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

Summary

EudraCT number	2006-000436-27
Trial protocol	GB
Global end of trial date	02 March 2021

Results information

Result version number	v1 (current)
This version publication date	18 March 2022
First version publication date	18 March 2022

Trial information

Trial identification

Sponsor protocol code	BR3031

Additional study identifiers

ISRCTN number	ISRCTN09768535
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Edgbaston, Birmingham, United Kingdom, B15 2TT
Public contact	Elizabeth Southgate, University of Birmingham, 044 1214143604, e.m.southgate@bham.ac.uk
Scientific contact	Daniel Rea, University of Birmingham, neoexcel@trials.bham.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 March 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether the addition of a COX2 inhibitor to an aromatase inhibitor results in greater objective clinical response, with acceptable toxicity, than an aromatase inhibitor alone.
Primary endpoint is objective clinical response (Complete Response, Partial Response) during neoadjuvant treatment.

Protection of trial subjects:

Patients taking medications thought to interact with study drugs with not eligible to take part.

A safety report was submitted annually to MHRA and MREC and all SUSARs were reported promptly.

The trial has both a Data Monitoring Committee and Trial Steering Committee which monitored the safety of trial participants.

Background therapy:

All trial participants have breast cancer surgery as appropriate, with radiotherapy if needed, following trial drug treatment.

Evidence for comparator:

A placebo was used as a comparator to celecoxib as this is an additional drug to standard treatment (hormone therapy).

Actual start date of recruitment	20 November 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 269
Worldwide total number of subjects	269
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	114
From 65 to 84 years	141
85 years and over	14

Subject disposition

Recruitment

Recruitment details:

269 patients took part in the trial between 11th November 2007 and 29th April 2014 at 22 UK hospitals.

Pre-assignment

Screening details:

It is unknown how many patients were pre-screened for eligibility at the hospital sites. Assessments required at trial screening were as per standard care so are likely to have taken place before consent. 269 participants were randomised into the trial; 4 were found to be ineligible. 256 patients had evaluable primary end point data.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Blinding implementation details:

Celecoxib/Placebo Treatment Packs were pre-packaged and delivered to site pharmacies. They contained emergency unblinding information in the form of codebreak envelopes kept by the site pharmacies for availability 24 hours per day. Trial monitors checked these envelopes during monitoring visits.

Arms

Are arms mutually exclusive?	Yes
Arm title	Exemestane + Placebo

Arm description:

Patients who received Exemastane and Placebo.

Arm type	Placebo
Investigational medicinal product name	celecoxib placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

two placebo capsules twice daily

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25mg tablet once daily

Arm title	Letrozole + Placebo

Arm description:

Patients who received Letrozole and Placebo

Arm type	Placebo

Investigational medicinal product name	celecoxib placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
two placebo capsules twice daily

Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
2.5mg tablet taken orally once daily

Arm title	Exemestane + Celecoxib

Arm description:
Patients who received Exemestane and Celecoxib

Arm type	Experimental
Investigational medicinal product name	celecoxib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
200mg oral capsule twice daily

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
25mg tablet once daily

Arm title	Letrozole + Celecoxib

Arm description:
Patients who received Letrozole and Celecoxib

Arm type	Experimental
Investigational medicinal product name	celecoxib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
200mg oral capsule twice daily

Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
2.5mg tablet taken orally once daily

Number of subjects in period 1	Exemestane + Placebo	Letrozole + Placebo	Exemestane + Celecoxib
Started	67	66	67
Completed	63	64	65
Not completed	4	2	2
Consent withdrawn by subject	4	1	1
Lost to follow-up	-	1	1

Number of subjects in period 1	Letrozole + Celecoxib
Started	69
Completed	66
Not completed	3
Consent withdrawn by subject	-
Lost to follow-up	3

