



Clinical trial results:

A single arm phase IIa study (with combination safety run-in) to assess the safety and efficacy of AZD4547 in combination with either anastrozole or letrozole in ER positive breast cancer patients who have progressed on treatment with anastrozole or letrozole

Summary

EudraCT number	2011-000454-32
Trial protocol	GB
Global end of trial date	08 November 2018

Results information

Result version number	v1 (current)
This version publication date	02 February 2020
First version publication date	02 February 2020

Trial information

Trial identification

Sponsor protocol code	C/23/2011
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Additional study identifiers

ISRCTN number	ISRCTN80307982
ClinicalTrials.gov id (NCT number)	NCT01791985
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	South Kensington Campus, London, United Kingdom, SW7 2AZ
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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	08 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2016
Global end of trial reached?	Yes
Global end of trial date	08 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Stage 1 (Safety run-in): To assess the safety and tolerability and determine the dose of AZD4547 to be used together with a standard dose of anastrozole or letrozole (a class of drugs called non-steroidal aromatase inhibitors) i.e. a dose which does not cause too many unacceptable side effects. This dose of AZD4547 will then be used in stage 2 (phase IIa study).

Stage 2 (Phase IIa study): To assess the effectiveness of AZ4547, based on the change in tumour size at 12 weeks (or progression if prior to week 12), when used in combination with either anastrozole or letrozole in ER positive breast cancer patients who have progressed on treatment with either anastrozole or letrozole in any setting.

Protection of trial subjects:

None

Background therapy:

NSAI (anastrozole (1mg) or letrozole (2.5mg)), orally, once daily.

Evidence for comparator: -

Actual start date of recruitment	23 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 52
Worldwide total number of subjects	52
EEA total number of subjects	52

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)	41
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited between 2012 and 2016.

Pre-assignment

Screening details:

The screening was conducted according to the study protocol.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No blinding - open label IMP

Arms

Arm title	AZD4547
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Arm description:

Subjects received 80mg of AZD4547 twice daily, one week on and one week off in addition to daily AI (letrozole (2.5mg) or anastrozole (1mg) on which they progressed until disease progression or the development of unacceptable toxicities

Arm type	Experimental
Investigational medicinal product name	AZD4547
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Twice daily AZD4547 (80mg), was given on an intermittent schedule of one week on / one week off.

Number of subjects in period 1	AZD4547
Started	52
Completed	44
Not completed	8
Consent withdrawn by subject	1
Adverse event, non-fatal	7

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial
Reporting group description: -	

Reporting group values	Overall Trial	Total	
Number of subjects	52	52	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	41	41	
From 65-84 years	11	11	
85 years and over	0	0	
Age continuous			
Units: years			
median	56.5		
inter-quartile range (Q1-Q3)	50 to 64	-	
Gender categorical			
Units: Subjects			
Female	52	52	
Male	0	0	
Ethnicity			
Units: Subjects			
White	49	49	
Black	2	2	
Not reported	1	1	
Smoking			
Units: Subjects			
Never	29	29	
Past	18	18	
Current	3	3	
Not specified	2	2	
ECOG			
Units: Subjects			
Fully Active	33	33	
Restricted in Physically Strenous Activity	19	19	
Tumour Grade			
Units: Subjects			
G1/2	25	25	
G3/4	14	14	
Unknown	13	13	

ECG			
Units: Subjects			
Normal	33	33	
Abnormal	19	19	
ECHO/MUGA Scan			
Units: Subjects			
Normal	49	49	
Abnormal	3	3	

End points

End points reporting groups

Reporting group title	AZD4547
Reporting group description: Subjects received 80mg of AZD4547 twice daily, one week on and one week off in addition to daily AI (letrozole (2.5mg) or anastrozole (1mg) on which they progressed until disease progression or the development of unacceptable toxicities	

Primary: Proportion of Tumour Size Change at 12 Weeks (or Progression if Prior to Week 12)

End point title	Proportion of Tumour Size Change at 12 Weeks (or Progression if Prior to Week 12) ^[1]
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End point description:

This is the primary outcome measure in the Randomised Phase IIa part of the study. This is the proportion of tumour size change from baseline to week 12 (or progression if prior to week 12) based on local review of results.

End point type	Primary
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End point timeframe:

12 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Proportion of change in tumour size at 12 weeks (or progression if prior to week 12), when used in combination with either anastrozole or letrozole in ER positive breast cancer patients who have progressed on treatment with either anastrozole or letrozole in any setting. Estimated Value is 0.08, SD 0.32.

End point values	AZD4547			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: proportion of size change				
arithmetic mean (standard deviation)	0.08 (± 0.32)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Tumour Size Change at 6, 20 Weeks, Then Every 8 Weeks

End point title	Proportion of Tumour Size Change at 6, 20 Weeks, Then Every 8 Weeks
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End point description:

Proportion of tumour size change at 6 weeks, 20 weeks, then every 8 weeks, as per study plan to assess the efficacy of AZD4547 in combination with anastrozole or letrozole. This outcome measure is based on local review.

End point type	Secondary
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End point timeframe:

6, 20 weeks, then every 8 weeks

End point values	AZD4547			
Subject group type	Reporting group			
Number of subjects analysed	48 ^[2]			
Units: Proportion of Size Change				
arithmetic mean (standard deviation)				
Proportion of tumour size change at week 6	0.04 (± 0.29)			
Proportion of tumour size change at week 20	0.09 (± 0.36)			
Proportion of tumour size change at week 28	0.10 (± 0.36)			

Notes:

[2] - The number of subjects analyzed at 6 weeks is 48, at 12 weeks is 41 and at 28 weeks is 40.

Statistical analyses

No statistical analyses for this end point

Secondary: Tumour Response (RECIST Criteria) at 6 Weeks

End point title	Tumour Response (RECIST Criteria) at 6 Weeks
End point description:	
Tumour response (RECIST criteria) at 6 weeks to assess the efficacy of AZD4547 in combination with anastrozole or letrozole. This outcome measure is based on local review.	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	AZD4547			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: participants				
Complete response	0			
Partial response	2			
Stable disease	31			
Progressive disease	16			
Progressive disease before scan	1			
Withdrawn before scan	2			
Scan not done or not available	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Tumour Response (RECIST Criteria) at 12 Weeks

End point title	Tumour Response (RECIST Criteria) at 12 Weeks
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End point description:

Tumour response (RECIST criteria) at 12 weeks to assess the efficacy of AZD4547 in combination with anastrozole or letrozole. This outcome measure is based on local review.

End point type	Secondary
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End point timeframe:

12 weeks

End point values	AZD4547			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: participants				
Complete response	0			
Partial response	1			
Stable disease	18			
Progressive disease	8			
Progressive disease before scan	17			
Withdrawn before scan	6			
Scan not done or not available	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Tumour Response (RECIST Criteria) at 20 Weeks

End point title	Tumour Response (RECIST Criteria) at 20 Weeks
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End point description:

Tumour response (RECIST criteria) at 20 weeks to assess the efficacy of AZD4547 in combination with anastrozole or letrozole. This outcome measure is based on local review.

End point type	Secondary
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End point timeframe:

20 weeks

End point values	AZD4547			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: participants				
Complete response	0			
Partial response	2			
Stable disease	13			
Progressive disease	3			

Progressive disease before scan	26			
Withdrawn before scan	8			
Scan not done or not available	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Tumour Response (RECIST Criteria) at 28 Weeks

End point title	Tumour Response (RECIST Criteria) at 28 Weeks
End point description:	
Tumour response (RECIST criteria) at 28 weeks to assess the efficacy of AZD4547 in combination with anastrozole or letrozole. This outcome measure is based on local review.	
End point type	Secondary
End point timeframe:	
28 weeks	

End point values	AZD4547			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: participants				
Complete response	0			
Partial response	2			
Stable disease	10			
Progressive disease	1			
Progressive disease before scan	30			
Withdrawn before scan	9			
Scan not done or not available	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response at 6, 12 Weeks, Then Every 8 Weeks

End point title	Objective Response at 6, 12 Weeks, Then Every 8 Weeks
End point description:	
Objective Response at 6 weeks, 12 weeks, then every 8 weeks, as per study plan to assess the efficacy of AZD4547 in combination with anastrozole or letrozole. The ORR is defined as the proportion of overall complete response (CR) and overall partial response (PR) among all patients who receive at least one dose of study treatment. This outcome measure is based on local review.	
End point type	Secondary
End point timeframe:	
6, 12 weeks, then Every 8 weeks	

End point values	AZD4547			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: participants				
Objective response at week 6	0			
Objective response at week 12	2			
Objective response at week 20	3			
Objective response at week 28	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

End point title	Progression Free Survival
End point description: Progression Free Survival (PFS) was defined as the time from study enrolment to first evidence of progression. Progression is defined as overall progressive disease identified at follow-up or confirmed disease progression at the end of the trial or death.	
End point type	Secondary
End point timeframe: 42	

End point values	AZD4547			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: months				
median (confidence interval 95%)	3.1 (2.4 to 6.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected throughout the study, from the point that the RADICAL team confirmed patient eligibility until the end of patient follow-up, 42 months

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16
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Reporting groups

Reporting group title	AZD4547 Arm
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Reporting group description: -

Serious adverse events	AZD4547 Arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 52 (19.23%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Injury, poisoning and procedural complications			
Fractured bone			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Surgical or medical procedure - prolongation of hospital stay			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Unsteadiness on feet			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Aspiration pneumonia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
UTI			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Fractured femur			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Infections and Infestations - Other subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders Dehydration subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	AZD4547 Arm		
Total subjects affected by non-serious adverse events subjects affected / exposed	52 / 52 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Metastases to eye subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	2		
Metastases to skin subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Vascular disorders Embolism subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Epistaxis subjects affected / exposed	9 / 52 (17.31%)		
occurrences (all)	12		
Eye contusion			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	4		
Hypotension			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Surgical and medical procedures			
Breast operation			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Tooth extraction			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	12 / 52 (23.08%)		
occurrences (all)	20		
Influenza like illness			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Lethargy			
subjects affected / exposed	7 / 52 (13.46%)		
occurrences (all)	9		
Mucosal inflammation			
subjects affected / exposed	6 / 52 (11.54%)		
occurrences (all)	6		
Oedema peripheral			

subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 3		
Wound secretion subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2		
Social circumstances Corrective lens user subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Reproductive system and breast disorders Breast atrophy subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Breast discomfort subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Breast inflammation subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Genital discharge subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Pelvic pain subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Vaginal discharge subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Vaginal haemorrhage subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Vulvovaginal dryness			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Chest pain			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	9 / 52 (17.31%)		
occurrences (all)	10		
Dysphonia			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	5		
Haemoptysis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Lower respiratory tract infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Nasal discharge discolouration			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Nasal dryness			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Oropharyngeal pain			
subjects affected / exposed	6 / 52 (11.54%)		
occurrences (all)	6		
Pleuritic pain			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	2		
Pneumonia aspiration			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	5		
Panic attack			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 52 (17.31%)		
occurrences (all)	15		
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 52 (17.31%)		
occurrences (all)	15		
Blood albumin decreased			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	13		
Blood alkaline phosphatase increased			

subjects affected / exposed	8 / 52 (15.38%)		
occurrences (all)	12		
Blood bilirubin increased			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	4		
Blood calcium increased			
subjects affected / exposed	7 / 52 (13.46%)		
occurrences (all)	9		
Blood calcium decreased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Blood cholesterol increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Blood creatine increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	2		
Blood glucose increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Blood magnesium increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	2		
Blood magnesium decreased			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	5		
Blood phosphorus decreased			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	7		
Blood phosphorus increased			
subjects affected / exposed	17 / 52 (32.69%)		
occurrences (all)	30		
Blood potassium decreased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	2		
Blood pressure increased			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Blood urine present			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Calcium phosphate product increased			
subjects affected / exposed	7 / 52 (13.46%)		
occurrences (all)	11		
Carbohydrate antigen 15-3 increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Dermatologic examination abnormal			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Ejection fraction abnormal			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	2		
Neutrophil count decreased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	5		
Platelet count increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Protein urine present			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	6		
Weight increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
White blood cell count decreased			

subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
White blood cells urine			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Excoriation			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Face injury			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Ligament sprain			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Limb crushing injury			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Post procedural discharge			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Cardiac aneurysm			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Left ventricular dysfunction			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Mitral valve incompetence			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Ventricular hypokinesia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Nervous system disorders			
Ageusia			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Balance disorder			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Convulsion			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	4		
Dysgeusia			
subjects affected / exposed	15 / 52 (28.85%)		
occurrences (all)	17		
Headache			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	5		
Hypoaesthesia oral			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		

Neurotoxicity subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Paraesthesia subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Somnolence subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	7 / 52 (13.46%) 9		
Lymphopenia subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 2		
Metastases to lymph nodes subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 2		
Neutropenia subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 5		
Thrombocytopenia subjects affected / exposed occurrences (all)	6 / 52 (11.54%) 7		
Ear and labyrinth disorders Ear infection subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Eye disorders Age-related macular degeneration subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Cataract subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Conjunctival hyperaemia			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Corneal erosion multiple			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Corneal oedema			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Detachment of macular retinal pigment epithelium			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Detachment of retinal pigment epithelium			
subjects affected / exposed	9 / 52 (17.31%)		
occurrences (all)	14		
Dry eye			
subjects affected / exposed	9 / 52 (17.31%)		
occurrences (all)	10		
Eye disorder			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Eye pruritus			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Growth of eyelashes			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Increased intraocular pressure			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Iritis			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Keratitis			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	4		
Lacrimation increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Macular degeneration			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Maculopathy			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Ocular hyperaemia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Papilloedema			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Relative afferent pupillary defect			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Retinal detachment			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Retinal pigment epitheliopathy			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	6		
Ulcerative keratitis			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Vision blurred			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Visual impairment			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	20 / 52 (38.46%)		
occurrences (all)	23		
Diarrhoea			
subjects affected / exposed	16 / 52 (30.77%)		
occurrences (all)	30		
Dry mouth			
subjects affected / exposed	23 / 52 (44.23%)		
occurrences (all)	30		
Dyspepsia			
subjects affected / exposed	12 / 52 (23.08%)		
occurrences (all)	17		
Gastrointestinal pain			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Glossodynia			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	5		
Haemorrhoids			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Hypogeusia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		

Lip dry			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	6 / 52 (11.54%)		
occurrences (all)	14		
Nausea			
subjects affected / exposed	21 / 52 (40.38%)		
occurrences (all)	26		
Oesophagitis			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	4		
Oral pain			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	8 / 52 (15.38%)		
occurrences (all)	11		
Tongue coated			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Tongue eruption			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Tongue ulceration			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	6		
Toothache			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	8 / 52 (15.38%)		
occurrences (all)	10		

Hepatobiliary disorders			
Hypoalbuminaemia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	20 / 52 (38.46%)		
occurrences (all)	25		
Cellulitis			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Contusion			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	8 / 52 (15.38%)		
occurrences (all)	9		
Erythema			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Flushing			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Laceration			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Nail discolouration			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	5		
Nail disorder			
subjects affected / exposed	8 / 52 (15.38%)		
occurrences (all)	8		
Nail dystrophy			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Nail infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Onycholysis			
subjects affected / exposed	6 / 52 (11.54%)		
occurrences (all)	6		
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	4		
Palmar erythema			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	2		
Paronychia			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	4		
Pigmentation disorder			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Rash macular			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	2		
Skin disorder			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Skin odour abnormal			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Skin toxicity			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		

Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	9 / 52 (17.31%)		
occurrences (all)	15		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 52 (21.15%)		
occurrences (all)	13		
Back pain			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	6		
Femur fracture			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Fibroma			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Foot fracture			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Joint stiffness			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Joint swelling			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Ligament sprain			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	5		
Musculoskeletal chest pain			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	4		
Musculoskeletal stiffness			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	4		
Pain in jaw			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Laryngitis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Lung infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Neutropenic sepsis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	2		
Oral candidiasis			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	6		

Wound infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Pneumonia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Viral pharyngitis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Aphagia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Decreased appetite			
subjects affected / exposed	10 / 52 (19.23%)		
occurrences (all)	17		
Dehydration			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Hypercalcaemia			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	4		
Hyperphosphataemia			
subjects affected / exposed	10 / 52 (19.23%)		
occurrences (all)	14		
Hypoalbuminaemia			

subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Hypophosphataemia			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 July 2012	Addition of new exclusion criteria.
27 July 2012	Change in the consent form
27 July 2012	<p>The statement was in the original draft of the document and was somehow lost when finalising the document:</p> <p>In addition, I give permission for any residual blood and tissue samples, as described in the information sheet to be used for further ethically approved research into the field of breast cancer. (If you do not wish to give this permission, do not initial the box - you can still participate in the trial).</p>
27 January 2014	The Trial Steering Committee and Trial Management Group decided to re-design the study following discussion with the breast cancer research community. The new design will be a non-randomised single-arm study.
17 October 2016	The Study Protocol has been updated
14 March 2018	Extend Study End date

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported