. It is also approved for treatment of ER positive operable primary breast cancer to downstage the disease to facilitate less extensive surgery. In addition letrozole is also licensed for use after adjuvant tamoxifen as extended adjuvant therapy.

#### Preclinical pharmacology

Letrozole competitively inhibits the human placental aromatase enzyme *in vitro* ( $IC_{50}$  11.5nM,  $K_i$  2.1nm), is 170 times more potent than aminoglutethimide<sup>40</sup> and does not significantly affect adrenal steroidogenesis. *In vivo* studies have shown letrozole to be over 10,000 times as potent as aminoglutethimide<sup>41</sup>.

#### Clinical pharmacology

In postmenopausal women with advanced breast cancer letrozole suppressed plasma levels of oestradiol, oestrone and oestrone sulphate by 75-95% of baseline in a dose dependent manner with 0.5mg and higher suppressing oestrogen oestrone and oestrone sulphate below the limits of detection. There is no detectable effect of letrozole on adrenal corticosteroid synthesis, aldosterone synthesis or androgen levels in healthy postmenopausal volunteers<sup>42</sup>.

Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability of 99.9%). Food slightly decreases the rate of absorption (median  $t_{max}$ : 1 hour fasted versus 2 hours fed; and mean  $C_{max}$ : 129 $\pm$  20.3nmol/l fasted versus 98.7 $\pm$  18.6nmol/l fed) but the extent of absorption (AUC) is not changed. The minor effect on the absorption rate is not considered to be of clinical relevance and therefore letrozole may be taken without regard to meal times. Clearance is via conversion to an inactive hydroxymetabolite. Elimination is almost exclusively via the kidneys as the inactive metabolite, clearance is however not dependent on renal function.

#### Letrozole in advanced breast cancer treatment

Early phase experience with letrozole has been reproduced in large Phase III trials where the drug was generally well-tolerated, with the most frequently reported adverse events being bone pain, hot flushes, back pain, nausea and arthralgia. These were similar in both first-line and second-line settings<sup>9,43</sup>. In the neoadjuvant setting letrozole is well-tolerated and safe, with hot flushes, arthralgia and nausea the most frequently reported adverse events. In the adjuvant context, letrozole has been compared to placebo after prior tamoxifen exposure. Here hot flushes and musculoskeletal complaints were more common with letrozole. Vaginal bleeding was less common. In addition osteoporosis was more common with letrozole and fractures were numerically, but non-significantly, more common<sup>44</sup>.

Letrozole (2.5mg/day) was compared to tamoxifen (20mg/day) in a large Phase III trial in women with locally advanced or metastatic breast cancer<sup>43</sup>. In this study of 907 patients, letrozole was associated with a superior median time to progression of 9.4 months versus 6.0 months,  $p < 0.0001$ . Overall response was 32% versus 21%,  $p = 0.0002$ . Letrozole (2.5 mg/day) has also been compared with megestrol acetate in women with advanced breast cancer failing prior tamoxifen. In this trial letrozole was the more active agent, with a response rate of 23.6%

versus 16.4%,  $p=0.04$ . Here letrozole, at the lower dose of 0.5mg/day, was also less active than the 2.5mg cohort.

### **Letrozole as adjuvant therapy**

Letrozole has also been studied in the adjuvant context. A large trial comparing tamoxifen for 5 years with letrozole for 5 years and two sequential arms in which the two drugs are administered in sequence, switching after 2.5 years to the alternative agent, has been conducted and preliminary data are expected shortly. Letrozole has also been compared with placebo after the completion of 5 years adjuvant therapy. In this study of 5187 women an improvement in disease-free survival emerged after a median follow-up of 2.4 years when the study was unblinded. The Hazard Ratio (HR) was 0.58, with an estimated 4 year disease free survival of 93% versus 87%. Preliminary data from a complex adjuvant letrozole trial, BIG 1-98, has also been released. This large randomised study compares tamoxifen for 5 years with letrozole for 5 years and sequential tamoxifen/letrozole and letrozole/tamoxifen. Data from all four arms has been analysed to provide a comparison of tamoxifen versus letrozole, with patient data censored at the crossover point within the switching arms. This shows superiority for letrozole versus tamoxifen, HR 0.81 (95% CI 0.7-0-0.93). While generally well-tolerated this trial has reported a non-significant excess of fatal myocardial infarctions in the letrozole treated group (13 versus 6 in over 8000 patients). As it is non-significant and was not seen in the MA-17 trial the importance and potential cause is speculative and unlikely to be relevant to a short-term 16 week exposure to letrozole (Thurliman et al. ASCO 2005).

### **Neoadjuvant tolerability**

The clinical efficacy of neoadjuvant letrozole was discussed earlier; letrozole is well-tolerated with serious adverse events only rarely encountered (one pulmonary embolus reported in the P024 study). Adverse events occurring in  $>2\%$  of patients are reproduced from this study in Table 1.

**TABLE 1: Adverse Events with neoadjuvant letrozole and tamoxifen**

ADVERSE EVENTS	Letrozole, n= 157	Tamoxifen, n=170
Hot Flushes	20%	24%
Nausea	5%	5%
Asthenia	2%	3%
Fatigue	3%	2%
Increased sweating	2%	3%
Weight gain	2%	2%
Leukorrhea	0%	4%
Pruritis	1%	2%
Headache	3%	1%
Dyspepsia	1%	2%
Hair Thinning	2%	1%

### 3.6.2 Exemestane

Exemestane is a very potent, orally active, selective and long lasting steroid, irreversible inactivator of aromatase. In *in vitro* studies exemestane appeared to be 2.8 and 156 times more potent than the steroid formestane and the non-steroidal aminoglutethimide (AG), respectively, in inhibiting human placental aromatase<sup>45</sup>.

*In vivo* studies of aromatase inactivation indicate that exemestane, by the oral route, is several times more potent than formestane and suppresses plasma oestrogen by approximately 98% compared with baseline<sup>46</sup>. Exemestane has no noteworthy binding to oestrogen, progesterone, glucocorticoid or mineralocorticoid receptors and only a very low binding to the androgen receptor (Relative Binding Affinity, RBA, 0.2% from that of dihydrotestosterone, DHT)<sup>47</sup>. However, its metabolite FCE 25071 (17-hydro-exemestane) was found to have a binding affinity to the androgen receptor (100-fold higher than that of exemestane (RBA 27% from and 0.28% that of DHT, respectively) (Pfizer Inc, data on file).

#### **Exemestane in the treatment of advanced breast cancer**

Exemestane (25mg/day) has been compared to tamoxifen (20mg/day) in first-line therapy for advanced breast cancer in the EORTC 10951 randomised Phase III study. Preliminary data shows a significant response rate advantage to exemestane (46% versus 31%,  $p=0.005$ ). Time to progression was also longer, 10 months versus 6 months. This was not significant in the primary analysis using a log rank test,  $p=0.121$ , but was significant with a secondary Wilcoxon sensitivity analysis,  $p=0.028$ . Exemestane was well-tolerated with hot flushes, bone pain and gastrointestinal adverse events the most commonly reported events.

Exemestane (25mg daily) was evaluated in a Phase III, randomised double-blind, comparative study of postmenopausal women with advanced breast cancer who had disease progression after hormonal treatment with anti-oestrogens (primarily tamoxifen) for metastatic disease or as adjuvant therapy. In this study, 769 patients were randomised to receive exemestane 25mg once daily ( $n=366$ ) or megestrol acetate 40mg four times daily ( $n=403$ ). Response rate for exemestane was 15.0% versus 12.4% for megestrol acetate. Time to progression was longer with exemestane (20.3 weeks versus 16.6 weeks,  $p=0.037$ ) and survival was superior, median survival for exemestane was not reached versus 123 weeks for megestrol acetate,  $p=0.039$ <sup>48</sup>.

#### **Exemestane as adjuvant therapy**

The Intergroup Exemestane Study (IES) randomised women with early breast cancer who were disease free after 2-3 years of prior tamoxifen therapy to either continue to complete 5 years of adjuvant tamoxifen or to commence exemestane (25mg) once daily. This double-blind study of over 4,700 patients has recently published interim findings after a median follow-up of 30 months. This study, in a different population, has shown a somewhat larger difference than the ATAC study with a HR of 0.68. This translates to an absolute advantage of 4.77% at 36 months<sup>14</sup>. Within the receptor positive subgroup the hazard ratio rises to 0.64 (95% CI 0.52-0.79).

In this study exemestane was well-tolerated, with arthralgia and hot flushes again the commonest reported adverse events, but diarrhoea was also seen here. Osteoporosis was more commonly reported with letrozole and fractures were numerically but not significantly more common (Table 2).

The TEAM trial is a large multinational study initially designed to compare 5 years of exemestane with 5 years of tamoxifen. This trial has been revised in the light of the IES data to

compare exemestane as initial therapy versus a switching policy in which women initiated on tamoxifen cross over to exemestane after 2-3 years.

### Exemestane tolerability

Exemestane has been reported as well-tolerated in the small neoadjuvant studies described but a detailed breakdown of the adverse events has not been reported. Table 2 summarises data from the IES trial, which has provided the most detailed comparative information on the tolerability of exemestane and tamoxifen. The most significant toxicities that are worse with exemestane are joint pains and diarrhoea. The TEAM study has also reported short-term tolerability data in the adjuvant setting which demonstrates predominantly better tolerability with exemestane<sup>49</sup>.

**TABLE 2: Adverse events in the IES trial significantly different, or different by >1% or common (>5%)**

ADVERSE EVENTS (ANY GRADE)	Exemestane % (n = 2309)	Tamoxifen % (n = 2332)	P value
Arthralgia	5.4	3.6	<b>0.01</b>
Diarrhoea	4.3	2.3	<b>0.001</b>
Throboembolic AEs	1.0	2.0	0.01
Thromboembolic SAEs	1.3	2.4	0.005
Vaginal bleeding	4.0	5.6	<b>0.01</b>
Other gynaecological symptoms	5.8	9.0	<b>&lt;0.001</b>
Endometrial cancer	0.21 (5 events)	0.46 (11 events)	Not stated
Other malignancy	22	42	Not stated
Cramp	2.8	4.4	<b>0.0007</b>
Sweating	18.6	18.1	
Headache	18.6	16.4	0.09
Dizziness	12.5	12.1	0.93
Visual disturbance	7.4	5.8	<b>0.04</b>
Depression	5.2	4.0	
Osteoporosis	7.4	5.7	<b>0.05</b>
Clinical fracture	3.1	2.3	0.08

## 4. STUDY RATIONALE / TREATMENT SELECTION

The hypotheses to be addressed in this bifactoral Phase III trial are that exemestane may be superior to letrozole (arguably the present standard of care), as primary neoadjuvant endocrine therapy for early stage ER positive breast cancer in postmenopausal women, and that the activity of aromatase inhibitors in this setting may significantly be enhanced by the addition of the selective COX 2 inhibitor, celecoxib.

The rationale for the comparison of letrozole and exemestane is the ostensibly greater response rate reported for exemestane in randomised Phase II studies of exemestane versus tamoxifen than for letrozole in Phase III studies versus tamoxifen. Further justification for the formal comparison refers to their different mechanisms of action. Lastly, the Investigators feel that further exploration of their clinical activity of neoadjuvant endocrine therapy in this population is long overdue and has the potential to impact on clinical practice, notwithstanding the benefits of breast cancer screening.

The conventional tool for the development of new systemic therapies is presently the randomised Phase III clinical trial. Conventionally, in the adjuvant setting this endeavour requires 2-3000 patients and may take 10 years from inception, funding, launch, execution, follow-up and

analysis. By contrast, randomised trials of systemic therapy in the primary or neoadjuvant setting offer economies of scale and the opportunity for time-scale compression. Over recent years compelling evidence has accumulated to link various measures of primary tumour response to eventual disease-free survival, thus validating their candidacy as surrogate endpoints. Two recent trials demonstrated that primary hypotheses tested in the neoadjuvant setting have the power to answer therapeutic questions with a relatively small number of patients because the biological predictors of response are likely to be strong.

## 5. TRIAL DESIGN / OBJECTIVES AND OUTCOME MEASURES

### TRIAL OBJECTIVES

To determine if exemestane is superior to letrozole as primary neoadjuvant endocrine therapy for early stage ER positive breast cancer in postmenopausal women, and whether the activity of aromatase inhibitors in this setting may be enhanced by the addition of the selective COX 2 inhibitor celecoxib.

### TRIAL DESIGN

Prospective Phase III, multicentre, bifactorial (four-arm), randomised clinical trial, with both open label and placebo-controlled comparisons.

### OUTCOME MEASURES

#### Primary

- Objective clinical response (Complete Response, Partial Response) to neoadjuvant treatment

#### Secondary

- Objective ultrasound-determined response (CR, PR) to neoadjuvant treatment
- Type of surgery
- Axillary lymph node involvement at surgery
- Complete pathological response
- Local recurrence-free survival
- Progression-free survival
- Overall survival

#### Translational sub-study

- Biological profiling for prognostic and predictive indicators

## 6. PATIENT SELECTION

### 6.1 Inclusion criteria

The study population consists of postmenopausal women diagnosed with resectable breast cancer, who meet the following eligibility criteria:

- Biopsy proven, ER positive invasive breast cancer (where ER positive is defined as equivalent to an ER “Quick or Allred score” of 3 or greater)
- Tumour, measured on U/S, as greater than 2 cm in diameter
- Postmenopausal, defined as:
  - Any Age:- bilateral surgical oophorectomy
    - amenorrhea  $\geq$  5 years (any cause)

Age  $\geq$  50 yrs:- natural amenorrhea for  $\geq$  1 year

Age  $<50$  yrs: - if amenorrhea  $< 5$  years or hysterectomy without bilateral surgical oophorectomy, then FSH, LH and oestradiol must be assayed to confirm postmenopausal status

- Adequate haematological, renal and liver function, defined as a platelets of  $>100 \times 10^9/l$ , white blood cell count of  $>3 \times 10^9/l$ , creatinine  $<110$  mmol/l, AST and/or ALT  $< 1.25 \times$  upper limit of normal
- Patients must be fit to complete surgery for their breast cancer
- Written informed consent
- ECOG performance status 0,1 or 2

## 6.2 Exclusion criteria

- Bilateral breast cancer
- Evidence of distant metastases (M1)
- Patients who have received previous treatment for invasive breast cancer
- Concomitant active malignancy except for adequately treated carcinoma in situ of the uterine cervix or basal cell carcinoma of the skin
- Co-morbid disease which would preclude safe surgical treatment of the primary cancer
- Other physical or psychiatric disorder that may interfere with subject compliance, adequate informed consent or determine the causality of adverse events
- Contraindications to celecoxib: active peptic ulcer disease, renal impairment, asthma exacerbated by NSAIDs, congestive cardiac failure (NYHA II-IV\*), ischaemic heart disease, cerebrovascular disease, uncontrolled hypertension

### \*NYHA classification

Class I: Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain.

Class II: Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.

Class III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain.

Class IV: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

- Patients with an ongoing requirement for regular NSAID or COX 2 inhibitor therapy (Asprin 75mg daily is permitted)
- Regular selective COX 2 inhibitor use in the 2 years prior to randomisation
- History of hypersensitivity to celecoxib, exemestane or letrozole or to any of the excipients
- Known hypersensitivity to sulphonamides
- Patients who have experienced asthma, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or other allergic-type reactions after taking acetylsalicylic acid or NSAIDs including COX-2 inhibitors
- Inflammatory bowel disease



- Patients with ongoing requirements for fluconazole or ketoconazole therapy
- Patients with ongoing requirement for lithium therapy
- Patients with ongoing requirement for ACE inhibitor therapy
- Patients who are anticoagulated

## 7. RANDOMISATION

A Randomisation Form (& Eligibility Form) must be completed prior to randomisation. These details should be telephoned or faxed through to the Randomisation Office at the Cancer Research UK Clinical Trials Unit, University of Birmingham.

### RANDOMISATION

(9:00am till 5:00pm, Monday to Friday)

☎ 0800 371 969 or 0800 731 7625

✉ 0800 328 6412

During the randomisation procedure eligibility criteria and randomisation details will be confirmed and verification that the patient has signed the NEO-EXCEL Informed Consent Form will be requested. A unique sequential Trial Number (TNO) will be allocated. This number should be used on all Case Report Forms (CRFs) and all subsequent correspondence relating to that patient. The TNO and allocated treatment must also be recorded on the Randomisation Form, and the Form then signed and dated. The completed original Forms should be sent to the NEO-EXCEL Study Office, with copies retained at site. Confirmation of the randomised treatment allocation will be sent to the Investigator and appointed Pharmacist.

Randomisation will be stratified by tumour size (>2-5cm, >5cm), grade (I, II, III), ER Q-score (3-4, 5-6, 7-8), Her2 (-ve, +ve, not determined), and low dose aspirin use (yes, no). This information therefore must be available at randomisation. A computerised minimisation algorithm, developed by the Trials Unit, will be used to ensure that allocation of treatment to patients is balanced within these strata.

## 8. TREATMENT DETAILS

### 8.1 Trial plan

**Treatment should begin within 5 working days of randomisation. The planned duration of treatment is 16 weeks.**

## **Subjects will be randomised (1:1:1:1) to receive either:**

### **Exemestane + Celecoxib**

Patients will receive exemestane 25mg, one tablet daily and celecoxib 400mg, one capsule twice daily

### **Exemestane + Celecoxib-Placebo**

Patients will receive exemestane 25mg, one tablet daily and celecoxib-placebo, one capsule twice daily

### **Letrozole + Celecoxib**

Patients will receive letrozole 2.5mg, one tablet daily and celecoxib 400mg, one capsule twice daily

### **Letrozole + Celecoxib-Placebo**

Patients will receive letrozole 2.5mg, one tablet daily and celecoxib-placebo, one capsule twice daily

Treatment in all arms will continue until the day of surgery (patients should not take study medication after requirement of 'nil by mouth' for anaesthetic purposes). The surgical date should be planned in advance and will be between 16 weeks and 18 weeks from the commencement of treatment. Sufficient drug supplies will be included to cover this 2-week window.

Dose modifications of trial treatment are not permitted. Patients who are unable to tolerate the trial treatment should be withdrawn from study.

Patients whose tumours progress during the neoadjuvant phase will be withdrawn from study and treated according to local practice.

## **8.2 Concomitant medication**

Patients on oestrogen replacement therapy (HRT) at diagnosis should discontinue this at the time they start trial treatment. Treatment of menopausal symptoms may be initiated as per local protocol during the treatment phase. Systemic oestrogen therapy is prohibited and if required patients must come off study.

### **Aspirin**

NSAIDS and COX 2 inhibitors (except as study medication) are prohibited during the study, except for low dose aspirin. Celecoxib is not a substitute for acetylsalicylic acid for prophylaxis of ischaemic heart disease because of the lack of effect on platelet function. Because celecoxib does not inhibit platelet aggregation antiplatelet therapies should not be discontinued. Therefore continuation of low dose aspirin (75mg daily) is permitted.

### **Fluconazole & Ketoconazole**

Clinical studies have identified potentially significant reactions of celecoxib with fluconazole and ketoconazole. Concomitant administration of fluconazole at 200mg once daily resulted in a 2-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of

celecoxib metabolism via CYPP450 2C9 by fluconazole. Patients on these medications are not eligible.

### **ACE inhibitors**

There is a potential for interactions with ACE inhibitors as inhibition of prostaglandins may diminish their antihypertensive effect. Patients taking ACE inhibitors are excluded from this study.

### **Lithium**

In healthy subjects, lithium concentrations are increased approximately 17% in subjects receiving lithium together with celecoxib. Patients on lithium are not eligible for this study.

### **Diuretics**

Clinical studies have shown that NSAIDS, in some patients, can reduce the natriuretic effect of frusemide and thiazides by inhibition of renal prostaglandin synthesis. Caution is advised for patients on diuretics.

### **Warfarin**

Because of possible interference with INR and also due to multiple biopsies being required, patients on warfarin are ineligible. Tumour measurements may also be affected by excessive bleeding.

Caution is advised when patients are receiving drugs with a narrow therapeutic index and which are mainly dependant on cytochrome CYP 450 enzymes 2A6 and 2C19.

## **8.3 Surgery**

Surgery appropriate to the tumour size determined at the end of treatment will be performed according to national and local guidelines.

### **Complete clinical response**

All patients require surgery. Even if no tumour is palpable or visible on ultrasound to allow an ultrasound marker then a wide local excision of the tumour site should be performed. Some centres with appropriate expertise may choose to insert clips at the same time as the day 14 biopsy in smaller tumours so that if complete clinical response occurs wide local excision can be centred on the clip.

## **8.4 Postoperative management**

Postoperative management will depend on operative pathology and be determined by local protocol. It is expected that all patients will receive a total of 5 years endocrine therapy; continuation of aromatase inhibitor therapy is recommended.



## 9. SCHEDULE OF ASSESSMENTS

The schedule of assessments and investigations required is described below and summarised in Figure 1. This information should be recorded in the patient notes where not explicitly required in the Case Report Forms.

### At Screening

- Relevant medical history including:
  - cardiac history
  - thromboembolic history
  - rheumatological history
  - other serious acute or chronic conditions
- Concomitant medication (description of other medication prescribed for more than 7 days and taken within one month of randomisation)
- ECOG performance status (Appendix 1)
- Clinical examination, including height and body weight
- Uni-dimensional tumour measurement by calipers of the greatest dimension
- Tumour assessment by ultrasound
- Base-line blood tests: full blood count; urea + creatinine + electrolytes; liver function tests
- Blood pressure measurement
- NYHA classification (see section 6.2)

### At Baseline

- Clinical examination
- Core biopsy - if insufficient material left from diagnostic core biopsy. (See separate Pathology Consent Form. If this Consent Form is used before diagnostic biopsy and sufficient cores taken, other additional biopsies will not be necessary at baseline).
- Frozen core biopsy (**only for sites participating in the frozen tissue sub-protocol**)
- Trans NEO-EXCEL bloods (pre-treatment)

### At Day 14

- Treatment side-effects
- Core biopsy
- Frozen core biopsy (**only for sites participating in the frozen tissue sub-protocol**)
- Trans NEO-EXCEL bloods

### Every 4 weeks, on treatment

- Clinical examination
- Treatment side-effects and events
- Uni-dimensional tumour measurement by calipers of the greatest dimension

## On completion of treatment (no more than 2 weeks prior to surgery)

- Clinical examination
- Treatment side-effects and events
- Uni-dimensional tumour measurement by calipers of the greatest dimension
- Tumour assessment by ultrasound – response will be assessed by RECIST criteria (Appendix 4)
- Routine blood tests including full blood count; urea + creatinine + electrolytes; liver function tests
- Trans NEO-EXCEL bloods
- Additional tumour tissue to be frozen that has been cut from surgical specimen by pathologist (**only for sites participating in the frozen tissue sub-protocol**)
- Formalin-fixed tumour tissue cut from surgical specimen by pathologist

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**Please refer to separate Trans NEO-EXCEL lab manuals for full details of sample preparation and collection**

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### Disease progression

Disease progression is defined by RECIST criteria as an increase in the largest uni-dimensional tumour measurement by > 30%. Response will be assessed by RECIST criteria at every visit. If disease progression does occur, taking into account accepted operator variability, patients will be withdrawn and a biopsy taken as soon as possible and before commencement of alternative therapy. Full details of disease progression/death should be recorded on the trial CRFs.

A summary of treatment offered at progression will also be requested. Sites are strongly urged to take serum/plasma samples, core biopsies (and for sites participating in the frozen tissue sub-protocol, an additional core biopsy to be frozen) as these may help provide invaluable information about the mechanisms of treatment failure.

### Follow-up after completion of treatment

All patients, provided that they have not withdrawn consent for follow up, should have long-term follow-up of at least 5 years, irrespective of whether they have discontinued trial treatment prematurely. The anticipated follow-up frequency is once every year, unless otherwise clinically indicated. Follow-up after relapse should be according to local policy.

The following information will be collected:

- Local/distant relapse
- Response to other agents used to treat recurrent/progressive tumour
- Toxicity
- Survival
- Important information relevant for the trial (unforeseen circumstance that may have led to changes in interpretation of the results, for instance, cause of death)



## FIGURE 1: FLOWCHART OF ASSESSMENTS

This table provides a summary of the trial-related procedures required; refer also to full text in section 9

YEAR	1						FOLLOW-UP
	S <sup>1</sup>	B <sup>2</sup>	2	3	4	5	
Visit							
Timeframe		Day 1	Day 14	4 wks	8 wks	12 wks	16 wks
Medical history	X						
Clinical examination	X	X		X	X	X	X
Events <sup>3</sup>				X	X	X	X
Adverse Events/SAEs <sup>4</sup>			X	X	X	X	X
Tumour assessment by calipers	X			X	X	X	X
Tumour assessment by ultrasound	X						X
Routine bloods	X						X
Trans NEO-EXCEL Bloods		X	X				X
Core Biopsy		X	X				
Formalin fixed tumour tissue cut from surgical specimen							X*

FROZEN TISSUE SUB-PROTOCOL Frozen core biopsies** and frozen sample from* surgical specimen		X**	X**				X*	
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The Trans NEO-EXCEL sub-protocol is applicable to all sites

The frozen tissue sub-protocol will only apply to sites that are participating in frozen tissue collection

If for any reason Trans NEO-EXCEL blood samples cannot be taken always send all pathology samples

### Notes:

Medical history to include clinical examination, height, weight, ECOG status, concomitant medication.

1 - Screening visit

2 - Baseline visit (to take place *up to* 5 days before treatment start)

3 - Breast cancer events and survival (disease progression or recurrence, death with cause)

4 - As described in section 13

\*\*Frozen core biopsies \* From surgical specimen

If patients are withdrawn due to disease progression a core biopsy should be performed prior to initiation of alternative treatment and Trans NEO-EXCEL blood samples should also be taken

Patients should continue to take their trial medication until the day of surgery (patients should not take study medication after requirement of 'nil by mouth' for anaesthetic purposes)



## 10. TRIAL MANAGEMENT / DATA COLLECTION

NEO-EXCEL will be coordinated by the Cancer Research UK Clinical Trials Unit at the University of Birmingham according to the current guidelines for Good Clinical Practice. Participating sites may be monitored by Trials Unit staff to confirm compliance with the protocol and the protection of patients' rights as detailed in the Declaration of Helsinki (Appendix 3).

### 10.1 Trial start-up and core documents

Interested sites should contact the NEO-EXCEL Study Office to obtain information on the core documentation required prior to trial participation. All Principal Investigators taking part in the trial will be asked to sign a Clinical Trial Agreement (which will detail the responsibilities of the participating site) and should provide a current signed and dated *Curriculum Vitae* prior to trial activation.

It is recommended that all clinic and study-related personnel should attend a start-up meeting for training on trial procedures and data collection methods. Staff from sites that have attended the trial launch meeting will not require a start-up visit unless specifically requested by the local Investigator or NEO-EXCEL Study Office.

The Principal Investigator at each site must submit this protocol, any supporting documentation, and any subsequent amendments for Site-Specific Assessment from their Local Research Ethics Committee and, if locally required, Institutional Review Boards. Investigators must acquire ethical approval and R&D/Trust approval before they commence recruitment.

### 10.2 Case Report Forms

The CRFs will contain common information, but this information will be kept to a minimum. The CRFs must be completed and signed/dated by the Investigator or one of their authorised staff members as soon as the required information is available. The completed originals should be sent to the NEO-EXCEL Study Office, with a copy held by the Investigator at site. In all cases it remains the responsibility of the Investigator to ensure that they have been completed correctly and that the data are accurate. Entries should be made in ballpoint pen preferably in black ink and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not clear why a change has been made, an explanation should be written next to the change. Typing correction fluid should not be used. Data reported on each CRF should be consistent with the source data or the discrepancies should be explained. All sections are to be completed before returning to the NEO-EXCEL Study Office. If information is not known, this must be clearly indicated by entering NK on the form. All missing and ambiguous data will be queried.

Trial CRFs may be amended as appropriate; this will not constitute a protocol amendment. Revised CRFs should be used by all participating sites with immediate effect.

## Case Report Forms will include:

- Eligibility Form
- Randomisation Form
- On-study Form
- On treatment follow-up Forms
- Post-operative Form
- Withdrawal/long-term follow-up Forms
- Relapse/Death Forms
- Adverse Event (AE)/Serious Adverse Event (SAE) Forms

### 10.3 Early withdrawal from trial treatment

Patients should be withdrawn from the trial if there is evidence of disease progression. Patients can also be withdrawn at the discretion of the Investigator or at the patient's own request. *Patients have the right to withdraw from the trial at any time for any reason.* Full details of the reason(s) for withdrawal should be recorded on the CRFs if clinician-initiated, otherwise a simple statement reflecting patient preference will suffice.

Please note that patients who withdraw from trial treatment will not be regarded as having withdrawn consent for ongoing follow-up and data collection unless clearly specified at time of withdrawal, and should therefore be followed-up in accordance with the protocol.

### 10.4 Data monitoring

The Trial Coordinator will be in regular contact with site personnel (by phone/fax/email/letter) to check on progress and answer any queries that they may have. Trial staff will check incoming CRFs for compliance with the protocol, consistent data, missing data and timing. Sites may be barred from further recruitment in the event of serious and persistent non-compliance and/or very poor recruitment.

Monitoring will be done according to the Trials Unit policy and the NEO-EXCEL Monitoring Plan. Investigators will allow the trial monitors access to source documents as requested. If a monitoring visit is required the NEO-EXCEL Study Office will contact the site to arrange a date for the proposed visit. Data to be verified will include:

- Informed Consent
- Eligibility
- Adverse Events
- Outcome

Any major problems identified during monitoring will be reported to the NEO-EXCEL Steering Committee. All records will be maintained in accordance with local regulations and in a manner that ensures security and confidentiality. The completed original CRFs are the sole property of the NEO-EXCEL Steering Committee and should not be made available in any form to third parties (except for authorised representatives of appropriate Health/Regulatory Authorities) without written permission from the NEO-EXCEL Steering Committee.



## **10.5 Closure of trial – end date**

For the purposes of Clinical Trial Authorisation (CTA) under the European Union Directive 2001/20/EC, the study is deemed to have ended 30 days after the last patient receives the last dose of the Investigational Medicinal Product (IMP).

For the purposes of Multicentre Research Ethics Committee approval, the study end date is deemed to be the date of last data capture.

## **10.6 Archiving**

To enable monitoring, peer review and/or audits 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 Informed Consent Forms, copies of all CRFs and detailed records of drug disposition.

To comply with international regulations these records should be retained by the Investigator for 15 years, including assessments such as CT scans.

## **10.7 Trial Steering Committee / Trial Management Group**

The Trial Steering Committee will provide the overall supervision for the trial, in particular: trial progress, protocol compliance, patient safety and review of updated information.

The Trial Management Group will be responsible for the clinical set-up, on-going management, promotion of the study, and for the interpretation of the results.

This is a clinician-initiated and clinician-led trial, funded through a project grant from Cancer Research UK, and an educational grant from the pharmaceutical industry. The study has been independently peer reviewed and endorsed by Cancer Research UK Clinical Trials Awards & Advisory Committee (CTAAC), and is part of the National Cancer Research Network (NCRN portfolio).

## **10.8 Independent Data Monitoring Committee**

An Independent Data Monitoring Committee (IDMC) for the trial will be responsible for the regular monitoring of trial data. The Committee will consist of two clinicians not entering patients into the trial and an independent statistician. The IDMC will assess the progress of the trial and give advice on whether the accumulated data from the trial, together with the results from other relevant trials, justifies the continuing recruitment of further patients. The committee will first meet to review data from the first 400 patients randomised (see section 14.4) and then annually thereafter until the trial closes to recruitment. The IDMC may consider discontinuing the trial if the recruitment rate or data quality are unacceptable or if there are cases of excessive toxicity that in the IDMC's opinion jeopardise patient safety. In addition the IDMC may recommend the trial stop early if the interim analyses showed differences between treatment arms that are sufficient to be deemed convincing to the general clinical community. If a decision is made to continue, the IDMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDMC will make confidential recommendations to the Trial Steering Committee (TSC) as the decision-making Committee for the trial.



## 11. CONCURRENT STUDIES

Patients entering NEO-EXCEL may be considered for entry into additional trials provided compatibility has been agreed by Trial Management Groups or Steering Committees of both studies.

## 12. STUDY DRUG SUPPLIES

Full pharmacy details and guidelines for ordering study drug supplies, and labelling requirements are contained within the NEO-EXCEL Pharmacy File which will be sent to the appointed Pharmacist.

## 13. PHARMACOVIGILANCE

### ADVERSE EVENTS: DEFINITIONS AND REPORTING

The collection and reporting of data on Adverse Events and Serious Adverse Events will be in accordance with EU Directive 2001/20/EC and UK legislation.

#### 13.1 Adverse Event definitions

##### **Adverse Event**

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

##### *Comment*

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an Investigational Medicinal Product (IMP), whether or not considered related to the IMP.

##### **Adverse Reaction**

An Adverse Reaction (AR) is defined as all untoward and unintended responses to an IMP related to any dose administered.

##### *Comment*

An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

##### **Unexpected Adverse Reaction**

An Unexpected Adverse Reaction (UAR) is defined as an AR, the nature or severity of which is not consistent with the applicable product information (e.g. Summary of Product Characteristics (SmPC)).

##### *Comment*

When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.



Severity: The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

### **Serious Adverse Event or Serious Adverse Reaction**

An SAE or Serious Adverse Reaction (SAR) is defined as any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening\*
- Requires inpatient hospitalisation\*\* or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect

For cancer trials we would also include:

- New primary cancer

#### ***Comment***

Medical judgment should be exercised in deciding whether an AE or AR is serious in other situations. An AE or AR that is not immediately life threatening or does not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

\*Life threatening in the definition of an SAE or SAR refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

\*\*Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation.

### **Suspected Unexpected Serious Adverse Reactions**

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as a SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information.

A SUSAR should meet the definition of an AR, UAR and SAR as detailed above.

### **13.2 Procedures for collecting Adverse Events**

All medical occurrences (which meet any of the above definitions) from the first dose of IMP to 30 days after the last dose of IMP should be reported as adverse events and must be accurately recorded on the appropriate trial CRF and sent to the NEO-EXCEL Study Office.

Toxicities will be reviewed using the National Cancer Institute Common Toxicity Criteria (NCI CTC version 3.0, see Appendix 5). Any toxicities incurred but not categorised by the NCI CTC should be graded by the physician and be recorded on the CRF using a scale of (1) mild, (2) moderate or (3) severe (as defined in Appendix 6). For each sign/symptom, the highest grade observed since the last visit should be recorded.



## Exceptions to AE reporting

- A pre-existing condition should not be reported as an adverse event unless the condition worsens or episodes increase in frequency during the adverse event-reporting period
- Symptoms of the targeted cancer should not be reported as adverse events
- Symptoms relating to disease progression or death unless the investigator deems them related to use of the study drug
- Symptoms related to treatment for disease progression

### 13.3 Recording and reporting Serious Adverse Events

In the case of a SAE the Investigator (or person delegated that responsibility) must **immediately** on becoming aware of the event:

- **Complete a ‘Serious Adverse Event Form’.** This should contain all of the information known at the time of the report
- **Fax** within 24 hours of becoming aware of the event the signed and dated ‘Serious Adverse Event Form’ to the NEO-EXCEL Study Office at the CRCTU, Birmingham: **UK Fax: 0800 328 6412 or 0121 414 3700**
- In addition, **send by post** the original copy of the SAE form and ensure that the reporting clinician has signed/dated it. Forms can be signed by nurse but must be co-signed by the reporting Investigator.

Investigators should also report SAEs in accordance with their local institutional policy.

#### Documenting SAEs

The responsible clinician must determine the severity of an event (according to the NCI CTCAE-3, see Appendix 5), and relatedness of the events to the study drugs. Seriousness, relatedness, and expectedness will also be independently assessed by the Clinical Coordinator(s). A SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). If the event meets the definition of a Serious Adverse Reaction that is unexpected in nature it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

#### Reporting period for SAEs

Details of all SAEs will be documented from the commencement of treatment until 30 days post-treatment (i.e. 30 days from last administration of the study drug). SAEs occurring thereafter should be reported only if the Investigator believes them to be related and unexpected (i.e. SUSAR).

#### Reporting of SAEs to Regulatory Authorities

The CRCTU, Birmingham will report all fatal or life threatening SUSARs to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Multi-Centre Ethics Committee (MREC) within 7 days of receiving initial notification from the study site. Any follow-up information will be provided within an additional 8 days. Non-fatal and non-life threatening SUSARs will be reported within 15 days. The CRCTU, Birmingham will submit an Annual Safety Report to the MHRA and MREC summarising all reported SARs.

The CRCTU, Birmingham will forward details of SUSARs to all Investigators in the form of an Annual Safety Report. SAEs will be reported to the relevant Pharmaceutical Companies as appropriate.



### 13.4 Follow-up of AEs/SAEs

All AEs will be recorded on the CRFs until 30 days after the last treatment dose on study or until the start of other anti-cancer treatment, whichever occurs first. Additionally, all AEs deemed possibly related to the trial medication will be followed until resolution, or the Investigator assesses them to be chronic or stable, or initiation of other anti-cancer therapy, whichever occurs first.

In the case of SAEs, the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised. Follow-up may continue after completion of protocol treatment if necessary. Follow-up information will be collected on a new SAE form. Follow-up information need not be signed off by an Investigator. Extra annotated information and/or copies of test results should also be provided where available.

Receipt of all SAE forms will be acknowledged via fax.

### 13.5 Codebreaks

Codebreaks should be avoided whenever possible. Approval must be given from one of the NEO-EXCEL Clinical Coordinators before a codebreak is undertaken. This will be checked before the code is broken (except in emergency situations). Unblinding should only be undertaken for medical reasons. When assessing SAEs both Investigator and Clinical Coordinator must assume that the patient received the IMP (i.e celecoxib and not the celecoxib-placebo). If the event is thought to be related, unblinding will be performed by the coordinating centre.

**To break the randomisation code for a patient:**

**During the hours 9:00am-5:00pm**

☎ NEO-EXCEL Trial Office on: 0121 4143797

**Refer to Investigator Site File/Pharmacy File for procedure outwith office hours.**

## 14. STATISTICAL CONSIDERATIONS

### 14.1 Definition of Outcome Measures

The treatment arms will be compared in terms of the following outcome measures:

#### **Primary Outcome Measure**

- Objective clinical response (CR, PR) to neoadjuvant treatment

Objective clinical response as measured by callipers is defined as either a partial or complete response. A complete clinical response (CR) is defined as no palpable lesion from which to take calliper measurements. A partial clinical response (PR) is defined as a decrease in the greatest uni-dimensional measurement by callipers of at least 30%.

Patients who achieve a CR or a PR will be defined as achieving an objective clinical response to neoadjuvant treatment.



## Secondary Outcome Measures

- Objective ultrasound-determined response (CR, PR) to neoadjuvant treatment

Objective ultrasound-determined response is defined as either a partial or complete response. A partial response (PR) is defined as at least a 30% decrease in the longest dimension of the lesion in accordance with RECIST criteria. A complete response (CR) is defined as complete disappearance of the radiological (USS) lesion. Patients who achieve a CR or a PR will be defined as achieving an objective ultrasound-determined response to neoadjuvant treatment.

## Type of surgery

This is a binary outcome recorded as either breast conserving surgery or mastectomy.

## Axillary lymph node involvement at surgery

This is a binary outcome recorded as either lymph node involvement or not.

## Complete pathological response

This determined by the pathologist and defined as when all detectable tumour has disappeared.

## Local recurrence-free survival

Local recurrence-free survival is defined as time from date of trial entry to date when local recurrence is first observed and is censored at date last seen free of local recurrence in those patients who have not experienced the event.

## Progression-free survival

Progressive disease is defined by the tumour growing significantly or new tumours appearing. Progression-free survival is defined as the time from date of trial entry to date when progression is first observed and is censored at date last seen free of local recurrence in those patients who have not experienced the event.

## Overall survival

Overall survival is defined as the time from date of trial entry to date of deaths from any cause and is censored at date last seen alive in those patients who have not experienced the event.

## 14.2 Statistical analysis

The main analysis will be carried out when all patients have completed their neoadjuvant therapy and have had their assessment of response. The main analyses comparing the objective clinical response rates will be carried out with and without adjustment for the additional randomisation; e.g. in the 500 patients receiving celecoxib vs 500 patients receiving celecoxib-placebo, objective clinical response rates will be assessed using the chi-squared test, and repeated using the Mantel-Haenszel test to allow for the adjustment of exemestane or letrozole. An additional pre-planned analysis will be the comparison of the 250 patients in each of the 4 treatment groups using one test statistic; this will be powered to detect larger differences (~13%). We do not plan to carry out multiple comparisons between the 4 treatment groups, instead we will perform one test statistic to determine if there are differences between any of the 4 treatment groups.

The secondary outcomes of survival and local control will be assessed using Kaplan-Meier survival curves, and treatments will be compared using the Log-rank test. The effect of

prognostic factors in addition to treatment will also be assessed using Cox-regression models. All analyses will be carried out on an intention-to-treat basis.

### **14.3 Sample size**

The trial will accrue a total of 1000 patients.

The objective clinical response rate for patients receiving letrozole is reported to be around 55%, thus randomising 250 patients into each of the 4 treatment arms will allow the detection of an absolute difference of 13% between any of the treatments, with 5% significance and 85% power (Machin and Campbell 1987). Within the 2x2 factorial design, the comparison of the 500 patients receiving celecoxib vs 500 patients receiving placebo will allow the detection of an absolute difference of at least 9% with an 80% power; similarly for 500 patients receiving exemestane vs the 500 patients receiving letrozole. Recruiting 1000 patients will also allow the comparison of the secondary endpoints of type of surgery and biological profiling as well as correlating objective clinical response with overall survival and local control.

### **14.4 Timing of interim and final analyses**

The first interim analysis will be carried out and presented to the Independent Data Monitoring Committee (IDMC) after 400 patients have been recruited into the trial. This analysis will assess recruitment, toxicity, compliance, number of adverse/treatment related events and response. It is anticipated that interim analyses will be carried out and presented to the IDMC annually thereafter. See Section 10.8 for further details. The final analysis and publication of results for all outcomes except time-to-event measures, will be carried out once all randomised patients have completed surgery. The final analyses and publication for time-to-event outcome measures will occur when all randomised patients have a minimum of 2 years follow-up and again at a minimum of 5 years follow-up.

## **15. ETHICAL AND REGULATORY STANDARDS**

### **15.1 Ethical / Regulatory conduct of the study**

This study will be conducted in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18<sup>th</sup> World Medical Association (WMA) Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996) and Scotland (2000) amendments (Appendix 3).

This study will be carried out under a Clinical Trial Authorisation (CTA) and conducted in accordance with EU Directive 2001/20/EC and UK legislation.

The protocol will be submitted for ethical approval prior to circulation, in accordance with the new guidance in force from March 1<sup>st</sup> 2004. Before enrolling patients into the study, each site must apply for Site Specific Assessment from their Local Research Ethics Committee and must also obtain Trust Research & Development (R&D) approval. Sites will not be permitted to enrol patients until written confirmation of ethical and R&D approval is received by the NEO-EXCEL Study Office. It is the responsibility of the Investigator to ensure that all subsequent amendments



gain the necessary approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

## **15.2 Informed Consent**

It is the responsibility of the local Investigator to obtain fully Informed Written Consent from each patient prior to inclusion in the trial or, where relevant, prior to evaluating the patient's suitability for the trial. The approved Patient Information Sheet should be given to each patient prior to randomisation, with the risks and benefits of participating in the trial clearly explained. The patient should be given ample time to read the information sheet and the opportunity to inquire about details of the trial. They should also be given time to discuss their participation with others outside of the clinical trials team and given another opportunity to ask the clinician and the research nurse questions regarding their participation in the study if required. All questions or concerns about the trial should be answered to the satisfaction of the patient. Sufficient time should be allowed (at least 24 hours) for the patient to reach a decision. It should be explained that they are free to refuse to take part and informed about their right to withdraw from the trial at any time. If the patient agrees to take part in the trial they should be asked to sign and date the approved Informed Consent Form, which should also be signed and dated by the Investigator. A copy of the Informed Consent Form should be given to the patient, a copy filed in the hospital notes and a copy filed in the Investigator Site File. Throughout the study the patient should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient's willingness to continue participation in the trial should be shared with the patient in a timely manner.

The Informed Consent Form and Patient Information Sheet will be available in electronic format from the NEO-EXCEL Study Office to enable individual hospitals to copy onto their headed paper. A copy of the Informed Consent Form and Patient Information Sheet is included in Appendices 7 and 8 for information. The Breast Biopsy Patient Information Sheet and Consent is included in Appendices 9 and 10.

With the patient's consent their General Practitioner (GP) should be informed about their participation in the trial. The approved GP Information Letter (Appendix 11) should be sent to the GP, along with any other related correspondence.

## **15.3 Patient confidentiality**

The personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the 1998 Data Protection Act. With the patient's consent, their full name will be collected at randomisation to allow tracing through the Office of National Statistics to assist with long-term follow-up. However, patients will be identified using only their unique trial number, initials, hospital number and date of birth on all CRFs and any correspondence between the NEO-EXCEL Study Office and the participating site.

The Investigator must maintain documents not for submission to the Study Office (e.g. patients' written Informed Consent Forms) in strict confidence. In the case of special problems and/or governmental queries, it will be necessary to have access to the complete study records, provided that patient confidentiality is protected.

The Cancer Research UK Clinical Trials Unit, Birmingham will maintain the confidentiality of all patient data and will not disclose information by which patients may be identified to any third

party, other than those directly involved in the treatment of the patient's breast cancer. Representatives of the trial team may 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.

## 16. TRANSLATIONAL SCIENCE

Whilst there is extensive in vivo and in vitro data to suggest that inhibition of the COX 2 mediated synthesis of prostaglandins may promote tumour response and prevent tumour spread, there is no clear consensus as to the relevant mechanisms and their relative importance. Early experimental evidence suggests that prostaglandin E2 (PGE2) expression is elevated in breast cancer<sup>50</sup> and that this is associated with tumour invasion<sup>51</sup>. Prostaglandins are implicated in a wide range of molecular actions including: the induction of interleukin6 (IL-6) and other inflammatory cytokines<sup>52</sup>, neo-vascularisation and tumour invasion/proliferation. The rationale for linking COX 2 inhibitors with aromatase inhibitors in endocrine-responsive disease is due to the action of PGE2, mediated via the 1.3 promoter of the aromatase gene itself and leading to enhanced aromatase expression as a direct consequence of COX 2 activity. Given the increasingly widespread use of celecoxib as a novel anti-tumour agent there is a strong need for a clearer understanding of the mechanisms by which COX 2 mediates its actions in vivo. NEO-EXCEL represents an ideal opportunity to investigate this question and to provide strong evidence for predictive factors that may be used to inform future treatment decisions.

As a secondary objective, we intend to exploit the tissue collected by the NEO-EXCEL study to investigate expression profiles relating to tumour response to steroidal (exemestane) versus non-steroidal (anastrozole/letrozole) aromatase inhibitors. Patients with metastatic disease who have progressed after treatment with non-steroidal inhibitors (anastrozole and letrozole) have been treated with exemestane. Of 241 patients treated, 24% experienced clinical benefit (CR + PR + SD) lasting for a median time of 37 weeks<sup>53</sup>. This suggests that there is a degree of non cross-resistance between these classes of aromatase inhibitors. Secondly, there appear to be differences between the molecular profiles of tumours responsive to steroidal irreversible (exemestane) and non-steroidal reversible inhibitors of aromatase, as suggested by data presented at the San Antonio breast cancer symposium<sup>54</sup>. We therefore propose, within NEO-EXCEL, to establish a tissue and serum bank for future gene expression profiling and proteomic analysis to answer two key questions. Firstly and most importantly, we hypothesise the expression profiling of sequential tumour biopsies will identify molecular mechanisms which underpin the effects of the COX 2 inhibitor celecoxib in the context of neoadjuvant therapy of breast cancer. Secondly, we further hypothesise that markers of differential response to aromatase inhibitors will be identified in a linked analysis.

Our aim is to collect three sequential tumour samples (pre-treatment, 2 weeks after therapy initiation and at surgery) from patients randomised between the different aromatase inhibitors and also between celecoxib and placebo; these timepoints have been chosen to link to previous studies (Dixon et al, Dowsett et al) of early response to hormone therapy. We also aim to analyse, in a subset of patients (participating in the frozen tissue sub-protocol), sequential tumour biopsies and the changes in Gene Expression Profiles (GEPs) of breast tumours from each treatment arm to determine, at the level of gene expression, the molecular differences induced in tumours during treatment with exemestane and letrozole +/- celecoxib combination therapy. We predict that a number of the identified differentially expressed genes will serve as useful response markers for adjuvant studies (e.g. TEAM/ATAC). A significant change post treatment

may provide useful candidate response markers in the context of neoadjuvant treatment, which may be profiled in the wider tumour databank (tissue microarrays) from the NEO-EXCEL trial.

It is now clear that only a small number of genes are up-regulated in all breast tumours<sup>55</sup>. Furthermore, while single genetic markers in clinical specimens have often failed to be predictive of prognosis, recent studies have demonstrated that the GEP of multiple genes in combination can predict the response to tumours in terms of outcome<sup>56</sup> and can provide prognostic<sup>57</sup> and response information<sup>58</sup>.

Affymetrix human GeneChip microarrays will be used to undertake this analysis, each containing oligonucleotides representing more than 39,000 transcripts derived from approximately 33,000 well-substantiated human genes. Such a set will include the majority of genes whose expression changes have been shown in the above studies to be relevant to the development or progression of different types of breast cancer. We propose to select 100 patients (50 patients from each treatment group) to yield 300 samples for expression array analysis. Our aim is to collect this material during the course of recruitment and to bank this material in a central laboratory prior to submission of a TRICC translational science project or CRUK project grant for the expression profiling of this material in conjunction with the CRUK Genome Profiling Laboratory at the Paterson Institute. Subsequently the predictive value of genes shown to be linked to tumour response from the study will be tested using material collected as formalin fixed tissue from the remainder (900 cases + 100 entered into the profiling sub-study). These profiles may also inform the analysis of samples in TRANS-REACT and TRANS-MA27.

### Fixed tissue bank and serum bank

All 1000 patients randomised into the NEO-EXCEL trial will have primary core biopsies (taken prior to treatment) in order to provide material for diagnosis. Additional core biopsies will be taken for formalin fixation to provide material for the TRANS NEO-EXCEL research tissue bank. This will ensure that sufficient tissues, since core biopsies are not suitable for modifying into a tissue micro-array, will be available to test the hypotheses outlined below and those which may arise from the expression profiling described above.

In addition, we will retrieve tumour resection specimens to construct a tissue microarray in which to evaluate markers of clinical response identified by tissue expression profiling. Tissue will be collected at the central research laboratory (Endocrine Cancer Group) where material will be sectioned for further study/made into tissue microarrays.

The key hypothesis to be tested prospectively within TRANS NEO-EXCEL relates to the observed interaction between COX 2 and aromatase expression as a model to explain the efficacy of COX 2 inhibitors, such as celecoxib, in the treatment of invasive breast cancer. The product of the COX 2 enzyme, PGE2, induces expression of the transcription factors Snail/Slug which co-operatively modulate the I.3 promoter region of the aromatase gene. Paradoxically Snail/Slug are also closely involved in the regulation of E-Cadherin expression. Loss of E-Cadherin has been associated with increased tumour metastatic potential. Using paired pre/post treatment samples from TRANS NEO-EXCEL we will test the hypothesis that reduction of PGE2 production in breast cancer, via celecoxib treatment, reduces the metastatic potential by up-regulation of E-Cadherin expression. We will further test the hypothesis that down-regulation of Snail/Slug expression is linked both to alterations in E-Cadherin expression and to a reduction in aromatase expression (each of these markers will be measured by immunohistochemistry). There has been significant recent progress towards the identification of an appropriate antibody for aromatase analysis in paraffin embedded tissues (presented at the AROMATASE 2004 meeting in Edinburgh). We recognise however that this latter hypothesis may be also influenced

by the ability of aromatase inhibitors to initiate a positive feedback regulation pathway to increase aromatase expression. Thus we will explore both the relationship between changes within COX 2 treated and placebo treated tumours exposed to the two aromatase inhibitors selected for this trial. The secondary hypothesis which we will test in the context of NEO-EXCEL is that resistance to anastrozole, a competitive inhibitor of aromatase, may be related to up-regulation of aromatase, a mechanism which is less likely to impact exemestane, which is an enzyme poison.

It is likely that 10 sections will be available for most patients from the pre-treatment core biopsies. Using IHC ER, PgR, HER2 and COX 2 will be measured on all primary specimens. All subsequent results will be correlated with HER2 expression, COX 2 expression and also the degree of ER and PgR positivity (Allred scale) and any changes in these during aromatase inhibitor therapy. There will also be comparison with basic histology: nodal positivity, presence of LVI and grade of tumour as well as apoptosis (tunel assay) characteristics at the time of definitive surgery.

### **Serum response markers**

Whilst tumour markers may be of value in predicting early response (de novo resistance/sensitivity) we recognise the value of dynamic markers of response which, it is widely accepted, are likely to be those detected in the serum of patients with cancer. Both serum and plasma will be collected. We aim to utilise known and identify novel response markers for dynamic assessment of response in the serum of breast cancer patients collected at routine clinical assessment/treatment visits. Serum samples will be collected at baseline, 2 and 16 weeks. All patients will, as appropriate, have a sample at the time of surgery or relapse. Serum HER2/EGFr, CA125, CA15-3 and CRP will be assessed as each has been implicated in the monitoring of disease response in breast cancer. In addition we aim to use a novel approach, protein expression profiling ([www.raybio.com](http://www.raybio.com)), to simultaneously profile 64 cytokines in the serum of patients to prospectively identify potential novel markers of response. Markers which show significant expression levels in pre-treatment sera, and a significant decline post treatment, may provide useful candidate response markers.

## **17. SPONSORSHIP AND INDEMNITY**

This trial is a clinician-initiated and clinician-led study with a grant provided by Cancer Research UK and an educational grant from the pharmaceutical industry.

The Chief Investigator's NHS Trust hospital and the University of Birmingham will share responsibilities for co-sponsorship of the trial.

The trial is being coordinated by the Cancer Research UK Clinical Trials Unit at the University of Birmingham. These offices do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is a clinician-initiated study, ABPI guidelines for patient compensation by the pharmaceutical industry will not apply. There are no specific arrangements for compensation made in respect of any serious adverse events occurring through participation in the study, whether from the side effects listed, or others yet unforeseen.



In terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial. Compensation is only available via NHS indemnity in the event of clinical negligence being proven.

## 18. PUBLICATION POLICY

The results of the analysis will be published in the name of the NEO-EXCEL trial in a peer reviewed journal, on behalf of all collaborators. All presentations and publications, including abstracts, relating to the main trial must be authorised by the NEO-EXCEL Steering Committee.

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## Appendix 1: ECOG Performance Status

Status	Description
<b>0</b>	Asymptomatic, fully active and able to carry out all pre-disease performance without restriction.
<b>1</b>	Symptomatic, fully ambulatory but restricted in physically strenuous activity and able to carry out performance of a light or sedentary nature e.g. light housework, office work.
<b>2</b>	Symptomatic, ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours: in bed less than 50% of day.
<b>3</b>	Symptomatic, capable of only limited self-care, confined to bed or chair more than 50% of waking hours, but not bed-ridden.
<b>4</b>	Completely disabled. Cannot undertake any self-care. Totally bed-ridden.

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## Appendix 2: Royal College of Pathologists Guidelines

National recommendations for assessment of steroid hormone positivity by immunostaining.

### Suggested scoring system

Score for proportion staining		Score for staining intensity	
0	No nuclear staining	0	No staining
1	<1% nuclei staining	1	Weak staining
2	1–10% nuclei staining	2	Moderate staining
3	11–33% nuclei staining	3	Strong staining
4	34–66% nuclei staining		
5	67–100% nuclei staining		

**Adding the two scores together gives a maximum score of 8.**

(*J Clin Pathol* 2000; 53:634-635)



## Appendix 3: Declaration of Helsinki

### Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18<sup>th</sup> WMA General Assembly Helsinki, Finland, June 1964  
and amended by the:

29<sup>th</sup> WMA General Assembly, Tokyo, Japan, October, 1975  
35<sup>th</sup> WMA General Assembly, Venice, Italy, October, 1983  
41<sup>st</sup> WMA General Assembly, Hong Kong, September, 1989  
48<sup>th</sup> WMA General Assembly, Somerset West, Republic of South Africa, October, 1996  
52<sup>nd</sup> WMA General Assembly, Edinburgh, Scotland, October, 2000

#### A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

#### B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

#### **C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE**

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

## Appendix 4: RECIST Criteria

### Response Evaluation Criteria In Solid Tumours (RECIST) Quick Reference:

#### ELIGIBILITY

Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

**Measurable disease:** the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

**Measurable lesions:** lesions that can be accurately measured in at least one dimension with longest diameter  $\geq 20$  mm using conventional techniques or  $\geq 10$  mm with spiral CT scan.

**Non-measurable lesions:** all other lesions, including small lesions (longest diameter  $<20$  mm with conventional techniques or  $<10$  mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and:

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

#### Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumours of the chest, abdomen and pelvis. Head and neck tumours and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumour lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilisation of endoscopy and laparoscopy for objective tumour evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated

equipment and a high level of expertise that may only be available in some centres. Therefore, the utilisation of such techniques for objective tumour response should be restricted to validation purposes in specialized centres. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Tumour markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalise for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g. after treatment to differentiate between residual benign lesions and residual malignant lesions in tumour types such as germ cell tumours).

### **Baseline documentation of “Target” and “Non-Target” lesions**

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

## **RESPONSE CRITERIA**

### **Evaluation of target lesions**

- \* Complete Response (CR): Disappearance of all target lesions.
- \* Partial Response (PR): At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
- \* Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
- \* Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

## Evaluation of non-target lesions

- \* Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.
- \* Incomplete Response/ Stable Disease (SD): Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
- \* Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1).

*(1) Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).*

## Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

## Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for

response are first met. Longer intervals as determined by the study protocol may also be appropriate.

- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

#### ***Duration of overall response***

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

#### ***Duration of stable disease***

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

## **RESPONSE REVIEW**

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

## **REPORTING OF RESULTS**

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub-



analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

- The 95% confidence intervals should be provided.

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## Appendix 5: Common Terminology Criteria for Adverse Events

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. The full CTCAE document is available on the National Cancer Institute (NCI) website, at the following address:

<http://ctep.cancer.gov/reporting/ctc.html>

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## Appendix 6:

### Classifications of severity and relationship to therapy for adverse events

#### Relatedness

A determination of relatedness (yes/no) to trial medication, concomitant trial specific and other medication is required for all SAEs reported in clinical trials.

The criteria applied are a determination of whether there is a reasonable possibility that the event is related to the investigational product. Note that a “reasonable possibility” does not include cases where there is only a remote or unlikely possibility that the SAE may have been caused by the product.

#### Severity

Adverse events will be reviewed using the National Cancer Institute Common Toxicity Criteria (NCI CTC) (Appendix 4). Any adverse events incurred but not categorised by the NCI CTC should be graded by the physician and be recorded using a scale of (1) mild, (2) moderate, (3) severe or (4) life threatening on the case report form, as defined below:

<b>MILD</b>	Does not interfere with subject's usual function
<b>MODERATE</b>	Interferes to some extent with subject's usual function
<b>SEVERE</b>	Interferes significantly with subject's usual function
<b>LIFE THREATENING</b>	Resulting in risk of death, organ damage or disability

Note the distinction between the gravity and the intensity of an adverse event. **Severe** is a measure of intensity; thus, a **severe** reaction is not necessarily a **serious** reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria that define serious events.



## Appendix 7: Patient Consent Form

Version 1.1: 04.07.2006

(To be printed on local headed paper)

Patient Initials	
Trial Number	

# NEO-EXCEL

Name of Researcher: \_\_\_\_\_

## PATIENT CONSENT FORM

Please initial  
box

1. I confirm that I have read and understood the Patient Information Sheet (Version 1.1: 04.07.2006) for the above study. I have had the opportunity to ask questions and discuss the study.
2. I give permission for my name to be given to the trials office when I am registered on the NEO-EXCEL study.
3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.
4. I understand that the doctors in charge of this study may close the study, or stop my participation in it at any time, without my consent.
5. I give permission for my GP to be informed of my participation and sent details of the trial.
6. I agree to the collection and storage of additional blood and tumour tissue samples.
7. I agree to the use of my stored blood and tumour samples for future research into breast cancer.
8. I understand that confidential data which identifies me by name may be looked at by responsible individuals from the trials office, or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. However, I understand that I will not be identified by name in any reports or publications resulting from this study.
9. If necessary, I give permission for information about my progress to be obtained from my GP or through the Office for National Statistics, and understand that this will be done using my full name and/or NHS number.
10. I also understand that data collected about me for this study is covered under the Data Protection Act 1998 and stored electronically in a secure encoded format.
11. I agree to take part in this study.

\_\_\_\_\_  
Name of Patient

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Name of person taking consent  
(if different from researcher)

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Researcher

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes.



## Appendix 8: Patient Information Sheet

Version 1.1:04.07. 2006

(To be printed on local headed paper)

# NEO-EXCEL

## PART 1

### Study title:

**Neoadjuvant trial of pre-operative exemestane or letrozole +/- celecoxib in the treatment of ER positive postmenopausal early breast cancer**

*These sheets provide some written information about a **clinical research trial**, and are intended to supplement your discussions about the trial with your doctor and nurses. Having read it you may well have further questions, and these should be discussed with your consultant or one of the doctors on the team.*

You are being invited to take part in a breast cancer research study (also called a clinical trial). Before you decide whether to take part we would like you to read the following information carefully so that you understand why the research trial is being done. Please discuss this information with anyone you wish to help you decide. Please ask us any questions you may have. Part 1 of this sheet tells you about the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study.

### **WHAT IS THE PURPOSE OF THE NEO-EXCEL TRIAL?**

Your breast cancer feeds on hormones, ie. is oestrogen receptor (ER) positive. Rather than just use this information to treat you after your surgery we now can use it to treat your cancer even before your operation. Treatment before your operation with a drug called an aromatase inhibitor will cut off the supply of oestrogen to the cancer, this may shrink the tumour and make the surgery you then require less extensive. As a result of the treatment some patients may be able to avoid a mastectomy and have breast-conserving surgery ('lumpectomy') instead. In general the more tumour shrinkage achieved the less extensive surgery will need to be. The main purpose of this trial is to see if the drug celecoxib, when given in combination with an aromatase inhibitor can make the tumour shrink even more.

Another aim is to see which aromatase inhibitor, exemestane or letrozole, is better in this role.

Patients in NEO-EXCEL will be allocated to treatment with an aromatase inhibitor drug, letrozole or exemestane. In addition patients will take a second tablet, either a drug called celecoxib or a dummy (placebo) tablet. Treatment will continue for 16 weeks during which tumour shrinkage will be measured by examination and ultrasound and followed by surgery. Whether this will be mastectomy or could be 'lumpectomy' will be assessed and decided with patients at the end of the four months. Patients who still need mastectomy and are suitable will be offered reconstruction. 14 days after starting treatment a repeat biopsy will be taken. A small piece of tissue from the cancer at operation will also be analysed for the trial. In addition, we will collect blood samples for storage and later analysis for factors that may help us understand how to predict treatment response in future. At the end of the study we will be able to see how each treatment group responded and what kind of surgery was performed. We will also perform multiple complex analyses of the trial data to establish which of many biochemical features in your blood samples and cancer biopsies can be used to help guide doctors in selecting the best treatments in future.



## WHY HAVE I BEEN ASKED TO TAKE PART IN NEO-EXCEL?

You have been chosen because you have been diagnosed with breast cancer that is oestrogen receptor (ER) positive at a hospital that participates in clinical trials.

## DO I HAVE TO TAKE PART?

No. If having discussed it and read this information sheet you decide not to take part your standard of care will remain the same. For patients in your situation there will be a number of options available. You may choose to proceed immediately to surgical removal of your tumour following which it is very likely that we will recommend that you take hormone therapy after surgery. In addition we may also recommend radiation therapy and possibly chemotherapy. Even if you do not wish to take part in the study your doctor may offer hormone treatment for several months before your surgery with the aim of shrinking the cancer and permitting less extensive surgery. If you decide to take part you are free to withdraw at any time, without explanation, and again this will not affect your standard of care.

## WHAT WILL HAPPEN TO ME IF I TAKE PART?

First of all we would ask you to sign a Consent Form and answer any questions you have about the trial. Then we would find out which treatment you will receive by telephoning the Trials Office.

- Firstly you will be allocated an aromatase inhibitor (an antioestrogen). This will be either **exemestane or letrozole**. You have an equal chance of receiving either. You and your doctor will know which aromatase inhibitor you have been allocated and it will be clearly shown on the packaging. This part of the trial will be able to show us if exemestane or letrozole is better or if they are both equally as good at shrinking down tumours.
- Secondly you will be allocated another tablet and this will be either **celecoxib or placebo**. You have an equal chance of receiving either. A placebo is a “dummy treatment”, which looks like the genuine medicine but contains no active ingredient. This time neither you nor your doctor will know which tablet you have because they will look identical in identical packaging. This part of the trial will be able to tell us if aromatase inhibitors are more effective if given with celecoxib, or if the celecoxib doesn’t make any difference.

Placebo tablets are used in trials because if you or your doctor knew which tablet you were taking the results might be influenced by for example what you had read about the drug or what the doctor wanted the results to show. This is the safest way of getting true unbiased information.

You will be reviewed every 4 weeks during treatment when we will examine and measure the size of the cancer. Just before surgery we will perform a second ultrasound scan to measure the tumour size.

## WHAT DO I HAVE TO DO?

Take the study medication regularly as directed and attend the hospital as requested which will be after 14 days of treatment and then 4-weekly until your surgery, which will take place between 16- 18 weeks from the start.

## WHAT ARE THE DRUGS BEING TESTED?

### LETROZOLE

Letrozole is an aromatase inhibitor and reduces the oestrogen supply to breast cancer cells. It is licenced to be used before surgery to shrink a tumour that is oestrogen receptor positive or after

surgery to reduce risk of recurrence or to treat relapsed breast cancer. Letrozole is generally well tolerated in women with breast cancer. The main side effects of letrozole are similar to the menopause with hot flushes or sweats, some patients get joint stiffness or joint pain. When taken for long periods (i.e. years) it can lead to an increased risk of bone fractures so if you carry on with letrozole after surgery you will need to discuss bone health monitoring with your doctor.

### **EXEMESTANE**

Exemestane is a drug that is currently used to treat early breast cancer after surgery and when patients have been on tamoxifen for 2-3 years and also to treat relapsed breast cancer. It is generally well tolerated with similar side effects to letrozole. It is like letrozole, an aromatase inhibitor, but works in a different way. This is why we are interested in comparing the activity of exemestane and letrozole.

### **CELECOXIB**

We know that people taking drugs such as aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) have a lower risk of developing some cancers including breast cancer. These drugs reduce inflammation by blocking certain enzymes called COX 1 and COX 2. Interfering with COX 1 however causes increased risk of stomach ulcers and bleeding. Celecoxib or celebrex is a specific inhibitor of the COX 2 enzyme. It is in widespread use to treat painful inflammatory conditions such as rheumatoid arthritis. It is safer than NSAIDs, causing less stomach bleeding. Celecoxib is also licenced to treat patients with a pre-cancerous condition called polyposis coli where it is known to reduce risk of colon cancer formation. Research shows that it is COX 2 that is involved in breast cancer formation and growth. Experiments have shown celecoxib can cause breast cancer shrinkage and there is evidence that using celecoxib and aromatase inhibitors together is particularly potent. Using a COX 2 inhibitor such as celecoxib has the potential to add to the cancer shrinking properties of hormone therapy in women with breast cancer.

### **WHAT ARE THE ALTERNATIVES FOR DIAGNOSIS OR TREATMENT?**

Diagnosis would be the same. Treatment alternatives would be to choose to have your surgery before any other treatment or to have neoadjuvant (primary) treatment with an aromatase inhibitor without the COX 2 inhibitor/placebo.

### **WHAT ARE THE SIDE-EFFECTS OF ANY TREATMENT WHEN TAKING PART?**

The main side effects of letrozole are similar to the menopause with hot flushes or sweats, some patients get joint stiffness or joint pain. When taken for long periods (i.e. years) it can result in reduced bone density and there is an increased bone fracture risk so if you carry on with letrozole after surgery you will need to discuss bone health monitoring with your doctor.

Exemestane has a similar side effect profile to letrozole.

COX 2 drugs have been the subject of safety reviews after the COX 2 inhibitor rofecoxib was withdrawn by the manufacturer over concerns that patients taking this drug for long periods were experiencing an increased incidence of heart disease. Celecoxib is a COX 2 inhibitor but is biochemically distinct from rofecoxib and has been the subject of very extensive research and a review of the data from many studies involving over one million patients is almost all reassuring. Only one of the many studies has reported an increase in heart disease with prolonged treatment. All other studies and epidemiological reviews have shown no association of celecoxib with heart disease. Published evidence strongly suggests that short-term exposure to celecoxib will not increase the risk of heart disease. We have however decided that we should proceed with caution and women with risk factors or established heart disease such as poorly controlled high blood pressure, angina or a previous heart attack should not take part in this research. This approach



has been developed in conjunction with the Medicines and Healthcare products Regulatory Authority (MHRA). Understanding drug safety is an important part of any drug trials in medicine and we will be monitoring safety of patients in this trial closely. Celecoxib can make indigestion worse and very rarely cause stomach bleeding which is why we ask patients with a history of ulcers or severe indigestion not to take part.

## **WHAT ARE THE OTHER POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART?**

If your tumour got bigger then you would stop the trial and have your operation, or other necessary treatment as soon as possible. Since you will be reviewed every 4 weeks we would discover if this was the case very quickly. Experience has shown that it is unusual for tumours to grow whilst you are taking an aromatase inhibitor.

Patients with heart disease or at increased risk of it, kidney failure or peptic ulcers should not take part in this study. Patients who have taken any other regular NSAIDs or have asthma that is made worse by these drugs should also not take part. Patients with an allergy to aspirin or similar drugs should not take part. It is OK to take part if you are taking low dose aspirin. If you take fluconazole, ketoconazole, warfarin, ACE inhibitors, diuretics or lithium you should not take part in this study as these drugs may not mix well together.

## **WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?**

If we treat you before your operation with an aromatase inhibitor to cut off the supply of oestrogen to the cancer, this may shrink the tumour and make the surgery you then require less extensive. As a result of the treatment some patients may be able to avoid a mastectomy and have breast-conserving surgery (lumpectomy) instead. In general the more tumour shrinkage achieved the less extensive surgery will need to be. The main aim of this trial is to see if the drug celecoxib, when given in combination with an aromatase inhibitor can make the tumour shrink even more.

## **WHAT HAPPENS WHEN THE RESEARCH STUDY STOPS?**

After the 16 weeks of treatment you will be admitted to hospital in the normal way for an operation on your breast cancer. You will then be followed-up in clinic at least once a year for at least 5 years.

## **WHAT IF THERE IS A PROBLEM?**

Any complaint about the way you have been treated during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in part 2.

## **WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL?**

Yes. All the information about your participation in this study will be kept confidential. The details of this are included in part 2.

## **CONTACT DETAILS**

See part 2.

## **PART2**

## **WHAT IF RELEVANT NEW INFORMATION BECOMES AVAILABLE?**

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you about it



and discuss whether you want to or should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

### **WHAT HAPPENS IF I DON'T WANT TO CARRY ON WITH THE STUDY?**

You can withdraw from treatment but keep in contact with us to let us know your progress. Information collected may still be used. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish.

### **WHAT IF THERE IS A PROBLEM?**

#### **Complaints:**

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions (Contact number). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure (or Private Institution). Details can be obtained from the hospital.

#### **Harm:**

In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against (name of Sponsor Organisation, NHS Trust, Private Clinic) but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

### **WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?**

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from the Trials Unit. They may also be looked at by representatives of regulatory authorities and by authorised people from (the Trust, other NHS bodies) to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site. All information which is collected about you during the course of the research will be kept strictly confidential. To assist with long term follow-up your name and identifiable information will be sent to the Office of National Statistics (ONS). Procedures for handling, processing, storage and destruction of data are compliant with the Data Protection Act 1998. Your own GP will be notified of your participation in the trial, with your consent

### **WHAT WILL HAPPEN TO ANY SAMPLES I GIVE?**

Pre-treatment tumour samples and post-treatment tumour samples obtained at surgery will be centrally collected at the University of Edinburgh under the direct supervision of Dr John Bartlett. Serum samples at baseline, day 14 and pre-surgery will also be collected centrally at the University of Edinburgh. Samples will be stored for 5 - 10 years. Access will be available to all researchers whose projects are approved by the Trial Steering Committee and appropriate ethics



committees. If a participant withdraws from the study they can request their material to be destroyed (frozen tissues/bloods) or de-coded from the database so that no research information from this material is gathered. Your tumour sample and blood samples used for research will be identified by a unique trial number only. This will allow us to study what we find out about your tumour in relation to the information about your response to treatment. Because we need to make this comparison it is not possible to completely anonymise your samples.

### **WILL ANY GENETIC TESTS BE DONE?**

There is currently no intention to look at inherited genes. We will however be looking at the expression of genes within tumour samples and seeing how this changes with treatment. We will therefore be analysing DNA and RNA (gene messages) in tumour samples. In the future it may be very important to use these samples for new research on tumour genes. Clearly we cannot describe what this future research might involve. We would approach an ethics committee to approve this future research but in most circumstances would not seek further consent from patients. All research samples will be held on behalf of the Trial Steering Committee who will control the research and information performed on these samples.

### **WHAT WILL HAPPEN TO THE RESULTS?**

It is intended to publish the results. You will not be identified in any report/publication.

### **WHO IS ORGANISING AND FUNDING THE RESEARCH?**

The NEO-EXCEL study is a clinician-initiated and clinician-led study. The study is being run by the Cancer Research UK Clinical Trials Unit (CRCTU) in Birmingham. Financial support is being provided an educational grant from Cancer Research UK and the pharmaceutical industry.

### **WHO HAS REVIEWED THE STUDY?**

This study was given a favourable ethical opinion for conduct in the NHS by the ..... Regional Ethics Committee.

## **THANK YOU FOR TAKING THE TIME TO READ THIS INFORMATION**

### **LOCAL CONTACT DETAILS:**

#### **Additional Information**

The NEO-EXCEL study is a clinician-initiated and clinician-led study. The study is being run by the Cancer Research UK Clinical Trials Unit (CRCTU) in Birmingham. Financial support is being provided an educational grant. Neither the CRCTU nor the supporting pharmaceutical company hold insurance against claims for compensation for injury caused by participation in this trial and they cannot offer any indemnity. However, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial. Compensation is only available in the event of clinical negligence being proven. There are no specific arrangements for compensation made in respect of any serious adverse events occurring through your participation in this study, whether side effects listed above, or others as yet unforeseen.

Consumers for ethics in research (CERES) publish an information leaflet 'Medical research and you' which may help answer any questions you have. A copy may be obtained from CERES, PO Box 1365 London N16 OBW or [www.ceres.org.uk](http://www.ceres.org.uk).

**Patient to be given a copy of the information sheet and a signed consent form to keep.**



## Appendix 9: Breast Biopsy - Patient Information Sheet

Version 1.1: 04.07.2006

(To be printed on local headed paper)

### NEO-EXCEL

#### Studies in Breast Disease

You are advised by your doctor to have a core biopsy performed on your breast. The purpose of this procedure is to obtain samples of tissue that can be analysed to determine the nature of the abnormality that has been detected in your breast. Following the injection of local anaesthetic, several samples will be removed with a specially designed needle and sent to the Pathology Laboratory for analysis.

<*Name of institution*> is involved in a number of research projects studying breast tissue, in particular the changes that occur in association with the development and treatment of breast cancer. We would like to request your permission to use some of the tissue samples from your breast for current and future research. You may not benefit directly from the study of these biopsies, but the information gained may aid research into breast disease.

**ONLY TISSUE TAKEN IN EXCESS OF THAT REQUIRED TO EVALUATE YOUR  
CONDITION WILL BE USED FOR RESEARCH PURPOSES.**

Patient to be given a copy of the information sheet and a signed consent form to keep.



## Appendix 10: Pathology Consent Form (Studies on breast disease)

Version 1.1: 04.07.2006

(To be printed on local headed paper)

Patient Initials	
Hospital Number	
Patient Date of Birth	

### NEO-EXCEL

**Please initial box**

1. I have read and understood the Breast Biopsy information sheet (Version 1.1: 04.07.2006).

2. I agree to undergo the procedure of core biopsy. I understand that my agreement to allow samples to be analysed for research purposes is voluntary and that I am free to withdraw approval at any time without giving a reason and without my medical care and legal rights being affected.

3. I understand that the purpose of the research performed on the tissue samples is to improve understanding of breast disease and its treatment.

4. I understand that these extra samples are used for research, ethical approval will be obtained for the research project and that I will be asked to sign a separate consent form giving permission so these extra samples can be used.

5. I have read and understand the Pathology Consent Form.

\_\_\_\_\_  
Name of Patient

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Name of person taking consent  
(if different from researcher)

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Researcher

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

**When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes.**



## Appendix 11: GP Letter

Version 1.1: 04.07.2006

(To be printed on local headed paper)

### NEO-EXCEL

Dear Dr  
Regarding your patient \_\_\_\_\_

As she has been diagnosed with an ER positive breast cancer which is >2 cms she has been invited to take part in NEO-EXCEL, a randomised Phase III neoadjuvant trial of pre-operative exemestane or letrozole +/- celecoxib for the treatment of ER positive postmenopausal early breast cancer. This is a multicentre national clinical trial run through the Cancer Research UK Clinical Trials Unit at the University of Birmingham.

The aim of the trial is to see if the addition of a COX 2 inhibitor to an aromatase inhibitor in the neoadjuvant setting produces a greater objective clinical response than an aromatase inhibitor alone. By comparing two aromatase inhibitors we are also investigating whether exemestane is more effective than letrozole neoadjuvantly with and without celecoxib. Celecoxib as a possible treatment for cancer has resulted from an incidental finding that people taking nonsteroidal anti-inflammatory drugs (NSAIDS) for long periods seem to get less of certain cancers such as bowel and breast cancer.

If the neoadjuvant therapy causes the tumour to shrink then less extensive surgery may be possible. Some tumours previously only suitable for mastectomy may become suitable for breast conserving surgery.

We propose to establish a tissue and serum bank for future gene expression profiling and proteomic analysis to answer 2 key questions. Firstly, will expression profiling of sequential tumour biopsies identify molecular mechanisms which underpin the effects of celecoxib in the context of neoadjuvant breast cancer treatment? Secondly we hypothesise that markers of differential response to aromatase inhibitors will be identified in a linked analysis.

The randomisation is:

**16 weeks of,**

**Exemestane 25mg + Celecoxib 400mg bd or placebo**

**OR**

**Letrozole 2.5mg + Celecoxib 400 mg bd or placebo**

➤ followed by surgery

The patient would attend breast clinic 4 weekly during the study period for tumour measurement. If the disease progresses patients will be withdrawn from trial and alternative treatment given.

There is a substantial body of evidence supporting the safety of celecoxib: a pooled analysis of 30,000 patients who completed arthritis trials (including the CLASS and SUCCESS trials) indicates that celecoxib did not increase the incidence of



thromboembolic events versus placebo or in comparison with traditional NSAIDS. In CLASS, a long-term (12 month) prospective study, celecoxib even at 2-4 times the approved dose for arthritis and pain, was not associated with an increased risk for serious cardiovascular events such as heart attack, stroke or unstable angina compared to non-specific NSAIDS.

A recent American Federal Drug Agency (FDA) analysis of 1.4 million patients who were treated with COX 2 inhibitors or traditional NSAIDS showed that celecoxib demonstrated no increase in the relative risk of acute cardiac events when compared with those who had not taken any NSAID for at least 60 days.

In an analysis of over 138,000 people aged 65 or over, patients on celecoxib had a significantly less chance of being hospitalised for congestive heart failure than users of traditional NSAIDS and rofecoxib. A retrospective study of more than 54,000 elderly patients published in the journal Circulation showed that celecoxib was not associated with an increased risk for acute myocardial infarct compared with rofecoxib, traditional NSAIDS and no NSAID therapy.

In December 2004 important safety information was reported from the Independent Data Safety Monitoring Boards (IDSMB) of the US National Cancer Institute monitoring the two clinical trials involving celecoxib. Results from a third long-term celecoxib study, a US National Institute of Aging Alzheimer's Prevention study (ADAPT), were also recently reported. The results of these 3 studies are summarised below:

- In the Adenoma Prevention with Celecoxib (APC) trial, celecoxib demonstrated a statistically significant increased cardiovascular risk over placebo. The doses of celecoxib in this trial were 400-800mg per day. These findings were unexpected. Patients taking 400 and 800mg of celecoxib daily had an approximately 2.5-fold increase in their risk of experiencing a major fatal or non-fatal cardiovascular event compared to those patients taking placebo.
- In a separate long-term study, the Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial, there has been no increased risk for celecoxib patients taking 400mg daily compared with placebo. These two studies, which are following patients for 5 years, have enrolled a total of about 3,600 patients.
- A third trial (ADAPT) compared celecoxib to either naproxen sodium or placebo in a group of patients at risk for Alzheimer's disease treated for up to 3 years. Preliminary safety results from that study indicate an increased cardiovascular risk with naproxen sodium but not celecoxib relative to placebo.

As a result of this new data, in February 2005 the CSM issued prescribing advice for all selective COX 2 inhibitors (celecoxib, etoricoxib, valdecoxib and parecoxib) which has been entirely incorporated into the NEO-EXCEL protocol. The summary of the advice is to not prescribe COX 2 inhibitors to patients suffering from or at particular risk of heart disease and these patients will not be entered into NEO-EXCEL.

Please contact us if you have any questions.

Thank you for your support.

Yours sincerely

Att. Patient Information Sheet, Celecoxib safety data.



## ABBREVIATIONS AND DEFINITION OF TERMS

ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
AG	Aminoglutethimide
AI	Aromatase inhibitor
ALT	Alanine aminotransferase
AST	Aspartate transaminase
BC	Breast Cancer
BUN	Blood Urea Nitrogen
CHF	Chronic Heart Failure
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CRCTU	Cancer Research UK Clinical Trials Unit (UK National Data Centre)
CRF	Case Report Form
CTA	Clinical Trial Authorisation
DHT	Dihydroxytestosterone
DSMC	Data and Safety Monitoring Committee
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ECOG	Eastern cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
ER	Oestrogen Receptor
FCE	17- Hydro-exemestane (exemestane metabolite)
FISH	Fluorescent In-Situ Hybridization
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
Hb	Haemoglobin
HPLC	High Performance Liquid chromatography
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
IBCSG	International Breast Cancer Study Group
ICCG	The International Collaborative Cancer Group
IRB	Institutional Review Board
ICH	International Conference of Harmonization
IHC	Immunohistochemistry
LFTs	Liver Function Tests
LREC	Local Research Ethics Committee
MREC	Multicentre Research Ethics Committee
MTD	Maximum Tolerated Dose
NCI-CTC	National Cancer Institute Common Toxicity Criteria
NSABP	The National Surgical Adjuvant Breast and Bowel Project
NSAID	Non Steroidal Anti Inflammatory Drug
OS	Overall Survival
PgR	Progesterone Receptor
PLT	Platelets
PR	Partial Response
RBA	Relative Binding Affinity
RFS	Relapse (Recurrence)-Free Survival
RIA	Radio immuno-assay
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNO	Trial Number
TTF	Time to Treatment Failure
TPP	Time To Progression
TWIST	Time Without Symptoms or Toxicity
UNL	Upper Normal Limit
WBC	White Blood Cell Count
WMA	World Medical Association



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