Baseline characteristics

Reporting groups	
Reporting group title	Exemestane + Placebo
Reporting group description: Patients who received Exemastane and Placebo.	
Reporting group title	Letrozole + Placebo
Reporting group description: Patients who received Letrozole and Placebo	
Reporting group title	Exemestane + Celecoxib
Reporting group description: Patients who received Exemestane and Celecoxib	
Reporting group title	Letrozole + Celecoxib
Reporting group description: Patients who received Letrozole and Celecoxib	

Reporting group values	Exemestane + Placebo	Letrozole + Placebo	Exemestane + Celecoxib
Number of subjects	67	66	67
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	68.05	67.48	67.83
standard deviation	± 9.5	± 10.6	± 9.1
Gender categorical Units: Subjects			
Female	67	66	67
Male	0	0	0
Inflammatory Breast Cancer Units: Subjects			
No	67	66	67
Yes	0	0	0
Location within Breast Units: Subjects			
Central	16	6	13
Lower inner	10	9	9
Lower outer	7	6	13
Not know	0	0	0

Upper inner	10	13	11
Upper outer	24	32	21
Previous cancer Units: Subjects			
No	56	58	63
Yes	11	8	4
Suitable for breast conserving surgery Units: Subjects			
No	24	17	21
Probably	13	24	17
Yes	30	25	29
Tumour laterality Units: Subjects			
Left	35	35	35
Right	32	31	32
Tumour screen detected Units: Subjects			
No	50	50	50
Yes	17	16	17
Alkaline Phosphate Units: iu/l			
median	89.50	86	90
full range (min-max)	45 to 454	44 to 481	32 to 305
ALT Units: iu/l			
median	18.5	17	20
full range (min-max)	8 to 42	7 to 34	11 to 56
AST Units: iu/l			
median	21	21	20
full range (min-max)	15 to 40	0 to 35	14 to 30
Bilirubin Units: umol/l			
median	8	7	7
full range (min-max)	3 to 34	0.6 to 26	3 to 19
Creatinin Units: umol/l			
median	67	71	69
full range (min-max)	43 to 130	46 to 116	45 to 99
Diastolic BP Units: mmHg			
median	81.5	82	85
full range (min-max)	56 to 108	56 to 105	60 to 106
Haemoglobin Units: g(/dl)			
median	13.7	13.6	13.7
full range (min-max)	10.5 to 15.8	10.5 to 17.2	10.05 to 16
Height Units: metre			
median	1.60	1.58	1.6
full range (min-max)	1.42 to 1.78	1.45 to 1.80	1.43 to 1.78

MCV			
Units: fl			
median	90.3	91.45	91.05
full range (min-max)	80.4 to 103.9	0.94 to 103.9	75 to 103
Neutrophils			
Units: x10^9/l			
median	4.5	4.58	4.28
full range (min-max)	1.9 to 9.4	1.5 to 10.3	1.5 to 7.8
Platelets			
Units: x10^9/l			
median	263	269	286
full range (min-max)	179 to 522	9.1 to 724	21.4 to 476
Serum Ca			
Units: mmol/l			
median	2.36	2.33	2.37
full range (min-max)	2.17 to 2.57	2.08 to 2.53	2.1 to 2.63
Systolic BP			
Units: mmHg			
median	145.5	140	147
full range (min-max)	99 to 187	107 to 190	105 to 189
Urea			
Units: mmol/l			
median	5.2	5.3	5.05
full range (min-max)	2.5 to 9.7	0.2 to 12.3	0.4 to 7.8
WBC			
Units: x10^9/l			
median	7.5	7.24	6.8
full range (min-max)	3.98 to 12.9	3.2 to 13.3	3.39 to 11.4
Weight			
Units: Kg			
median	70.05	69.25	71.2
full range (min-max)	41 to 120.1	47.8 to 113.1	50.3 to 142.7

Reporting group values	Letrozole + Celecoxib	Total	
Number of subjects	69	269	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	68.32		
standard deviation	± 67.64	-	

Gender categorical Units: Subjects			
Female	69	269	
Male	0	0	
Inflammatory Breast Cancer Units: Subjects			
No	69	269	
Yes	0	0	
Location within Breast Units: Subjects			
Central	16	51	
Lower inner	4	32	
Lower outer	8	34	
Not know	1	1	
Upper inner	10	44	
Upper outer	30	107	
Previous cancer Units: Subjects			
No	65	242	
Yes	4	27	
Suitable for breast conserving surgery Units: Subjects			
No	27	89	
Probably	16	70	
Yes	26	110	
Tumour laterality Units: Subjects			
Left	44	149	
Right	25	120	
Tumour screen detected Units: Subjects			
No	56	206	
Yes	13	63	
Alkaline Phosphate Units: iu/l			
median	82		
full range (min-max)	30 to 259	-	
ALT Units: iu/l			
median	16.5		
full range (min-max)	2.6 to 42	-	
AST Units: iu/l			
median	21		
full range (min-max)	15 to 36	-	
Bilirubin Units: umol/l			
median	6		
full range (min-max)	3 to 21	-	
Creatinin Units: umol/l			

median	68		
full range (min-max)	45 to 103	-	
Diastolic BP Units: mmHg			
median	80		
full range (min-max)	60 to 109	-	
Haemoglobin Units: g(/dl)			
median	13.7		
full range (min-max)	10.9 to 15.4	-	
Height Units: metre			
median	1.6		
full range (min-max)	1.44 to 1.73	-	
MCV Units: fl			
median	90.6		
full range (min-max)	72.2 to 101	-	
Neutrophils Units: x10^9/l			
median	4.1		
full range (min-max)	1.55 to 9.6	-	
Platelets Units: x10^9/l			
median	264		
full range (min-max)	21 to 457	-	
Serum Ca Units: mmol/l			
median	2.35		
full range (min-max)	1.99 to 2.54	-	
Systolic BP Units: mmHg			
median	140		
full range (min-max)	92 to 223	-	
Urea Units: mmol/l			
median	5		
full range (min-max)	0.2 to 30.8	-	
WBC Units: x10^9/l			
median	6.8		
full range (min-max)	4.16 to 14.2	-	
Weight Units: Kg			
median	70		
full range (min-max)	52 to 104	-	

End points

End points reporting groups

Reporting group title	Exemestane + Placebo
Reporting group description:	
Patients who received Exemastane and Placebo.	
Reporting group title	Letrozole + Placebo
Reporting group description:	
Patients who received Letrozole and Placebo	
Reporting group title	Exemestane + Celecoxib
Reporting group description:	
Patients who received Exemestane and Celecoxib	
Reporting group title	Letrozole + Celecoxib
Reporting group description:	
Patients who received Letrozole and Celecoxib	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All the patients who met the criteria to be included for analysis of the primary outcome and were allocated to either Exemestane + Placebo or Letrozole + Placebo arms.	
Subject analysis set title	Celecoxib
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All the patients who met the criteria to be included for analysis of the primary outcome and were allocated to either Exemestane + Celecoxib or Letrozole + Celecoxib arms.	

Primary: Objective clinical response

End point title	Objective clinical response
End point description:	
End point type	Primary
End point timeframe:	
Objective clinical response determined by repeated measurement of tumor sizes using calipers over the 16 week treatment period.	

End point values	Placebo	Celecoxib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	133	133		
Units: Response				
Response	74	97		
No Response	59	36		

Statistical analyses

Statistical analysis title	Chi squared test

Statistical analysis description:

Objective clinical response rates are compared between the Celecoxib and Placebo arms using a Chi-squared test.
The primary hypothesis to be tested is the objective clinical response rate does not differ between the two treatment groups.
A significance level of 10% will be used.

Comparison groups	Placebo v Celecoxib
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Chi-squared

Statistical analysis title	Univariate Regression

Statistical analysis description:

A univariate model was fit to assess the difference in response between treatment groups.

Comparison groups	Placebo v Celecoxib
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	2.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.29
upper limit	3.61

Statistical analysis title	Multivariate analysis

Statistical analysis description:

Multivariate logistic regression was used to explore treatment effect adjusted for stratification factors and randomised treatment. The following variables were included: Treatment (placebo/celecoxib), Tumour size (2-5cm/ > 5cm), Tumor grade (Well diff/Mod diff/Poor diff), ERQ score (3-4/5-6/7-8), HER2 (negative/positive), Aspirin (no/yes), Aromtase inhibitor (Exemestane/Letrozole)

Comparison groups	Placebo v Celecoxib
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	2.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.34
upper limit	3.83

Secondary: Objective ultrasound determined response

End point title	Objective ultrasound determined response

End point description:

End point type	Secondary

End point timeframe:

Objective ultrasound determined response by repeated measurement of tumor sizes using ultrasounds over the 16 week treatment period.

End point values	Placebo	Celecoxib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	102	111		
Units: Response				
Response	42	54		
No Response	60	57		

Statistical analyses

Statistical analysis title	Chi squared test

Statistical analysis description:

Objective ultrasound determined response rates are compared between the Celecoxib and Placebo arms using a Chi-squared test.
The primary hypothesis to be tested is that the response rate does not differ between the two treatment groups.

Comparison groups	Placebo v Celecoxib
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.339
Method	Chi-squared

Secondary: Axillary Lymph Node Involvement at Surgery

End point title	Axillary Lymph Node Involvement at Surgery

End point description:

End point type	Secondary

End point timeframe:

Assessed at surgery

End point values	Placebo	Celecoxib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80	85		
Units: Rates				
No lymph node involvement at surgery	44	47		
Lymph node involvement at surgery	36	38		

Statistical analyses

No statistical analyses for this end point

Secondary: Type of Surgery

End point title	Type of Surgery

End point description:

End point type	Secondary

End point timeframe:

At surgery

End point values	Placebo	Celecoxib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	128	133		
Units: Surgery type				
Breast Conserving	95	102		
Mastectomy	33	31		

Statistical analyses

Statistical analysis title	Chi Squared test

Statistical analysis description:

The rates of surgery types are compared between the Celecoxib and Placebo arms using a Chi-squared test.
The hypothesis to be tested is the type of surgery does not differ between the two treatment groups.

Comparison groups	Placebo v Celecoxib

Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.749
Method	Chi-squared

Secondary: Complete Pathological Response

End point title	Complete Pathological Response

End point description:

End point type	Secondary

End point timeframe:

Complete pathological response is determined by the pathologist at surgery

End point values	Placebo	Celecoxib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125	128		
Units: Response				
No complete pathological response	123	126		
Complete pathological response	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Local recurrence-free survival time

End point title	Local recurrence-free survival time

End point description:

End point type	Secondary

End point timeframe:

5 years follow-up

End point values	Placebo	Celecoxib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	133	136		
Units: 5 year survival estimate				
number (confidence interval 95%)	0.97 (0.97 to 1)	0.96 (0.93 to 1)		

Statistical analyses

Statistical analysis title	Log rank test
Comparison groups	Celecoxib v Placebo
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	Logrank

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

End point type	Secondary

End point timeframe:

5 years of follow-up

End point values	Placebo	Celecoxib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	133	136		
Units: 5 year survival estimate				
number (confidence interval 95%)	0.74 (0.67 to 0.82)	0.79 (0.73 to 0.86)		

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	Placebo v Celecoxib
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	Logrank

Secondary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Secondary

End point timeframe:

Follow-up of 5 years

End point values	Placebo	Celecoxib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	133	136		
Units: 5 year survival estimate				
number (confidence interval 95%)	0.87 (0.82 to 0.93)	0.83 (0.77 to 0.90)		

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	Placebo v Celecoxib
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected up until 30 days after the last dose of IMP.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTC
Dictionary version	3

Reporting groups

Reporting group title	Safety Population

Reporting group description: -

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 269 (4.46%)		
number of deaths (all causes)	42		
number of deaths resulting from adverse events			
Cardiac disorders			
cardiac arryhtmia			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial flutter with variable block			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Spinal cord compression			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Haematoma			
subjects affected / exposed	2 / 269 (0.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Hemorrhage			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Social circumstances			
Admission for social reasons			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulm/upper Resp			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SOB			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Uterine cyst			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Seroma			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscle weakness Left sided			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Left breast cellulitis			

subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	2 / 269 (0.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	221 / 269 (82.16%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	57 / 269 (21.19%)		
occurrences (all)	63		
Insomnia			
subjects affected / exposed	20 / 269 (7.43%)		
occurrences (all)	21		
Dizziness			
subjects affected / exposed	14 / 269 (5.20%)		
occurrences (all)	18		
Arthralgia			
subjects affected / exposed	63 / 269 (23.42%)		
occurrences (all)	38		
Breast pain			
subjects affected / exposed	21 / 269 (7.81%)		
occurrences (all)	23		
Headache			
subjects affected / exposed	19 / 269 (7.06%)		
occurrences (all)	21		
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	25 / 269 (9.29%)		
occurrences (all)	29		
Dyspepsia			
subjects affected / exposed	18 / 269 (6.69%)		
occurrences (all)	19		
Nausea			
subjects affected / exposed	29 / 269 (10.78%)		
occurrences (all)	33		
Skin and subcutaneous tissue disorders			
Dermatitis exfoliative			
subjects affected / exposed	21 / 269 (7.81%)		
occurrences (all)	25		
Endocrine disorders			
Hot flushes			
subjects affected / exposed	95 / 269 (35.32%)		
occurrences (all)	104		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 January 2007	Exclusion Criteria (section 6.2, page 22): the word 'invasive' has been added to the third exclusion criteria to clearly specify 'invasive breast cancer' Treatment Details (section 8.1, page 24): clarification has been made to explain until when patients should continue their trial treatment (also mentioned on page 28) Two stratification variables have been removed (page 23): 'clinical nodal involvement' and 'participation in translation sub protocol' Schedule of Assessments (section 9, page 26): updated to make clearer when samples are required Pharmacy/drug distribution contact details (throughout the protocol) have been modified to direct the reader to refer to the trial-specific Investigator Site Files for detailed information Trial management/data collection section (section 10, page 29): minor modifications have been made to reflect updates in CRFs required Administrative changes have been made throughout eg. replacing 'Centre' by 'Site', replacing/removing the abbreviation CRCTU and updating contact details where applicable
21 June 2007	Changes to Clinical Trial agreement
25 September 2009	• TRANS Neo-excel sub-study has been made optional, removing the requirement for tissue and blood sample collection and the additional 14 day biopsy. A new version of the PIS and ICF (Version A) has been created for use at sites that choose not to participate in this optional sub-study. • The existing PIS and ICF (Version B) have been simplified, although the basic information regarding the trial remains the same, so the intent is not to re-consent patients for this study. • The Breast Biopsy- PIS and Pathology ICF have been amended and renamed and are now called the PIS - Donating Tissue for Research and Research Tissue ICF respectively. • An optional PIS has been created which provides a very brief and simple summary about the trial, which sites can choose to give to patients prior to the PIS. • Statistical analysis and sample size sections have been rewritten to indicate that a meaningful analysis can be preformed between the celecoxib and placebo arms if only 434 patients are recruited. • Additional instructions regarding unbinding outside of office hours. • Section 15.2 patient confidentiality has been reworded in line with CRCTU procedures and also to indicates that from now on patient's signed and dated ICFs will be returned to the CRCTU. The PIS and consent has also been updated to include this information. • Appendix 3 has been updated with the 1996 version of the Declaration of Helsinki as specified by The Medicines for Human Use (Clinical Trials) Regulations 2004. • PIS, ICF, GP letter have been removed from appendix 7-11 and separate documents have been created. • In eligibility criteria, the breast tumour size now includes postmenopausal women with ER positive tumours ≥ 2 cm. Also tumours must be measured clinically as ≥ 2cm and not measured on ultrasound. • Changes to the definition of serious adverse event to bring it in line with current CRCTU definitions.

01 February 2010	Sample size reduced from 1000 to 256 subjects Changes to trial objectives. New objective is to whether the activity of aromatase inhibitors as primary neo-adjuvant endocrine therapy for early stage ER positive breast cancer in postmenopausal women may be enhanced by the addition of the selective COX 2 inhibitor celecoxib. Changes to trial design and statistical analysis. Prospective phase III, multicentre, randomised clinical trial, with placebo-controlled comparisons.
10 September 2010	The recruitment target has been reduced to 256 patients. The statistical analysis and sample size sections of the protocol have been rewritten to highlight this change. Other major changes to the protocol include: • Modification to the RECIST criteria. The RECIST is irrelevant to the trial as we are not reviewing target lesions and non-target lesions. • Introduction of Patient Contact Cards, which will be given to all patients randomised into the trial on which the patient trial number, allocated treatment and contact details for emergency unblinding will be recorded.
24 February 2012	In summary, the duration of treatment period (16 weeks) has been clarified throughout the protocol. In addition, Patient Information Sheets (A and B) and Informed Consent Forms (A and B) have also been amended to include subheadings "excludes Trans NEO-EXCEL sub-study" and "includes Trans NEO-EXCEL sub-study" to further clarify their separate uses within NEO-EXCEL study. Other major changes to the protocol include: • Changes to the Randomisation telephone an fax number • Changes to the SAE Reporting fax number • Unit for creatinine measurement corrected to µmol/l • Recruitment target amended from 1000 to 256 patients on Patient Information Sheet A and B • Changes in Principal Investigator at two sites: o Dr Tahir Farooq has taken over the role of Principal Investigator instead of Dr Alan Jewkes at Good Hope Hospital o Mr Simon Smith has taken over the role of Principal Investigator instead of Prof Paul Sauven at Broomfield Hospital (formerly known as Chelmsford and Essex County Hospital) We would also like to extend the recruitment period for this trial to 1 May 2014 and therefore the duration of the ethical approval for this trial from 1 May 2012 to 1 May 2019, which includes an extended recruitment phase and 5 years follow-up.

10 April 2013	In summary, due to the current Celecoxib/placebo stock expiring in the end of October 2013 and the recruitment period continuing until May 2014, we require a new stock of Celecoxib/placebo treatment packs. The current stock of Celecoxib is of 400mg strength but it is only possible to purchase 200mg strength for the new stock. Therefore the following changes have been made: • Protocol o Change from "celecoxib 400mg, one capsule twice daily" to "celecoxib 200mg, two capsules twice daily". o The drug distribution company has changed its name to Sharp Clinical Services. • GP Letter o Change from "Celecoxib 400mg bd" to "Celecoxib 2 x 200mg bd". In addition the following changes will occur: • Addition of four new sites: o Dr Karen McAdam will be the Principal Investigator at Peterborough City Hospital. o Mr Jibril Jibril will be the Principal Investigator at Lincoln County Hospital, Grantham and District Hospital, and Pilgrim Hospital. • Changes in Principle Investigator at one site: o Dr Diane Ritchie has taken over the role of Principal Investigator instead of Dr Peter Canney at Beatson West of Scotland Cancer Centre. • Protocol: o Dr Susanna Kallioinen has taken over from Dr Jaspreet Babrah as the Trial Co-ordinator. o Mrs Cassandra Brookes has taken over from Dr Laura Buckley as the Statistician.
05 May 2014	Change in principal Investigator
30 November 2017	Changes to end of trial definition, Chief Investigator and Trial Management Group

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

N/A

Notes: